## Original Article

**Corresponding author:**
Elysha Ringin;
Email: eringin@student.unimelb.edu.au;
Tamsyn E. Van Rheenen;
Email: tamsyn.van@unimelb.edu.au

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# Relative associations of behavioral and physiological risks for cardiometabolic disease with cognition in bipolar disorder during mid and later-life: findings from the UK biobank

Elysha Ringin[1] ⬤, David W. Dunstan[2,3], Denny Meyer[4], Roger S. McIntyre[5], Neville Owen[2,6], Michael Berk[7,8,9], Mats Hallgren[10], Susan L. Rossell[4,11] and Tamsyn E. Van Rheenen[1,4]

[1]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia; [2]Physical Activity Laboratory, Baker Heart & Diabetes Institute, Melbourne, VIC, Australia; [3]Deakin University, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Geelong, Australia; [4]Centre for Mental Health, School of Health Sciences, Swinburne University, Melbourne, Australia; [5]Department of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada; [6]Centre for Urban Transitions, Swinburne University of Technology, Melbourne, VIC, Australia; [7]Deakin University, The Institute for Mental and Physical Health and Clinical Translation, Barwon Health, Geelong, VIC, Australia; [8]Department of Psychiatry, University of Melbourne, Melbourne, Australia; [9]Orygen Youth Health, Melbourne, Australia; [10]Epidemiology of Psychiatric Conditions, Substance Use and Social Environment (EPiCSS), Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden and [11]St Vincent's Mental Health, St Vincent's Hospital, Melbourne, VIC, Australia

## 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 behaviors (physical activity, sedentary behavior, smoking, and sleep) and (2) physiological risk factors, stratified into (2a) anthropometric and clinical risk (handgrip strength, body composition, and blood pressure), and (2b) cardiometabolic disease risk biomarkers (CRP, lipid profile, and 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 behavior, 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 behaviors, 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.

## 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 and 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, dyslipidemia, hypertension, and the metabolic syndrome (Vancampfort et al., 2013), as well as the lifestyle/behavioral health risk factors that might drive such metabolic abnormalities, such as low physical activity, sedentary behavior, 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, hemodynamic 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 aging 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, dyslipidemia, 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 behaviors relevant to cardiometabolic disease, henceforth termed *health risk behaviors*, 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 behaviors 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 behaviors (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 behaviors (e.g. reading, using the computer), with mentally active sedentary behaviors 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 behaviors 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, utilizing 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.

## 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 centers 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).

### BD diagnostic criteria

UK Biobank participants categorized as having BD were included in this analysis. No healthy controls were included. A detailed description of the methodology for categorizing 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 utilized 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 categorized 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 online Supplementary Material for details).

### 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 behaviors*; including time spent in physical activity and mentally active and passive sedentary behavior, 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), hemoglobin A1c (HbA1c), LDL cholesterol, HDL-L cholesterol, and triglycerides. We also considered the following variables as *covariates*; sex, socioeconomic 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 *v.* BD II). Brief descriptions of the health risk behaviors and physiological risk factors can be found below, with more extensive information provided in the online 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 details of these studies can be found elsewhere (Firth et al., 2018a; Milton et al., 2021; Ringin et al., 2023).

### Health risk behaviors

Participants were categorized 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 categorized 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 categorization is provided in the online Supplementary Material. Mentally passive (TV viewing) and mentally active (non-occupational computer use) sedentary behavior were self-reported as average hours per day of each respective behavior. Participants who reported greater than 16 h per day (indicating potentially implausible levels) of total sedentary behavior (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 dichotomized into inadequate (<6 and >9 h) (=1) and adequate (6–9 h) (=0) average nightly sleep duration. Sleep duration was analyzed 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 analyzer. 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 meters 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 hematology analyzer; 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 dichotomized into normal (<5 mg/l) (=0) and elevated (≥5 mg/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 dichotomized into normal (<39 mmol/mol) and elevated (≥39 mmol/mol) (The elevated category includes pathological HbA1c levels (≥48mmol/mol) in line with references ranges from the American Diabetes Association and the International Diabetes Federation (International Diabetes Federation, 2021). Lipids were dichotomized 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 & Welfare, 2017). Abnormal levels were considered as follows: LDL cholesterol ≥ 3.5 mmol/l (Given inconsistency in suggested normal/abnormal thresholds, analyses were re-run with a threshold of 2 mmol/l. Results were unchanged, and thus are not presented for brevity).; HDL cholesterol <1.00 mmol/l for men, <1.3 mmol/l for women; triglycerides ≥ 2 mmol/l.

### Cognitive assessment

Cognitive functioning was assessed through a brief computerized battery obtained at the same time as the physical activity and sedentary behavior data collection. The battery, which took approximately 15 min 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 centers and included measurement of the following cognitive domains (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 utilize this component in the current study).; 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 online 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 equaling 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 interest and are more reliable (Harvey, 2019). A higher global cognitive score equates to better cognitive function.

