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Differential Associations of Mentally-Active and Passive Sedentary Behaviours and Physical Activity with Putative Cognitive Decline in Healthy Individuals and those with Bipolar Disorder: Findings from the UK Biobank Cohort

Running title: Sedentary behaviour, physical activity, and cognition in BD

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Abstract.

Objective: Physical activity confers protection against age-related cognitive dysfunction, but less is known about whether cognition is impacted by sedentary behaviour, specifically its mentally-active and passive forms. Both physical inactivity and sedentary behaviour are highly prevalent in bipolar disorder (BD), yet if and how they relate to the disorder's cognitive symptoms remains unclear. In this study, we explored whether individual variation in physical activity and sedentary behaviour was directly associated with cognition and/or moderated the extent of decrements in cognitive performance occurring as a function of age in people with BD versus psychiatrically-healthy controls.

Methods: Relevant UK Biobank data were available for 1074 BD patients and 59,653 psychiatrically-healthy controls, aged 40-70. Age, mentally-active (computer use) and passive sedentary behaviour (TV viewing), physical activity, diagnosis, and their interactions were regressed on a global cognitive score.

Results: Cognition was inversely associated with physical activity (β= -0.003, CI: -0.003, -0.003) and passive sedentary behaviour (β= -0.03, CI: -0.04, -0.02) and positively associated with mentally-active sedentary behaviour (β=0.13, CI: 0.12, 0.15). The latter association was stronger in the BD group. Mentally-active sedentary behaviour moderated the age-cognition association in both BD patients and controls (β=0.01, CI: 0.008, 0.01), such that age-related decrements in cognition were more apparent in those who engaged in less mentally-active sedentary behaviours compared to those who engaged in more.

Conclusions: Mentally-active sedentary behaviour may not only attenuate age-related cognitive dysfunction, but may be important for cognition irrespective of age, particularly in those with BD. These findings support the notion that intellectual stimulation is a protective factor conferring cognitive benefits, even in the context of a sedentary lifestyle.

Keywords: age-related decline; cognitive deterioration; cognitive reserve; intellectual stimulation; physical health; mood disorders

1. Introduction.

Cognitive dysfunction is a significant challenge in the clinical management of bipolar disorder (BD), affecting over 50% of patients (Burdick, Goldberg, & Harrow, 2010;Van Rheenen & Rossell, 2014) and resulting in psychosocial difficulties and decreased quality of life (Burdick et al., 2010; Rosa et al., 2008; Van Rheenen & Rossell, 2014). Cognitive dysfunction in BD has been hypothesised by some to reflect premature deterioration within, or acceleration of, the normal cognitive ageing process. In support of this, processing speed, executive function, and general cognitive performance in BD are impaired at an earlier age than would be expected on account of normal age-related decline (Gildengers et al., 2009; Lewandowski, Sperry, Malloy, & Forester, 2014; Seelye et al., 2019; Weisenbach et al., 2014). Moreover, those with more severe cognitive dysfunction score more highly on proxy markers of advanced cognitive ageing (Van Rheenen et al., 2017). Abnormalities in biological factors that change with age, including inflammation, neurotrophin levels, oxidative stress, telomere length, and brain structure and function, are also associated with BD (Juan & Adlard, 2019) and may represent the biological mechanisms by which cognition is affected (Rizzo et al., 2014).

In the ageing literature, physically or emotionally-stimulating activities such as reading, social interaction or exercise, have been shown to confer protection or resilience against cognitive dysfunction and decline (Bangsbo et al., 2019; Nithianantharajah & Hannan, 2009; Olanrewaju, Stockwell, Stubbs, & Smith, 2020; Opdebeeck, Martyr, & Clare, 2016; Stern, 2013). This is particularly true for the domains of memory, attention, and executive function (Nithianantharajah & Hannan, 2009; Opdebeeck et al., 2016; Stern, 2013), which tend to be the earliest to show the effects of age and are amongst those most typically affected in BD (Miskowiak & Petersen, 2019). Relevantly, physical activity is lower in BD (Vancampfort et al., 2017), and sedentary behaviour– a related, yet distinct behavioural health risk factor on

the physical activity spectrum, is higher (Janney et al., 2014; Vancampfort et al., 2017). It is plausible that these factors play a role in the cognitive dysfunction associated with BD, although there is limited research on this topic to date (Van Rheenen et al., 2020; Van Rheenen & Neil, 2022).

