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

Running title: Cardiometabolic disease risk factors and cognitive function in BD

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Abstract

Background: Cardiometabolic disease risk factors are disproportionately prevalent in bipolar disorder (BD) and are associated with cognitive impairment. It is, however, unknown which health risk factors for cardiometabolic disease are relevant to cognition in BD. This study aimed to identify the cardiometabolic disease risk factors that are the most important correlates of cognitive impairment in BD; and to examine whether the nature of the relationships vary between mid and later life.

Methods: Data from the UK Biobank were available for 966 participants with BD, aged between 40 and 69 years. Individual cardiometabolic disease risk factors were initially regressed onto a global cognition score in separate models for the following risk factor domains; 1) health risk behaviours (physical activity, sedentary behaviour, smoking, sleep) and 2) physiological risk factors, stratified into 2a) anthropometric and clinical risk (handgrip strength, body composition, blood pressure), and 2b) cardiometabolic disease risk biomarkers (CRP, lipid profile, HbA1c). A final combined multivariate regression model for global cognition was then fitted, including only the predictor variables that were significantly associated with cognition in the previous models.

Results: In the final combined model, lower mentally-active and higher passive sedentary behaviour, higher levels of physical activity, inadequate sleep duration, higher systolic and lower diastolic blood pressure, and lower handgrip strength were associated with worse global cognition.

Conclusions: Health risk behaviours, as well as blood pressure and muscular strength, are associated with cognitive function in BD, whereas other traditional physiological cardiometabolic disease risk factors are not.

Keywords: health risk behaviours, physiological risks, cardiometabolic disease, cognition, mania, depression, psychiatry, mental health, bipolar disorder, lifestyle.

1. Introduction

Cognitive deficits represent a significant and sustained challenge for over 50% of people with bipolar disorder (BD). Since these cognitive deficits contribute significantly to the psychosocial burden of BD (Van Rheenen et al., 2020), identifying the factors they are associated with, and potentially driven by, is crucial. Physical health is one potential factor, given that people with BD are disproportionately affected by cardiometabolic diseases (e.g. heart disease, diabetes) and experience higher rates of conventional risk factors for these diseases compared to the general population (Coello et al., 2019; Vancampfort et al., 2013; Weiner, Warren, & Fiedorowicz, 2011). These risk factors include metabolic abnormalities such as obesity, dyslipidaemia, hypertension, and the metabolic syndrome (Vancampfort et al., 2013), as well as the lifestyle/behavioural health risk factors that might drive such metabolic abnormalities, such as low physical activity, sedentary behaviour, poor diet, and smoking (Vancampfort et al., 2017).

General population studies have shown age-dependent associations of cardiometabolic diseases and their risk factors with both cognitive impairment and incident dementia (Qiu & Fratiglioni, 2015). Indeed, haemodynamic and serum markers of cardiac function have been associated with structural brain changes and accelerated cognitive decline and dementia (Hosoki et al., 2023; Jensen, Zeller, Twerenbold, & Thomalla, 2023; van der Velpen, Feleus, Bertens, & Sabayan, 2017). Cognitive impairments associated with these markers, as well as with the presence of cardiometabolic diseases and their risk factors, are evident across a number of cognitive domains including executive function, processing speed, memory, attention, fluency, and global cognition (Qiu & Fratiglioni, 2015; Tahmi, Palta, & Luchsinger, 2021; van der Velpen et al., 2017; Waldstein & Wendell, 2010; Zonneveld et al., 2023). As such, cardiometabolic health appears to be broadly relevant to cognitive function.

Poor cardiometabolic health has been linked to an acceleration in the biological ageing process in persons with BD (Rizzo et al., 2014), with cardiometabolic diseases manifesting during early mid-life and up to 17 years earlier than in the general population (Goldstein, Schaffer, Wang, & Blanco, 2015). In line with this, we recently reported that cardiometabolic disease (type 2 diabetes) in BD during mid to later life is associated with more severe processing speed and memory deficits and putatively with premature age-related cognitive decline (Ringin et al., 2022). Another recent large-scale study also found more pronounced adverse age-related changes in common risk factors for cardiometabolic disease, including blood pressure, pulse rate, body composition, and hand-grip strength, in BD patients compared to controls (Mutz, Young, & Lewis, 2022). However, in general, the association of cognition with these risk factors has received relatively sparse empirical attention in BD research to date. Indeed, a systematic review published in 2019 showed that only 11 neurocognitive studies of BD had examined *physiological* correlates of cardiometabolic disease, such as obesity, hypertension, dyslipidaemia, diabetes mellitus, and the metabolic syndrome. The review reported that a heightened physiological risk for cardiometabolic disease was associated with more severe cognitive abnormalities in BD, namely in domains of executive function, processing speed, attention, reasoning, and global cognition, although the sample sizes of included studies were mostly modest (Bora, McIntyre, & Ozerdem, 2019).

The association of cognition and lifestyle/health behaviours relevant to cardiometabolic disease, henceforth termed *health risk behaviours*, has received even less attention in BD (Van Rheenen et al., 2020; Van Rheenen & Neil, 2022). However, early studies on the topic generally indicate more detrimental cardiometabolic-disease-relevant health risk behaviours in those with cognitive impairment (Aas et al., 2019; Balanzá-Martínez, Crespo-Facorro, González-Pinto, & Vieta, 2015; Bradley, Anderson, Gallagher, &

McAllister-Williams, 2020; Burgess, Bradley, Anderson, Gallagher, & McAllister-Williams, 2022; Cardoso et al., 2016; Fellendorf et al., 2017; Ringin et al., 2023). Indeed, preliminary work on physical activity in BD suggests a positive association with executive function, attention and memory (Aas et al., 2019; Fellendorf et al., 2017), although our group recently observed worse global cognition in BD patients *and* controls with high self-reported physical activity levels (Ringin et al., 2023). Other research indicates that cognition (specifically executive function, memory, attention, processing speed, and global cognition) is worse in BD patients with comorbid alcohol use disorders, sleep abnormalities, and for those who engage in more *mentally-passive* sedentary behaviours (e.g., watching TV) (Balanzá-Martínez et al., 2015; Bradley et al., 2020; Burgess et al., 2022; Cardoso et al., 2016; Ringin et al., 2023). In contrast, global cognitive performance appears to be better in people with BD engaging in more *mentally-active* sedentary behaviours (e.g., reading, using the computer), with mentally-active sedentary behaviours appearing to protect against age-related cognitive decline (Ringin et al., 2023).