## 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 stabilizer 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 (See online Supplementary Table S1 for full results). 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 multi-variable linear regression models were fitted for each risk factor within each risk factor domain (1, health-risk behaviors; 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 (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). were added in block 1 of each respective model, and the risk factors of interest (either 1, health-risk behaviors; 2a, physiological risk - anthropometric and clinical risk factors; or 2b, physiological – cardiometabolic disease risk biomarkers) added in block 2. The cardiometabolic risk 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 that 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 $p < 0.05$ was applied to all results to account for multiple comparisons using the Benjamini-Hochberg method.

## Results

### 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 (s.d. = 8.01), and 45.7% were female.

### Domain-based models

Results of the three domain-based models are reported in online Supplementary Tables S2–S4. From the health-risk behavior domain, global cognitive performance was positively associated with mentally active sedentary behavior, negatively associated with passive sedentary behavior, 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.

### 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 behavior; cognition was lower by 0.11 points on average per one-hour decrease of mentally active sedentary behavior (CI 0.05–0.18) and by 0.07 points on average for every 1-h increase in mentally passive sedentary behavior (CI: −0.13 to −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 to −0.17), and by 0.48 points on average in the group that slept <6 or >9 h per night *v.* those that slept 6–9 h (CI −0.82 to −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

**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 behavior (hours/day) | 2.65 ± 1.87 |
| Mentally active sedentary behavior (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 |
| 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)[a] | 83.5 / 16.5 |
| HDL cholesterol (% abnormal) | 20.5 |
| LDL cholesterol (% abnormal) | 52.6 |
| Triglycerides (% abnormal) | 33.3 |
| Cholesterol-lowering medication (% using)[b] | 17.8 |
| Hypertension medication (% using) | 18.9 |
| Diabetes medication (% using) | 4.5 |
| Mood stabilizers (% using) | 11.7 |
| Antidepressants (% using) | 19.0 |
| First-generation antipsychotics (% using) | 1.3 |
| Second-generation antipsychotics (% using) | 5.1 |
| Sedatives / hypnotics (% using) | 3.0 |

[a]HbA1c data were missing for $n$ = 101 participants and cholesterol medication data were missing for $n$ = 8 participants.

increase in systolic blood pressure (CI −0.03 to −0.01) and by 0.03 on average points for every one mmHg decrease in diastolic blood pressure (CI 0.02–0.05).

### 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 online Supplementary Material. CRP was significantly and negatively associated with

global cognition, and this association was fully mediated by hand-grip strength (CI −0.16 to −0.03), inadequate sleep (CI −0.11 to −0.009) mentally passive sedentary behavior (CI −0.09 to −0.0002), systolic blood pressure (CI −0.19 to −0.02) and diastolic blood pressure (CI 0.02–0.17) (Fig. 1). There was no direct or total effect of waist circumference with global cognition (online Supplementary Fig. S1).

### Age-stratified models

#### Midlife
Results of the midlife model are reported in Table 3. 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 *v.* those with low-to-moderate physical activity, CI −0.65 to −0.11), those with a nightly sleep duration of <6 or >9 h (by 0.56 points on average *v.* those sleeping 6–9 h per night, CI −0.96 to −0.16), and those with lower hand-grip strength (by 0.04 points on average per one kg decrease, CI 0.02–0.05).

#### Later-life
Results of the later-life model are reported in Table 4. 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 *v.* those with low-to-moderate physical activity, CI: −0.93 to −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 behavior (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 to −0.004, respectively).

### 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 behaviors 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 behavior, hand-grip strength and diastolic blood pressure, and in those with higher levels of mentally passive sedentary behavior, systolic blood pressure, physical activity, and an average sleep duration of <6 or over 9 h 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 behaviors with executive, memory, processing speed, attentional, and global cognitive impairments in BD (Aas et al., 2019; Balanzá-Martínez et al., 2015; Bradley

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

| Variable (category coded as 1) | $B^a$ | S.E. | 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 behavior, hours/day | −0.07 | 0.03 | −0.07 | **0.026*** | −0.13 | −0.01 |
| Mentally active sedentary behavior, 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 h) | −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 $p < 0.05$ *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]Unstandardized regression coefficient.
[b]Standardized regression coefficient.
[c]95% confidence interval lower limit.
[d]95% confidence interval upper limit.