To our knowledge only three studies have examined physical activity (or exercise) and cognition in BD, with one showing no association (Burgess, Bradley, Anderson, Gallagher, & McAllister-Williams, 2022) and two demonstrating positive associations (Aas et al., 2019; Fellendorf et al., 2017). Additionally, once recent study demonstrated a positive association of muscular strength – a physical activity-related factor, with several domains of cognition in both BD and major depressive disorder (MDD) (Firth, Firth, et al., 2018). Physical activity has also been shown to buffer the impact of childhood trauma on the clinical severity of BD (Aas et al., 2021), and is associated with reduced BMI, waist circumference, insomnia, and episodic relapse (Melo et al., 2019) – all factors implicated in cognitive function. No BD studies have yet explored the association of sedentary behaviour and cognition, although one recent study of schizophrenia – which is genetically and phenotypically related to BD – found higher levels of sedentary behaviour related to worse motor reaction time, as well as worse cognitive processing speed (Stubbs, Ku, Chung, & Chen, 2017).

In the general population, sedentary behaviour is linked to cognition independent of physical activity levels (Falck, Davis, & Liu-Ambrose, 2017; Olanrewaju et al., 2020). However, recent evidence suggests that the nature of the association may depend on the *type* of sedentary behaviour (Mellow et al., 2022; Ringin, Meyer, et al., 2022). That is, mentally passive activities, like watching TV, appear to be *negatively* associated with cognition, while mentally active activities, like computer/internet use and reading, appear to be *positively* associated with cognition (Falck et al., 2017; Hoang et al., 2016; Olanrewaju et al., 2020; Ringin, Meyer, et al., 2022; Tun & Lachman, 2010; Wang et al., 2006). This is consistent

with evidence that verbal knowledge, which is increased by reading, fosters resilience against age-related brain deterioration by reducing its adverse impact on cognitive functioning (Sumowski, Wylie, Chiaravalloti, & DeLuca, 2010; Van Rheenen et al., 2020). Whether individual variability in physical activity or specific forms of sedentary behaviour is associated with cognitive dysfunction or cognitive decline in BD, however, has not been elucidated.

In this study we sought to address this gap in research, by comparing a large group of individuals with BD to healthy controls from the UK Biobank (UKB). Specifically, we explored both direct and moderating effects of physical activity and sedentary behaviour on cognition in these groups, using a quasi-longitudinal design in a cross-sectional dataset to assess *putative* cognitive 'decline' as indexed by changes in cognitive impairment as a function of age. In doing so we aimed to address three main questions; (1) whether cognition was inversely associated with age (as an indicator of putative decline), particularly in the BD group; (2) whether this inverse association was moderated by physical activity and sedentary behaviour (and whether there was any moderating effect of mentally passive or mentally active subtypes of sedentary behaviour); and (3) whether physical activity and sedentary behaviour (and its subtypes) were associated with cognitive function directly and irrespective of age.

We hypothesised that cognition would be positively associated with physical activity and mentally active sedentary behaviour, and inversely associated with mentally passive sedentary behaviour. We also expected weaker age-cognition associations, and by proxy, less age-related putative decline, in those with higher levels of physical activity and/or mentally active sedentary behaviour, and those with lower levels of mentally passive sedentary behaviour. Finally, we were interested in the extent to which these associations were moderated by diagnosis.

2. Methods

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

The UKB is a prospective dataset of 502,649 participants 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. Measures included in the current study are described below, and full details of the UKB data collection procedures are provided elsewhere (UK Biobank, 2007). All participants provided written informed consent. The UKB has approval from the Northwest Multi-Centre Research Ethics committee (reference 16/NW/0274 and 11/NW/0382).

2.1. Participant sampling

UKB participants categorised as either having BD or as being psychiatrically healthy were selected for this analysis. The full methodology for categorising participants is detailed elsewhere (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 used to identify participants as likely having BD type I or type II, MDD, or no indicated affective disorder. Those with MDD were excluded from the current analysis. This categorisation was validated against demographic and clinical information available in the dataset, and prevalence rates were consistent with population-based estimates of BD. In our analyses, participants presenting with any mental disorder (including personality disorder), or on any type of psychotropic medication, were excluded from the control group. Participants with neurological conditions known to affect cognitive

functioning (refer to supplementary material for list), as well as those who were pregnant, and those who reported being unable to walk, were also excluded.