While these preliminary studies indicate the importance of cardiometabolic disease risk factors in the context of cognitive impairment in BD, the extent to which health-risk behaviours compared to physiological risk factors, are more, less, or equally relevant to cognition, and whether this differs by age, remains unknown. Thus, it is not clear which aspects of cardiometabolic disease risk could most usefully be addressed in cognitive BD research or in preventative cognitive interventions, nor whether different aspects of risk should be targeted at different stages of life. Risk assessment for cognitive impairment/decline in BD in clinical settings is also hampered by this absence of knowledge regarding the relative importance of different cardiometabolic disease risk factors at different life stages, particularly in the context of primary care.

Here, we: i) identify which cardiometabolic disease risk factors are the more important correlates of cognitive impairment in BD, utilising a large cross-sectional dataset to study a range of these factors simultaneously; and ii) determine whether the nature of such relationships varies between mid and later life. In doing so, we aim to inform the strategic direction of resources in cognitive BD research, as well as the development of cognition-related risk assessment tools for use in clinical settings.

2. Materials and Methods.

Participants were drawn from the UK Biobank, a prospective dataset of 502,649 individuals aged 40-69. Baseline assessments were completed across 22 centres throughout the UK between 2005 and 2010, providing a range of lifestyle, health, demographic, cognitive, and biological data. Full details of the data collection procedures are provided elsewhere (*UK Biobank: Protocol for a large-scale prospective epidemiological resource*, 2007). All participants provided written informed consent. The UK Biobank has approval from the Northwest Multi-Centre Research Ethics committee (reference 16/NW/0274 and 11/NW/0382).

2.1. BD diagnostic criteria

UK Biobank participants categorised as having BD were included in this analysis. No healthy controls were included. A detailed description of the methodology for categorising participants as having BD has been provided previously (Smith et al., 2013). In brief, a touchscreen questionnaire, based on symptoms within the Structured Clinical Interview for DSM-IV axis I disorders (introduced in the final two years of recruitment), was utilised to identify participants with probable BD, major depressive disorder, or no indicated mental disorder. These classifications were validated against demographic and clinical information

available in the dataset. In our analyses, participants who were categorised as having major depressive disorder or no indicated mental disorder were excluded from the primary analyses. We also excluded those who were pregnant, as well as those with neurological conditions known to affect cognitive functioning (see Supplementary Material for details).

2.2. Cardiometabolic disease risk factors

We classified 16 individual cardiometabolic disease risk factors obtained at the baseline assessment into two key domains of interest, namely (1) *health risk behaviours*; including time spent in physical activity and mentally-active and passive sedentary behaviour, smoking status, and sleep duration, and (2) *physiological risk factors*; further broken down by (2a) *anthropometric and clinical risk* including systolic and diastolic resting blood pressure, waist circumference, handgrip strength, fat mass index, and fat free mass index, and (2b) *cardiometabolic disease risk biomarkers* including C-reactive protein (CRP), haemoglobin A1c (HbA1c), LDL cholesterol, HDL-L cholesterol, and triglycerides. We also considered the following variables as *covariates*; sex, socio-economic status (SES) – as measured by the Townsend Deprivation Index, educational level, and psychotropic medication use, as well as hypertension and cholesterol lowering medication use and BD subtype (BD I versus BD II). Brief descriptions of the health risk behaviours and physiological risk factors can be found below, with more extensive information provided in the Supplementary Material. It should be noted that some of the risk factors of interest have previously been studied in relation to cognition in BD using UK Biobank participants. Further detail of these studies can be found elsewhere (Firth, Firth, et al., 2018; Milton et al., 2021; Ringin et al., 2023).

Health risk behaviours:

Participants were categorised into low-to-moderate physical activity (=0) and high physical activity (=1) groups based on the self-report International Physical Activity Questionnaire data processing guidelines (International Physical Activity Questionnaire, 2005). Physical activity was categorised in this way given the previous observation in this sample that cognitive functioning did not significantly differ between the low and moderate IPAQ groups (Ringin et al., 2023). Detailed information on this categorisation is provided in the Supplementary Material. Mentally-passive (TV viewing) and mentally active (non-occupational computer use) sedentary behaviour were self-reported as average hours per day of each respective behaviour. Participants who reported greater than 16 hours per day (indicating potentially implausible levels) of total sedentary behaviour (TV viewing, computer use, and driving) *or* physical activity were excluded. Smoking status was defined based on participants reporting being either current smokers (=1) or non-smokers (=0). Non-smokers included participants with a history of smoking who did not currently smoke. Sleep duration was self-reported and dichotomised into inadequate (<6 and >9 hours) (=1) and adequate (6 – 9 hours) (=0) average nightly sleep duration. Sleep duration was analysed categorically given consistent evidence of a u-shaped relationship with cognitive function (Wennberg, Wu, Rosenberg, & Spira, 2017; Yaffe, Falvey, & Hoang, 2014).

Physiological risk factors:

Anthropometric and clinical risk factors: Seated systolic and diastolic resting blood pressure (mmHg) were measured twice using an Omron 705 IT digital monitor, and the average of the two measurements was calculated. Hand-grip strength (a measure of muscular strength and physical fitness) was measured once on each hand using a Jamar J00105 hydraulic hand dynamometer, in line with standard procedures (Roberts et al., 2011). The

score from the participant's self-reported dominant hand was used for the analyses. When handedness was not reported, the highest scoring hand was used. Body composition measures were obtained with a Tanita BC-418 MA body composition analyser. Fat Mass Index (FMI) and Fat Free Mass Index (FFMI) were calculated by dividing whole-body fat mass, and whole-body fat free mass, by height in metres squared. Waist circumference was measured by trained nurses.