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,
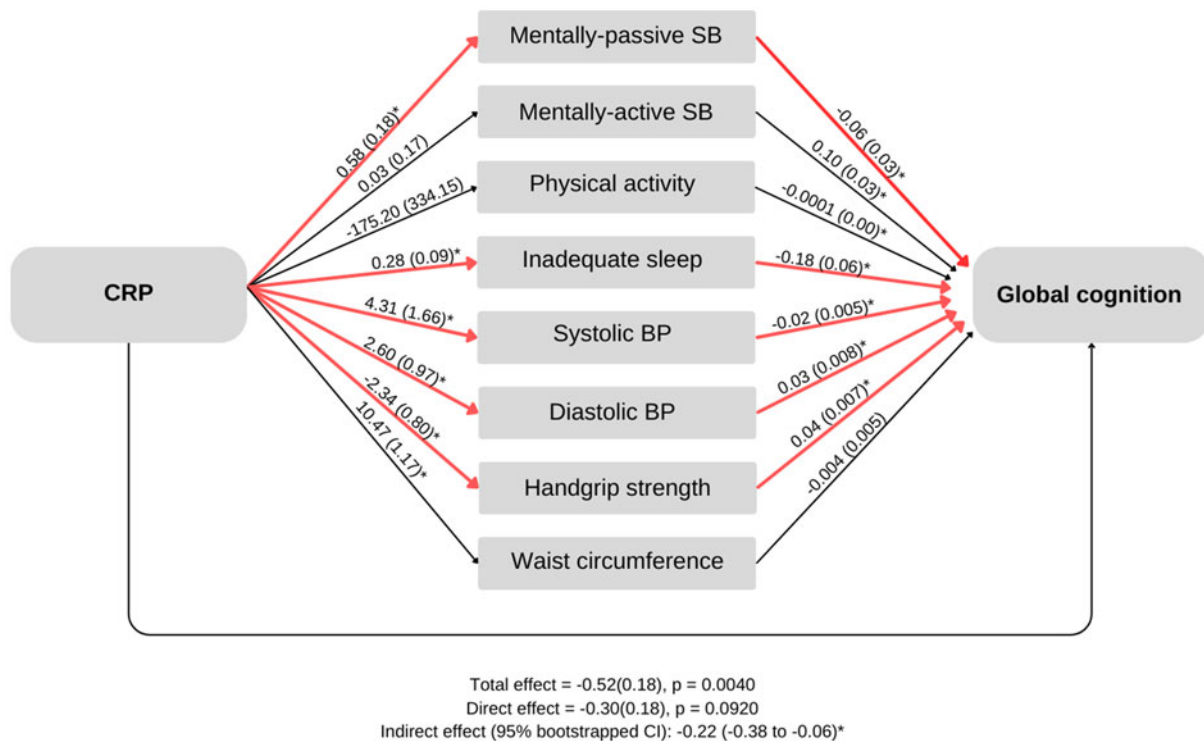


Total effect = -0.52(0.18), p = 0.0040
Direct effect = -0.30(0.18), p = 0.0920
Indirect effect (95% bootstrapped CI): -0.22 (-0.38 to -0.06)*

**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. *$p < 0.05$. Bolded (red) lines indicate significant mediation pathways (range of CI did not span 0).

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

| Variable (category coded as 1) | $B^a$ | S.E. | $B$ (standardized)[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 behavior, hours/day | −0.08 | 0.04 | −0.08 | 0.048* | −0.15 | −0.001 |
| Mentally active sedentary behavior, 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 h) | −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 $p < 0.05$ *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]Unstandardized regression coefficient.
[b]Standardized regression coefficient.
[c]95% confidence interval lower limit.
[d]95% confidence interval upper limit.

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 et al., 2018a, 2018b). 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

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

| Variable (category coded as 1) | $B^a$ | S.E. | $B$ (standardized)[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 behavior, hours/day | −0.04 | 0.06 | −0.04 | 0.455 | −0.15 | 0.07 |
| Mentally active sedentary behavior, 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 h) | −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 $p < 0.05$ *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]Unstandardized regression coefficient.
[b]Standardized regression coefficient.
[c]95% confidence interval lower limit.
[d]95% confidence interval upper limit.

may be explained by the theorized 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 (standardized $\beta = 0.23$) had the greatest association with global cognition of all continuously-measured variables, regardless of age, followed by systolic (standardized $\beta = -0.19$) and diastolic (standardized $\beta = 0.17$) blood pressure, mentally active sedentary behavior (standardized $\beta = 0.10$), and mentally passive sedentary behavior (standardized $\beta = -0.07$). 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 h (compared to 6–9 h) in only *midlife* patients, and with higher systolic blood pressure, lower diastolic blood pressure, and less mentally active sedentary behavior in only *later-life* patients. The blood pressure associations in later-life are consistent with known increases in systolic and decrease 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 recognized as risk factors for dementia in late-life (>65 years) (Forte, De Pascalis, Favieri, & Casagrande, 2020; Ou et al., 2020).

The inverse association of mentally active sedentary behavior, 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 behavior 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 a 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 recognized as reflecting good sleep (6–9 h) may explain the association between 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, 2021a). 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 are primarily normoglycemic 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 behavior, inadequate sleep, systolic blood pressure, and diastolic blood pressure were mediators of its association with global cognition (Fig. 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 behavior 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 behavior-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 behavior, 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 generalizability and suggests a potential underestimation of our findings.

Overall, our findings appear to suggest that *behavioral* 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 behaviors and cognition over and above that of physiological risk factors. Considering this, our findings provide preliminary evidence that health behavior-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-behaviors can be readily assessed and thus measured in multiple clinical settings (e.g. general practice, psychology) without the need for specialized equipment or knowledge. Given the clear importance of cognitive dysfunction in the clinical management of BD (Van Rheenen, Miskowiak, & Burdick, 2021b), health behavior 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 behaviors, 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 behaviors, 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 behaviors 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 between 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 recognized 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 behavior (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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