2.2. Participant characteristics (confounding factors).

Age, sex, educational level, and socio-economic status (SES) - measured by the Townsend Deprivation Index, waist circumference, sleep duration (hours per day), alcohol use (drinks alcohol versus does not drink alcohol), smoking status (smoker versus non-smoker), and occupational status were collected from questionnaires completed during baseline assessments. Education responses were used to create a dichotomous variable, categorising participants as either having a university/college degree or not having a university/college degree. Occupation responses were also dichotomised according to whether participants were either employed (paid employment, unpaid employment, or student) or not employed (unemployed, retired, unable to work due to sickness/disability, or looking after home/family).

2.3. Sedentary Behaviour

Participants completed a computerised questionnaire in which they were asked to self-report their hours per day spent in sedentary behaviour across three activities: TV viewing, driving, and non-occupational computer use. Given the extensive evidence base implicating *leisure time* sedentary behaviour as a risk factor for chronic disease (Patterson et al., 2018; Saunders et al., 2020; Sisson et al., 2009), only TV viewing (passive sedentary behaviour) and non-occupational computer use (mentally active sedentary behaviour) were analysed in the current study. 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. Responses of "less than an hour per day" were

coded as 0.5. The data was analysed continuously given there is no consensus definition of what constitutes high and low sedentary behaviour.

2.4. Physical Activity

Physical activity was measured using adapted questions from the International Physical Activity Questionnaire (IPAQ) short form, which uses six self-report questions to assess the frequency, intensity, and duration of walking, moderate-intensity, and vigorous-intensity physical activity (Craig et al., 2003). Time spent in each of these activities was weighted by the energy expenditure for each activity, which was then used to calculate metabolic equivalent of task (MET) minutes per week, a continuous measure of weekly physical activity. To be consistent with the sedentary behaviour measures described above, MET minutes per week was divided by 60 to reflect MET *hours* per week.

Participants who reported greater than 16 hours a day of physical activity (indicating implausible levels) were excluded from analyses, in line with IPAQ guidelines. Further, based on IPAQ data processing guidelines (IPAQ, 2005), participants were also categorised according to their level of physical activity as follows; *high* – those who engaged in an hour of moderate-vigorous activity or 30 minutes of vigorous activity per day *above* the basal level of daily physical activity; *moderate* - those who engaged in at least 30 minutes of moderate intensity activity most days; and *low* – those who did not meet criteria for the aforementioned high or moderate levels of physical activity specified. Further details about the categorisation can be found in the supplementary materials.

2.5. Cognitive Assessment

Cognitive functioning was assessed through a brief computerised battery collected at the same time as the physical activity and sedentary behaviour data. The battery, which took approximately 15 minutes to complete, was developed specifically for the UKB and was designed to be completed electronically without examiner supervision. Assessments were completed at the UKB assessment centres and included measurement of the following cognitive domains[1]; visuospatial memory (pairs matching), processing speed (reaction time), fluid intelligence (reasoning test), and prospective memory (prospective memory test). Full details of each measure can be found in the supplementary material. In the current study, scores for all measures were coded so that higher scores equated to better performance. Global cognitive scores were 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). Age-related differences in these scores between diagnoses, and as a function of physical activity or sedentary behaviour, were then examined as a proxy of putative age-related cognitive decline.

2.6. Statistical Analysis

All analyses were completed using the Statistical Package for the Social Sciences (SPSS) version 27 (IBM). Demographic data was assessed using χ^2 tests and one-way ANOVAs. The Preacher and Hayes PROCESS plugin for SPSS (v4.0) was used to assess inter-relationships between variables. An initial moderation model (using PROCESS model

[1] 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.

1) was specified to determine if there were diagnostic group differences in the association of age and cognitive scores (Research Question 1). Age was set as the independent variable (IV:X), global cognition as the dependent variable (DV:Y), and diagnostic group as the moderator (W). Sex, educational level, and SES, waist circumference, sleep duration, alcohol drinker status, smoking status, and occupational status were entered as covariates.