Cardiometabolic disease risk biomarkers: CRP, HbA1c, LDL cholesterol, HDL cholesterol, and triglycerides were measured in blood samples collected at baseline. Details on serum sample handling and protocol in the UK Biobank have been described previously (UK Biobank, 2019). Serum CRP (mg/L) and the following lipids were measured by immunoturbidimetric analysis on a Beckman automated haematology analyser; LDL cholesterol (mmol/L), HDL cholesterol (mmol/L) and triglycerides (mmol/L). HbA1c was measured by high performance liquid chromatography analysis on a Bio-Rad VARIANT II Turbo. 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), and elevated (≥39 mmol/mol)[1] in line with references 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 as per standard reference ranges provided by the Australian Institute for Health and Welfare (Australian Institute of Health and Welfare, 2017). Abnormal

[1] The elevated category includes pathological HbA1c levels (≥48mmol/mol).

levels were considered as follows: LDL cholesterol ≥ 3.5mmol/L[2]; HDL cholesterol <1.00mmol/L for men, <1.3mmol/L for women; triglycerides ≥ 2mmol/L.

2.3. Cognitive Assessment

Cognitive functioning was assessed through a brief computerised battery obtained at the same time as the physical activity and sedentary behaviour data collection. The battery, which took approximately 15 minutes to complete, was developed specifically for the UK Biobank and was designed to be completed electronically without examiner supervision. Assessments were completed at the UK Biobank assessment centres and included measurement of the following cognitive domains[3]; visuospatial memory (pairs matching), processing speed (reaction time), fluid intelligence (reasoning test), and prospective memory (prospective memory test). Detailed information regarding each cognitive test can be found in the Supplementary Material, but it should be noted that the tests were not validated in BD samples prior to their inclusion in the UK Biobank protocol. In the current study, scores for all tests were coded so that higher scores equated to better performance. A global cognitive score was then created by; 1) calculating z-scores for the continuous measures (visuospatial memory, processing speed, and fluid intelligence) based on means and standard deviations in the full sample, and 2) summing these z-scores with the raw prospective memory score (dichotomous variable equalling 0 or 1), as has been done previously (Anatürk, Suri, Smith, Ebmeier, & Sexton, 2021). A global cognitive score was used rather than individual domain scores, as aggregate scores are known to have greater validity in sampling the construct of

[2] Given inconsistency in suggested normal/abnormal thresholds, analyses were re-run with a threshold of 2mmol/L. Results were unchanged, and thus are not presented for brevity.

[3] A fifth cognitive domain, numeric memory, was tested at baseline. A recent publication has queried whether the numeric memory test designed for the UK Biobank accurately tests its intended cognitive domain, working memory (Fawns-Ritchie & Deary, 2020). Further, the test was removed during the early stages of testing due to time constraints, subsequently resulting in a very low number of participants with available data. For these reasons, we have decided not to utilise this component in the current study.

interest and are more reliable (Harvey, 2019). A higher global cognitive score equates to better cognitive function.

2.4. Statistical Analysis

All analyses were completed using the Statistical Package for the Social Sciences (SPSS) Version 29 (IBM). All variables were visually checked for extreme outliers and relevant statistical test assumptions were checked using the appropriate methods and residual plots. Preliminary analyses were run to determine whether the covariates of interest (sex, SES, educational level, BD subtype, mood stabiliser use, antidepressant use, first generation antipsychotic use, second generation antipsychotic use, sedatives/hypnotics use, cholesterol-lowering medication use, hypertension medication use, and diabetes medication use) were associated with cognitive function. Psychotropic medication use (all types), hypertensive medication use, diabetes medication use, and BD subtype were not significantly associated with global cognition[4] and were thus not included in the analyses specified below.

To identify individual cardiometabolic disease risk factors associated with global cognitive function in BD, separate multivariable linear regression models were fitted for each risk factor within each risk factor domain (1, health-risk behaviours; 2a, physiological risk - anthropometric and clinical risk factors; and 2b, physiological risk- cardiometabolic disease risk biomarkers; *domain-based models*, n=3). Global cognition was specified as the outcome, while sex, education, SES, and cholesterol-lowering medication use[5] were added in block 1 of each respective model, and the risk factors of interest (either 1, health-risk behaviours; 2a, physiological risk - anthropometric and clinical risk factors; or 2b, physiological – cardiometabolic disease risk biomarkers) added in block 2. The cardiometabolic risk

[4] See Table S1 for full results.
[5] Given its association with measures of cholesterol (LDL-cholesterol, HDL-cholesterol, triglycerides), cholesterol-lowering medication use was added as a covariate in the analysis of cardiometabolic disease biomarkers.

biomarkers model was re-run with participants with comorbid diabetes removed (n=31), to ensure that any findings related to HbA1c reflected its contribution as a *risk factor* for cardiometabolic outcomes, given HBA1C is a biological marker directly indicative of diabetes status. Findings did not change and thus are not presented for brevity. A final combined multivariable regression model (*combined model*, n=1) for global cognition was then fitted, including the aforementioned covariates in block 1 and only the predictor variables that were significantly associated with cognition in the previous models in block 2.

In cases in which specific risk factors showed associations with cognition in domain-specific models but not in the combined model, post-hoc mediation models were conducted to ascertain the extent to which the association of these specific risk factors with cognition was being mediated by the other risk factors that were significant in the combined model. This was done using model 4 of the Preacher and Hayes PROCESS plugin for SPSS (v4.0). Coefficients with 95% bias-corrected bootstrapped confidence intervals (CIs) were calculated for the indirect path (5000 bootstrap samples used), and mediation was considered significant if the range of the CI did not span zero.

To explore whether there were life stage differences in the association of specific cardiometabolic disease risk factors at mid or later-life, we stratified participants by age and re-ran the final model in the stratified groups (*age-stratified models*, n=2). Participants aged 40 – 59 years were grouped into the mid-life category and participants aged 60 – 69 years into the later-life category, based on a) existing approximations of the mid-life stage (Infurna, Gerstorf, & Lachman, 2020) and b) the maximum age of participants in the sample. All other variables in the model remained the same. A false discovery rate of $p<.05$ was applied to all results to account for multiple comparisons using the Benjamini-Hochberg method.

3. Results

3.1. Participants included in the analyses.

Demographic characteristics of the participants included in the analyses are displayed in Table 1. The final analysis included 996 participants, all of whom met UK Biobank criteria for BD. The mean age of the sample was 54.29 (SD=8.01), and 45.7% were female.