An additional 3 moderation models (using PROCESS model 3) were then specified to assess the extent to which associations between age and cognitive functioning[2] were moderated by sedentary behaviour or physical activity and whether this differed by diagnostic group (Research Question 2). The results of these same models were also used to assess direct associations (i.e., main effects) of physical activity/sedentary behaviour and cognitive function as a function of diagnostic group (Research Question 3). Age was set as the independent variable (X), global cognition as the dependent variable (Y), and either mentally passive sedentary behaviour (TV use), mentally active sedentary behaviour (non-occupational computer use) or physical activity (MET hours) as the primary moderator (W). Diagnostic group was included as the secondary moderator (Z). Sex, education, SES, sleep duration, alcohol drinker status, smoking status, and occupational status were set as covariates a-priori. In the models in which physical activity, mentally passive sedentary behaviour, or mentally active sedentary behaviour were not specified as moderators, they were entered as covariates to control their respective effects on the dependent variable. Appropriate post-hoc tests were used to follow up significant findings (see supplementary material for details).

An exploratory analysis was also conducted to examine associations between cognition and psychotropic medication use in the sample (see supplementary material). A

[2] Initial data cleaning revealed outliers for several key variables (global cognition, summed MET minutes, TV use, computer use, SES, waist circumference, and sleep duration), so sensitivity analyses were run with and without the outliers removed. Removing outliers of TV use (scores ≥ 8 hours), computer use (scores ≥ 5 hours), and global cognition (scores ≤ -4.5 or ≥ 6.4) significantly altered results, and thus the outliers were removed for the final analyses and are the sole findings reported. Removal of outliers for all other key variables did not significantly alter results, and thus outliers were left in for the final analyses.

false discovery rate of p<.05 was applied to all results from both moderation analyses and exploratory analyses 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 60,727 participants, 1074 of which met UKB criteria for BD. Participants with BD on average were significantly younger and of lower SES than controls. Additionally, those with BD reported significantly more MET hours of physical activity per week, less TV viewing, and significantly greater non-occupational computer use compared to controls.

3.2. Primary Analyses

3.2.1. Initial association of age and global cognition (Research Question 1)

Age was inversely associated with cognitive function, such that global cognition decreased by 0.06 for every one-unit increase in age (CI: -0.06, -0.06, p <.0001). Diagnostic group was also significantly associated with cognitive function, with global cognitive scores in the BD group lower than the control group by 0.16 (CI: -0.27, -0.04, p = .0065). The association of age with cognition was *not* moderated by diagnostic group (CI: -0.006, 0.02, p = .2447).

3.2.2. Main effects and interactions (with age and diagnosis) of sedentary behaviour and physical activity on global cognition (Research Questions 2 and 3)

The results of all models testing sedentary behaviour and physical activity as direct correlates of global cognition (Research Question 3) and moderators of global cognition's association with age (Research Question 2) in BD and control groups are reported in Table 2. Outcomes of full models, including covariates, can be founded in Supplementary Table S1. In all models, age was negatively associated with global cognition in both the BD and control groups, and there was a main effect of diagnosis in that BD patients had lower global cognitive scores than controls. For brevity, these findings are not repeated in the reporting of each model below.

3.2.2.1 Sedentary behaviour

Mentally passive sedentary behaviour

There was a main effect of TV viewing, with cognitive scores decreasing by 0.03 for every one-hour increase in TV viewing. There was no significant moderation of this inverse association by diagnosis, nor was there a significant moderation of the association between age and global cognition by TV viewing in either BD or control groups.

Mentally active sedentary behaviour

There was a main effect of non-occupational computer use, with cognitive scores increasing by 0.13 for every one-hour increase in computer use. The association of computer use on global cognition was moderated by diagnosis, with follow up analyses indicating a stronger association between these variables in the BD group (Figure 1 and supplementary Table S2). The relationship between age and cognition was also significantly moderated by computer use, but this did not differ by diagnosis. As indicated in Figure 2, in both BD and control groups cognitive performance was similar across those of ~40-50 years of age (the earliest age indexed in the UKB) irrespective of computer use, however as age increased

beyond ~50 years, those reporting low computer use had worse cognitive performance than those with high levels of computer use.