3.2. Domain-based models

Results of the three domain-based models are reported in Tables S2 – S4. From the health-risk behaviour domain, global cognitive performance was positively associated with mentally-active sedentary behaviour, negatively associated with passive sedentary behaviour, physical activity, and sleep duration, but not associated with smoking status. From the anthropometric and clinical subdomain of physiological risk factors, global cognitive performance was positively associated with diastolic blood pressure and hand-grip strength, and negatively associated with systolic blood pressure and waist circumference. From the cardiometabolic disease risk biomarkers subdomain of physiological risk factors, it was negatively associated with CRP, but not with HbA1c, HDL cholesterol, non-HDL cholesterol, or triglycerides.

3.3. Combined model

Results of the combined model are reported in Table 2. The full model explained 14.7% of the total variance of global cognition, and the included cardiometabolic disease risk factors explained 9.5% of the total variation after controlling for sex, SES, and educational level. In this model, global cognition was associated with the following variables (when other variables were controlled): **i)** mentally active and mentally passive sedentary behaviour; cognition was lower by 0.11 points on average per one-hour decrease of mentally-active

sedentary behaviour (CI: 0.05, 0.18) and by 0.07 points on average for every one-hour increase in mentally-passive sedentary behaviour (CI: -0.13, -0.01), **ii)** physical activity and sleep duration; cognition was lower by 0.40 points on average in the high compared to low-to-moderate physical activity group (CI: -0.62, -0.17), and by 0.48 points on average in the group that slept <6 or >9 hours per night versus those that slept 6 – 9 hours (CI: -0.82, -0.15); **iii)** handgrip strength; cognition was lower by 0.04 on average points for every one-kg hand-grip strength decrease (CI: 0.03, 0.05); and **iv)** blood pressure; cognition was lower by 0.02 on average points for every one mmHg increase in systolic blood pressure (CI: -0.03, -0.01) and by 0.03 on average points for every one mmHg decrease in diastolic blood pressure (CI: 0.02, 0.05).

3.4. Post-hoc analyses

Since waist circumference and CRP were significantly associated with cognition in the domain-based model only, post-hoc mediation models (n=2) were run to explore the extent to which associations of these risk factors with cognition was being mediated by the other risk factors that were significant in the combined model. *Continuous* measures of physical activity and inadequate sleep were included as mediators in this model, as PROCESS does not allow the use of *categorical* mediators. More details on these variables are provided in the Supplementary Material. CRP was significantly and negatively associated with global cognition, and this association was fully mediated by handgrip strength (CI: -0.16, -0.03), inadequate sleep (CI: -0.11, -0.009) mentally-passive sedentary behaviour (CI: -0.09, -0.0002), systolic blood pressure (CI: -0.19, -0.02) and diastolic blood pressure (CI: 0.02, 0.17) (Figure 1). There was no direct or total effect of waist circumference with global cognition (Figure S1).

3.5. Age-stratified models

3.5.1. Midlife

In participants below 60 years of age, cardiometabolic disease risk factors explained 6.9% of the total variance in global cognition after controlling for sex, SES, and educational level. For these participants, global cognition was lower in those with high physical activity (by 0.38 points on average versus those with low-to-moderate physical activity, CI: -0.65, -0.11), those with a nightly sleep duration of <6 or >9 hours (by 0.56 points on average versus those sleeping 6 – 9 hours per night, CI: -0.96, -0.16), and those with lower hand-grip strength (by 0.04 points on average per one kg decrease, CI: 0.02, 0.05).

3.5.2. Later-life

In participants 60 years of age or above, cardiometabolic disease risk factors of interest explained 10.9% of the total variance in global cognition after controlling for sex, SES, and educational level. For these older participants, global cognition was lower in those with high physical activity (by 0.51 points on average versus those with low-to-moderate physical activity, CI: -0.93, -0.09), those with lower muscular strength (by 0.04 per one kg decrease, CI: 0.01, 0.06), those with less mentally-active sedentary behaviour (by 0.17 points on average per one hour decrease, CI: 0.04, 0.30) and those with low diastolic and high systolic blood pressure (by 0.04 on average for every one mmHg decrease, CI: 0.01, 0.07 and by 0.02 on average for every one mmHg increase, CI: -0.04, -0.004, respectively).

4. Discussion

Our study leveraged a large publicly available dataset to investigate correlates of global cognitive functioning in the context of cardiometabolic disease risk during mid and

later life in BD. We specifically focused on understanding the relative importance of the health-risk behaviours and physiological risk factor domains, the latter including anthropometric, clinical, and cardiometabolic disease risk biomarkers. We found worse global cognition scores (encompassing an aggregate of visuospatial and prospective memory, processing speed, and fluid intelligence domain scores) albeit with small effect sizes, in BD patients with lower levels of mentally-active sedentary behaviour, hand-grip strength and diastolic blood pressure, and in those with higher levels of mentally-passive sedentary behaviour, systolic blood pressure, physical activity, and an average sleep duration of <6 or over 9 hours per night.

These findings are broadly concordant with the literature on cognitive risk factors in the context of dementia (Baumgart et al., 2015; Dintica & Yaffe, 2022). They also add to preliminary evidence linking health risk behaviours with executive, memory, processing speed, attentional, and global cognitive impairments in BD (Aas et al., 2019; Balanzá-Martínez et al., 2015; Bradley et al., 2020; Burgess et al., 2022; Cardoso et al., 2016; Fellendorf et al., 2017; Ringin et al., 2023), as well as to a considerable literature indicating blood pressure as a key marker of cognitive health (in domains of executive function, processing speed, attention, reasoning, and global cognition) both in BD and in the general population (Bora et al., 2019; Ou et al., 2020).

Further, hand-grip strength, a marker of muscular strength and physical fitness, has also been recently linked to memory, processing speed, reasoning, and global cognition in BD cohorts and elsewhere, as well as cognitive decline and dementia more generally (Aliño-Dies et al., 2020; Cui, Zhang, Liu, Gang, & Wang, 2021; Firth, Firth, et al., 2018; Firth, Stubbs, et al., 2018). Here, and in our recent UK Biobank study we also observed that physical activity, a correlate of physical fitness, was also associated with global cognition in BD patients and controls (Ringin et al., 2023), although this association was inverse in

direction. While this unexpected effect may be explained by the theorised negative effect on cognition of *sustained* activity (i.e., occupational activity, which may reflect more-manual job types) (see page 6 of Ringin et al., 2023 for further explanation), perhaps more weighting should be given to the handgrip strength findings in terms of validity. This is because handgrip strength is a readily repeatable physical fitness measure that likely reflects longer term physical activity, whereas in this study physical activity itself was measured with a subjective measure that relies on accurate recall over a 7-day period. Notably, handgrip strength (standardised β=0.23) had the greatest association with global cognition of all continuously-measured variables, regardless of age, followed by systolic (standardised β=-0.19) and diastolic (standardised β=0.17) blood pressure, mentally-active sedentary behaviour (standardised β=0.10), and mentally-passive sedentary behaviour (standardised β=-0.07). Average sleep duration was also more strongly associated with cognitive function than physical activity levels.

Associations of poorer global cognition with high physical activity and low hand-grip strength were evident in BD patients in our sample irrespective of age. However, global cognition was associated with an average nightly sleep duration of <6 or >9 hours (compared to 6-9 hours) in only *midlife* patients, and with higher systolic blood pressure, lower diastolic blood pressure, and less mentally-active sedentary behaviour in only *later-life* patients. The blood pressure associations in later-life are consistent with known increases in systolic and decreases in diastolic blood pressure with age, which in turn increase pulse pressure (Wells & Townsend, 2019) and predict cognitive impairment in middle aged and older people (Sha, Cheng, & Yan, 2018). Indeed, high systolic blood pressure and *low* diastolic blood pressure are recognised as risk factors for dementia in late-life (>65 years) (Forte, Pascalis, Favieri, & Casagrande, 2020; Ou et al., 2020).

The inverse association of mentally-active sedentary behaviour, a type of intellectual stimulation, and cognition in later-life participants is also in line with our earlier UK Biobank study in which we found that BD and control participants with less mentally-active sedentary behaviour were less protected against putative cognitive decline (Ringin et al., 2023). Regarding sleep, preliminary BD research has linked sleep abnormalities with attention and processing speed impairments, although none have examined this association as a function of age (Bradley et al., 2020; Burgess et al., 2022; Kanady, Soehner, Klein, & Harvey, 2017; Laskemoen et al., 2020; Menkes et al., 2021; Russo et al., 2015). Nonetheless, meta-analytic data from the general population has shown an negative association of short and long sleep duration with multi-domain cognitive performance, executive functions, verbal and working memory during later-life (Lo, Groeger, Cheng, Dijk, & Chee, 2016). Thus, it is possible that the relatively low number of late-life BD participants reporting a sleep duration outside of the range of hours recognised as reflecting good sleep (6-9 hours) may explain the association of sleep duration and cognition in only midlife participants.

Somewhat surprisingly, we found no associations between global cognition and most of the cardiometabolic disease risk biomarkers or body composition measures of interest. This contrasts with findings from extant research. For example, two previous, albeit small, BD studies, linked elevated triglycerides to poor executive function (Naiberg et al., 2016; Van Rheenen, McIntyre, Balanzá-Martínez, Berk, & Rossell, 2021). Another meta-analysis of BD also recently linked obesity to executive function and processing speed (Bora et al., 2019). However, there was no association between cognition and memory (verbal, visual, or working) or attention. This may help to explain the absence of adiposity - cognition associations in the current work, given two memory tests were included in the global cognitive score and potentially weighted it more heavily toward a cognitive domain that may not be relevant to measures of body composition. Recent work from our group found domain

specific associations of type 2 diabetes with processing speed and visuospatial memory in a similar UKB sample (Ringin et al., 2022), and as such, the lack of an association with elevated, but not necessarily pathological HbA1c here suggests that cognition in BD is more likely to be affected at pathological HbA1c levels. In support of this, two studies BD studies found no associations between glucose levels and cognition is primarily normoglycaemic samples (Hubenak, Tuma, & Bazant, 2015; Naiberg et al., 2016) , whereas *diagnosed* diabetes has been linked with cognition in another BD cohort (Tsai, Lee, Chen, & Huang, 2007).

Only elevated CRP was associated with worse global cognitive function in the domain-model, and in subsequent analyses it was revealed that handgrip strength, mentally-passive sedentary behaviour, inadequate sleep, systolic blood pressure, and diastolic blood pressure were mediators of its association with global cognition (Figure 1). All of these risk factors have been previously associated with CRP (Chuang et al., 2013; Irwin, Olmstead, & Carroll, 2016; Lakoski et al., 2005; Tuttle, Thang, & Maier, 2020; Wirth et al., 2017). Relevantly, although immune dysregulation and inflammation, as indexed by elevated CRP, has been associated with worse cognitive performance (namely in executive function , processing speed, attention, verbal fluency and memory domains) in several BD studies (Congio, Urbano, Soares, & Nunes, 2022; Dickerson et al., 2013; Millett et al., 2019; Milton et al., 2021), a recent meta-analysis of severe mental illness showed only weak associations between inflammation and global cognition (Morrens et al., 2022). In light of our findings, it is possible that this weak association may be explained as a function of CRP acting indirectly on cognition via a range of other risk factors from the health risk behaviour and anthropometric risk factor domains that are not typically considered in inflammation-cognition studies.

Indeed, although previous BD cognition research has focused on some of the variables we included in our analysis independently, to our knowledge, this is the first BD study to have examined associations of cognitive function with a broad range of health behaviour-related *and* physiological cardiometabolic disease risk factors concurrently. Although this was a strength of the study, other limitations should be considered when interpreting our findings. First, several important cardiometabolic disease risk factors were not measured, or did not have detailed measures, in the UK Biobank dataset (i.e., diet, alcohol use, other inflammatory markers), and as such were not included in our analyses. Moreover, detailed data describing the clinical characteristics of the sample that may impact cardiometabolic outcomes, such as illness duration or episode history, was not available. Second, physical activity, sedentary behaviour and sleep duration were self-reported by participants, and thus may be subject to measurement error. Third, the study was cross-sectional which precludes inferences regarding causality. Fourth, the cognitive data did not come from validated cognitive assessments, and only a few domains were measured. Although there is evidence to show that the available cognitive tests are valid measures of general cognitive functioning (Fawns-Ritchie & Deary, 2020), they have not been validated in BD and may not be particularly sensitive to the deficits common to this population. To offset this, we used an aggregate of the individual cognitive test scores to improve validity and reliability in the measurement of cognition, meaning that domain specific associations may have been missed. Nonetheless, readers are also cautioned to keep in mind that the global cognition score encompassed only four underpinning domains (visuospatial and prospective memory, processing speed, and fluid intelligence), and this score was also not an ideal global cognitive measure. The UK Biobank sample was limited to participants aged between 40 and 69 years of age living in the UK, and as such it is unclear whether these associations would be evident in younger or older cohorts, or in wider geographical regions.