3.2.2.2. Physical activity

A main effect of physical activity was evident, such that cognitive scores decreased by 0.003 for every one-unit increase in MET hours. The association of physical activity and cognition was moderated by diagnosis, with follow up analyses revealing a *slightly* stronger association in the BD group (Supplementary Tables S3 and S4). Further post-hoc analyses using categorical data revealed that there were no differences in the cognitive scores of those with low versus moderate levels of activity, but those with higher levels of physical activity performed significantly worse than those with low and moderate activity levels. This did not differ by diagnosis, although the differences between physical activity subgroups were slightly (significantly) larger in patients with BD (Figure 3 and Table S3 and S4). No significant moderation of the association between age and global cognition by physical activity was observed in either BD patients or controls.

3.3. Secondary medication analyses in the BD sample

There were no differences in the global cognition of BD users versus non-users of most psychotropic medication classes, except for second-generation antipsychotics for which a significant but near-negligible effect (d=0.09) was evident, favouring better cognition in non-users. Further details of these analyses can be found in Supplementary Table S6.

Discussion.

In this study we used a quasi-longitudinal design in the UKB dataset to investigate whether *putative* age-related cognitive decline was moderated by physical activity and

sedentary behaviour in psychiatrically healthy individuals and those with BD and explore if there were direct associations between physical activity and sedentary behaviour irrespective of age. As expected, cognitive performance worsened as a function of increasing age. However, there was no evidence that this age-related worsening in cognition was exacerbated by BD. Cognitive performance was also worse in those reporting higher levels of mentally passive sedentary behaviour, and lower levels of mentally active sedentary behaviour, irrespective of age or diagnosis. These findings are consistent with an emerging body of research demonstrating an association of TV viewing (mentally passive) with worse cognitive performance, and reading or computer use (mentally active) with better cognitive performance in the general population (Carson et al., 2015; Falck et al., 2017; Olanrewaju et al., 2020). The relationship between mentally active sedentary behaviour and cognition was stronger in the BD group than controls, which may relate to the increased computer use and cognitive deficits identified in this group in this study. An alternative explanation is that because people with BD tend to experience more 'insults' to their brain and body as a result of their illness (e.g., brain structural and functional abnormalities, medical comorbidities etc), they rely more heavily on intellectually enriching activities (which occur in the context of non-occupational computer use) to compensate for the known impacts of these insults on cognition than controls (Karantonis et al., 2021; Ringin, Dunstan, et al., 2022). While this is purely speculative and remains to be explored in empirical work on BD, it should be noted that there is literature from persons who live with schizophrenia – a phenotypically related disorder – showing evidence of a greater impact of brain structural abnormalities on cognitive functioning in those with lower versus higher levels of intellectual enrichment (Van Rheenen et al., 2020).

As predicted, higher levels of mentally active sedentary behaviour attenuated the magnitude of age-related decrements in cognitive performance. This attenuation was apparent

irrespective of diagnostic group and similar in magnitude between them, which is sensical in that there was no evidence of age-accelerated cognitive decline in the BD group per se. Specifically, cognitive performance was similar across participants in the 40–50-year age bracket (the beginning of the age range indexed in the UKB) irrespective of their level of mentally active sedentary behaviour. However, cognition incrementally worsened in participants beyond this age range who reported less mentally active sedentary behaviour compared to those reporting moderate or high levels. These findings support the notion that intellectual stimulation, even while sedentary, may be protective against age-related cognitive decline, and highlight that different forms of sedentary behaviour confer different cognitive risks and benefits. The underlying mechanisms by which mentally active sedentary behaviour is beneficially associated with cognition is not yet clear; factors such as motivation may act to moderate the relationship through increased engagement in mentally active behaviours and better cognitive performance (Vallet et al., 2020). Physiologically, the association is likely to involve a number of pathways that result in increased neurogenesis and neuroplasticity, both which have been linked to stimulating environments (Brown et al., 2003; Van Praag, Kempermann, & Gage, 2000).