Finally, participants with mental health disorders in the UK Biobank have been shown to be generally higher functioning than those with disorders in the general population (Kendall et al., 2017), which limits generalisability and suggests a potential underestimation of our findings.

Overall, our findings appear to suggest that *behavioural* cardiometabolic disease risk is particularly associated global cognitive function in BD, potentially more-so than physiological cardiometabolic disease risk factors given the predominant associations of health risk behaviours and cognition over and above that of physiological risk factors. Considering this, our findings provide preliminary evidence that health behaviour-related cardiometabolic disease risk may be considered a marker of cognitive function in BD. This has implications for patient phenotyping and clinical care given that health-behaviours can be readily assessed and thus measured in multiple clinical settings (e.g., general practice, psychology) without the need for specialised equipment or knowledge. Given the clear importance of cognitive dysfunction in the clinical management of BD (Van Rheenen, Miskowiak, & Burdick, 2021), health behaviour risk presence as a proxy for poor cognition in BD may be particularly helpful in clinical practice to facilitate; a) identification of those in need of more complex cognitive assessment, b) identification of which patients may benefit from additional support, and c) insight into patient behaviours, thus fostering empathy and understanding in the treating clinician which may lead to improved clinical outcomes. The overlap between measures of cardiometabolic risk and cognitive risk supports the notion that the drivers of neuroprogression, the processes driving progression of psychiatric disorders overlap substantially with those for somatoprogression, the drivers of progression of physical health disorders (Morris et al., 2019). This suggests the necessity for common approaches to prevention and management of these shared pathways for diverse non communicable disease endpoints (O'Neil et al., 2015).

For future research, our findings suggest that cognitive studies of BD with a cardiometabolic disease risk focus should consider concentrating efforts on better understanding the role of health risk behaviours, as well as measures of blood pressure and muscular strength, beyond other physiological risk factors such as lipids and inflammatory markers. It would be of particular benefit to explore how health-risk behaviours may aggregate or interact with one another using latent profile analysis, to better understand whether they collectively compound, or further explain, cognitive impairment in BD. Given recent evidence linking poor cognition to a high immune dysregulation subgroup of psychiatric patients (Sæther et al., 2022), exploring physiological risk factor profiles in relation to cognition in BD in that context may reveal more robust or stronger associations than those seen here. Future research would also do well to explore cardiac biomarkers and their relation to cognition and cognitive markers in BD. An association of these markers and cognition has already been established in the general population (Hosoki et al., 2023; Jensen et al., 2023; van der Velpen et al., 2017), where relevantly, troponin - a widely recognised indicator of heart muscle damage – has been linked to individual variation in the factors associated with cognition in BD in this study; blood pressure, physical activity, and sedentary behaviour (Aakre & Omland, 2019; Xue, Iqbal, Chan, & Maisel, 2014). Exploring the association of cognition and cardiac biomarkers like troponin could, therefore, help to delineate the mechanistic pathways involved in cognitive dysfunction within the disorder.

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Conflicts of Interest

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Table 1. Characteristics of participants (Mean ±Standard Errors)

Characteristic (BD, n=996)	
Age	54.29 ± 8.01
Sex (% female)	45.7
BD subtype (% BD I)	48.5
Townsend deprivation index	-0.12 ± 3.20
Educational level (% attended university)	39.3
Mentally-passive sedentary behaviour (hours/day)	2.65 ± 1.87
Mentally-active sedentary behaviour (hours/day)	1.50 ± 1.76
Physical activity (% high activity group)	44.3
Smoking status (% current smokers)	21.6
Sleep duration (% inadequate sleep)	12.8
Systolic blood pressure (mmHg)	133.79 ± 17.33
Diastolic blood pressure (mmHg)	81.78 ± 10.08
Hand-grip strength (kg)	32.01 ± 11.23
Waist circumference (cm)	92.51 ± 14.17

Table 1. Characteristics of participants (Mean ±Standard Errors)

Characteristic (BD, n=996)	
Fat Mass Index (kg/m^2)	8.75 ± 3.58
Fat Free Mass Index (kg/m^2)	19.14 ± 2.78
CRP (% elevated)	12.0
HbA1c (% normal/elevated)[‡]	83.5 / 16.5
HDL cholesterol (% abnormal)	20.5
LDL cholesterol (% abnormal)	52.6
Triglycerides (% abnormal)	33.3
Cholesterol-lowering medication (% using)[‡]	17.8
Hypertension medication (% using)	18.9
Diabetes medication (% using)	4.5
Mood stabilisers (% using)	11.7
Antidepressants (% using)	19.0
First-generation antipsychotics (% using)	1.3
Second-generation antipsychotics (% using)	5.1

Table 1. Characteristics of participants (Mean ±Standard Errors)

Characteristic (BD, n=996)	
Sedatives / hypnotics (% using)	3.0

[†]HbA1c data were missing for n=101 participants and cholesterol medication data were missing for n=8 participants

Table 2. Combined model of cardiometabolic disease risk factors and global cognition (all age groups)

	Variable (category coded as 1)	**B**[a]	**SE**	**B(standardised)**[b]	**p-value**	**LCI**[c]	**UCI**[d]
Covariates	Sex (female)	-0.27	0.17	-0.07	0.108	-0.60	0.06
	SES	-0.07	0.02	-0.12	**<0.001***	-0.11	-0.04
	Educational level (attended university)	0.38	0.12	0.10	**0.001***	0.15	0.61
Cardiometabolic disease risk factors	Mentally-passive sedentary behaviour, hours/day	-0.07	0.03	-0.07	**0.026***	-0.13	-0.01
	Mentally-active sedentary behaviour, hours/day	0.11	0.03	0.10	**<0.001***	0.05	0.18
	Physical activity (high physical activity)	-0.40	0.12	-0.10	**<0.001***	-0.62	-0.17
	Sleep duration (6-9 hours)	-0.48	0.17	-0.09	**0.005***	-0.82	-0.15
	Systolic blood pressure, mmHg	-0.02	0.01	-0.19	**<0.001***	-0.03	-0.01
	Diastolic blood pressure, mmHg	0.03	0.01	0.17	**<0.001***	0.02	0.05
	Hand-grip strength, kg	0.04	0.01	0.23	**<0.001***	0.03	0.05
	Waist circumference, cm	-0.01	0.01	-0.03	0.488	-0.01	0.006
	CRP (elevated)	-0.35	0.18	-0.06	0.056	-0.70	0.009