Contrary to expectations, high levels of physical activity were associated with worse cognitive performance, and this was slightly more pronounced in the BD group. The negative association of physical activity with cognition, along with the absence of cognitive differences between low and moderately active participants in either diagnostic group, conflicts with existing research that has generally shown improvements in cognition as a result of increased physical exercise (Aas et al., 2019; Bangsbo et al., 2019; Fellendorf et al., 2017). Nonetheless, one BD study and several general population studies have shown an absence of, or less robust, associations between these factors (Burgess et al., 2022; Erickson et al., 2019). There is also substantial heterogeneity in physical activity dose parameters

across studies, and thus little is known about the optimal dose, inclusive of both intensity and frequency, that is associated with, or needed to improve, cognition. Moderate intensity activities are most commonly investigated, meaning effects are often attributed to this type of activity (Erickson et al., 2019; Felez-Nobrega, Haro, Erickson, & Koyanagi, 2020; Nemoto et al., 2018; Omura et al., 2020), with effects of higher levels of physical activity remaining unclear.

In keeping with this notion, several papers unrelated to cognition have argued that high intensity activity may actually be detrimental to health; impairing immune function, increasing inflammation, and decreasing cerebral blood flow (Cerqueira, Marinho, Neiva, & Lourenço, 2020; Ogoh & Ainslie, 2009; Paolucci, Loukov, Bowdish, & Heisz, 2018; Rooks, Thom, McCully, & Dishman, 2010). Notably, these factors reflect mechanisms by which physical activity may link with cognition (Gorelick, 2010; Sahathevan, Brodtmann, & Donnan, 2012), with increased inflammation and decreased cerebral blood flow also commonly reported in BD (Rosenblat & McIntyre, 2016; Toma, MacIntosh, Swardfager, & Goldstein, 2018). The stronger inverse coupling of physical activity and cognition in the BD group here may thus reflect a cumulative effect of a BD diagnosis and excessive high intensity activity, resulting in cognitive impairment. It should be noted however, that high levels of physical activity as measured by the IPAQ can reflect either high-intensity activity OR sustained lower intensity activity (e.g., walking and moderate). Therefore, another explanation is that these findings reflect an outcome of a 'physical activity paradox', which has been used to explain the known link between occupational physical activity (a key contributor to high levels of *sustained* activity, measured by the IPAQ here) and poor mental and physical health, including the higher incidence of coronary heart disease and all-cause mortality (A. Holtermann, Hansen, Burr, Søgaard, & Sjøgaard, 2012; Andreas Holtermann, 2015; Andreas Holtermann, Krause, Van Der Beek, & Straker, 2018).

Alternatively, high levels of physical activity may actually represent a proxy for greater psychopathology (subthreshold in the case of controls), in that exercise may be used by highly active individuals as a form of self-medication. In this context there is potential that our findings reflect the association of cognition with psychopathology rather than with physical activity per se. However, given the limitations of the current data (i.e., absence of current symptom measurement and distinction between occupation and non-occupational physical activity), we were unable to explore these ideas further and they should be considered to be highly speculative. It is also possible that the negative association between physical activity and global cognition is a result of methodological limitations of the current study (discussed below). As such, further research is needed before clear interpretations can be made.

To our knowledge, this is the largest BD study to have examined the association of cognition and physical activity, and the only BD study to have examined the association of cognition and sedentary behaviour. It is also one of only a handful of studies in psychiatrically healthy individuals to have explicitly examined the cognitive associations of both mentally passive and mentally active sedentary behaviours. Nonetheless, several limitations exist. These include the use of a quasi-longitudinal design in cross-sectional data to infer age-related cognitive change, which limits the extent to which firm conclusions regarding causality/directionality in relationships can be made. Participants with mental health disorders in the UKB also appear to be generally higher functioning than those with the same disorders in the general population (Kendall et al., 2017), limiting generalisability. To this end, the number of BD participants taking psychotropic medication was relatively low (only 29% were using psychotropic medications). While secondary analyses of medication generally revealed no cognitive differences in users and non-users of most medication

classes, we cannot entirely discount that psychotropic medication use did not influence the findings.

Additionally, the cognitive data did not come from validated cognitive assessments and the number of cognitive domains measured in the UKB at baseline was sparse. Although there is evidence to show that the available cognitive tests are valid measures of general cognitive functioning (Fawns-Ritchie & Deary, 2020), the individual cognitive tests have not been well-used 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 here. In doing so, it is possible that associations seen in other more cognitively impaired psychiatric samples between particular cognitive domains and physical activity or sedentary behaviour were missed (Fellendorf et al., 2017; Stubbs et al., 2017). More comprehensive cognitive tests validated in BD samples are advised for future research on this topic, to gain a more nuanced understanding of domain-specific cognition – physical activity/sedentary behaviour associations.