A * 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. Sex, male=0, female=1; educational level, did not attend university=0, attended university=1; physical activity, low-moderate activity=0, high activity=1; sleep duration, <6 or >9=0, 6-9=1; CRP normal=0, elevated=1

[a] Unstandardised regression coefficient

[b] Standardised regression coefficient

[c] 95% confidence interval lower limit

[d] 95% confidence interval upper limit

Table 3. Age-stratified model of cardiometabolic disease risk factors and global cognition; midlife patients

	Variable (category coded as 1)	**B**[a]	**SE**	**B(standardised)**[b]	**p-value**	**LCI**[c]	**UCI**[d]
Covariates	Sex (female)	-0.10	0.21	-0.03	0.616	-0.51	0.30
	SES	-0.08	0.02	-0.14	**<0.001***	-0.13	-0.04
	Educational level (attended university)	0.28	0.14	0.07	0.047*	0.003	0.56
Cardiometabolic disease risk factors	Mentally-passive sedentary behaviour, hours/day	-0.08	0.04	-0.08	0.048*	-0.15	-0.001
	Mentally-active sedentary behaviour, hours/day	0.09	0.04	0.08	0.025*	0.01	0.16
	Physical activity (high physical activity)	-0.38	0.14	-0.10	**0.007***	-0.65	-0.11
	Sleep duration (6-9 hours)	-0.56	0.20	-0.10	**0.006***	-0.96	-0.16
	Systolic blood pressure, mmHg	-0.01	0.01	-0.11	0.058	-0.03	0.001
	Diastolic blood pressure, mmHg	0.01	0.01	0.08	0.201	-0.008	0.04
	Hand-grip strength, kg	0.04	0.01	0.22	**<0.001***	0.02	0.05
	Waist circumference, cm	-0.001	0.01	0.002	0.962	-0.01	0.01
	CRP (elevated)	-0.19	0.24	-0.03	0.443	-0.66	0.29

A * 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. Sex, male=0, female=1; educational level, did not attend university=0, attended university=1; physical activity, low-moderate activity=0, high activity=1; sleep duration, <6 or >9=0, 6-9=1; CRP normal=0, elevated=1

[a] Unstandardised regression coefficient

[b] Standardised regression coefficient

[c] 95% confidence interval lower limit

[d] 95% confidence interval upper limit

Table 4. Age-stratified model of cardiometabolic disease risk factors and global cognition; later-life patients

	Variable (category coded as 1)	**B**[a]	**SE**	**B(standardised)**[b]	**p-value**	**LCI**[c]	**UCI**[d]
Covariates	Sex (female)	-0.49	0.30	-0.12	0.104	-1.08	0.10
	SES	-0.07	0.03	-0.11	0.040*	-0.14	-0.003
	Educational level (attended university)	0.62	0.22	0.16	**0.005***	0.18	1.05
Cardiometabolic disease risk factors	Mentally-passive sedentary behaviour, hours/day	-0.04	0.06	-0.04	0.455	-0.15	0.07
	Mentally-active sedentary behaviour, hours/day	0.17	0.06	0.15	**0.009***	0.04	0.30
	Physical activity (high physical activity)	-0.51	0.22	-0.13	**0.019***	-0.93	-0.09
	Sleep duration (6-9 hours)	-0.40	0.32	-0.07	0.211	-1.03	0.23
	Systolic blood pressure, mmHg	-0.02	0.01	-0.17	**0.017***	-0.04	-0.004
	Diastolic blood pressure, mmHg	0.04	0.01	0.21	**0.003***	0.01	0.07
	Hand-grip strength, kg	0.04	0.01	0.19	**0.008***	0.01	0.06
	Waist circumference, cm	-0.01	0.01	-0.04	0.540	-0.03	0.01
	CRP (elevated)	-0.36	0.28	-0.07	0.197	-0.91	0.19

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. Sex, male=0, female=1; educational level, did not attend university=0, attended university=1; physical activity, low-moderate activity=0, high activity=1; sleep duration, <6 or >9=0, 6-9=1; CRP normal=0, elevated=1

[a] Unstandardised regression coefficient

[b] Standardised regression coefficient

[c] 95% confidence interval lower limit

[d] 95% confidence interval upper limit

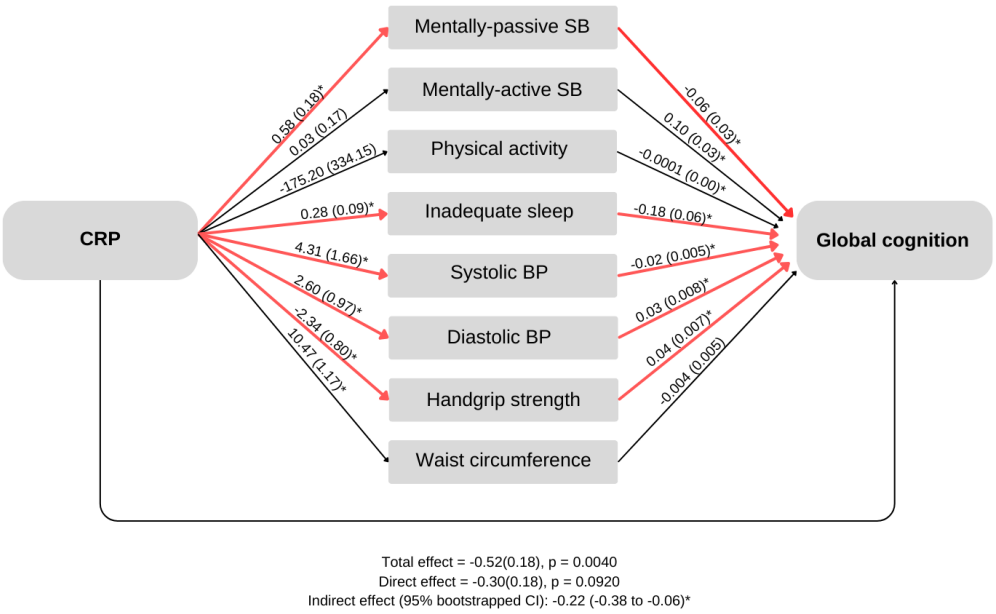

Figure 1. Effects (bootstrapped standard error in parenthesis) for mediation examining how elevated CRP was associated with global cognition after controlling for sex, educational level, and SES. *p <.05. Bolded (red) lines indicate significant mediation pathways (range of CI did not span 0).

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

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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	Comparisons[a]	Group	M	SD	d[b]
Sex	**F (1,976) = 9.60, p = 0.002***	Female Male	-0.93 -0.56	7.43 8.10	0.05
Educational level	**F (1,976) = 23.93, p < 0.001***	No university University	-1.03 -0.45	8.57 6.88	0.08
BD subtype	F (1,976) = 1.34, p = 0.248	BD I BD II	-0.67 -0.82	7.39 8.15	-0.02
Mood stabilisers	F (1,976) = 0.80, p = 0.371	NU U	-0.65 -0.83	10.51 3.92	-0.02
Antidepressants	F (1,976) = 1.86, p = 0.173	NU U	-0.64 -0.85	9.88 4.87	-0.03
First-generation antipsychotics	F (1,976) = 0.08, p = 0.772	NU U	-0.82 -0.67	7.40 2.02	0.03
Second-generation antipsychotics	F (1,976) = 4.17, p = 0.041*	NU U	-0.45 -1.03	10.32 2.89	-0.08
Sedatives/hypnotics	F (1,976) = 2.46, p = 0.117	NU U	-0.47 -1.02	9.84 2.43	-0.08
Cholesterol-lowering medication	**F (1,976) = 11.73, p < 0.001***	NU U	-0.43 -1.05	10.17 4.71	-0.08

Table S1. Associations of the categorical covariates with global cognition

Domain	Comparisons[a]	Group	M	SD	d[b]
Hypertension medication	F (1,976) = 1.34, p = 0.248	NU	-0.65	9.99	-0.02
		U	-0.84	4.85	
Diabetes medication	F (1,976) = 0.001, p = 0.971	NU	-0.74	9.95	0.00
		U	-0.75	2.84	

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.

[a]Results reported reflect raw values unadjusted for multiple comparisons. *Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons.

[b]d = Cohen's d effect sizes.

Table S2. Association of continuous covariates (SES) with global cognition

	B[a]	SD	B(standardised)[b]	p-value	LCI[c]	UCI[d]
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)	**B**[a]	**SE**	**B(standardised)**[b]	**p-value**	**LCI**[c]	**UCI**[d]
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)	**B**[a]	**SE**	**B(standardised)**[b]	**p-value**	**LCI**[c]	**UCI**[d]
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/m^2	0.06	0.04	0.12	0.083	-0.008	0.13
	Fat Free Mass Index, kg/m^2	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)	**B**[a]	**SE**	**B(standardised)**[b]	**p-value**	**LCI**[c]	**UCI**[d]
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

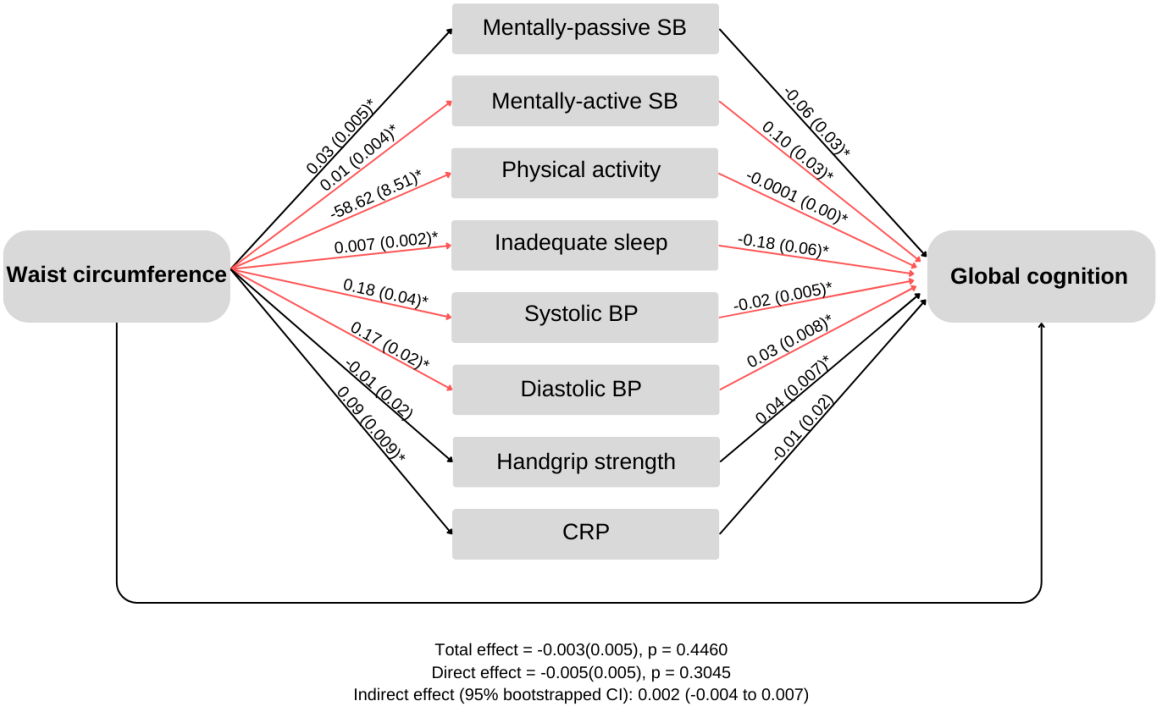

Figure S1. Effects (bootstrapped standard error in parenthesis) for mediation examining how waist circumference was associated with global cognition after controlling for sex, educational level, and SES. *p <.05. Red lines indicate significant mediation pathways (range of CI did not span 0).

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