Further, only two types of leisure time sedentary behaviour (TV viewing and non-occupational computer use) were assessed, and it remains possible that more detailed assessments of sedentary behaviour would result in different study outcomes. The short-form of the IPAQ was also used, and while it is a validated and commonly used measure, it is less detailed than its longer counterpart and does not provide domain-specific scores for subdomains of physical activity (e.g., leisure, occupational). Moreover, both physical activity and sedentary behaviour questionnaires relied on self-report, which may be biased by subjective recall as studies of both psychiatric (including BD specifically) and general populations have demonstrated an overestimation of moderate to vigorous physical activity in self-report measures (Firth, Stubbs, et al., 2018; Vancampfort et al., 2019, 2016). Currently,

the only way to differentiate between mentally active and passive sedentary behaviour is via self-report, but future work would do well to at least explore objective measures of physical activity in relation to cognition in BD. Relatedly, we were unable to easily assess the effects of comorbidities, both psychiatric and general health related, given the nature of the UKB data. Future research would do well to assess these given known associations of comorbidities with cognition in BD (Balanzá-Martínez et al., 2010). Current mood symptom assessments in BD patients were also not available, thus we could not explore whether sedentary behaviour simply proxied depression severity. However, as the sedentary behaviour-cognition associations observed in this study were present in both patients *and* controls, it is likely that sedentary behaviour at least partially represents a variable unto itself. This is in line with recent longitudinal evidence showing that passive sedentary behaviour prospectively increases, rather than is a consequence of, depression risk (Hallgren et al., 2019).

Finally, one further point warrants discussion, related to the absence of consensus regarding which specific activities constitute mentally active or passive subtypes of sedentary behaviour. On face validity, non-occupational computer use seems mentally active by nature, although it is likely that components of mentally passive behaviours are included within. Due to limited data, we were unable to contrast non-occupational computer use with occupational computer use - which is widely recognised to be cognitively active - although this would go some way toward contextualising the findings. Empirical validation of the activities that sit within each sedentary behaviour type is needed.

In summary, our findings from this large UKB cohort provide evidence that mentally active sedentary behaviour may not only attenuate age-related cognitive dysfunction broadly, but may also be important for cognition irrespective of age, particularly in those with BD. In contrast, mentally passive sedentary behaviour and higher levels of physical activity (relative

to low/moderate physical activity) appear to be detrimentally associated with cognition. These findings add to a growing literature implicating intellectual stimulation as a protective factor for cognitive dysfunction and decline, and highlight it as a potentially viable intervention target for cognitive dysfunction in BD. Further work should i) aim to replicate our findings using objective activity assessments in longitudinal designs, ii) investigate the biological mechanisms by which associations between sedentary behaviour and cognitive function exist, and iii) examine the extent to which variations in the different forms of sedentary behaviour alongside physical activity translate to different cognitive outcomes.

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Table 1. Characteristics of participants

Characteristic	BD (n = 1074)	HC (n = 59653)	Comparison	Effect size[a]
Age	54.44 ± 7.91	56.99 ± 8.13	F = 103.23, p < 0.001*	-0.32
Sex (% female)	48.8	47.9	χ^2 = 0.33, p = 0.566	-0.002
Townsend deprivation index	-0.18 ± 3.23	-1.54 ± 2.72	F = 267.49, p < 0.001*	0.46
Educational level (% attended university)	39.9	36.9	χ^2 = 3.82, p = 0.051	0.008
Employment status (% employed/student)	61.3	59.4	χ^2 = 1.56, p = 0.211	0.005
Waist circumference	92.08 ± 13.95	89.76 ± 13.02	F = 33.44, p < 0.001*	0.17
Alcohol use status (% alcohol user)	87.8	93.9	χ^2 = 68.17, p < 0.001*	-0.03
Smoking status (% smokers)	20.5	7.1	χ^2 = 277.02, p < 0.001*	0.07
Sleep duration (hours per day)	7.14 ± 1.33	7.17 ± 0.98	F = 1.14, p = 0.286	-0.03
Global cognitive score	0.77 ± 1.94	0.92 ± 1.93	F = 6.88, p = 0.009*	-0.08
Physical activity (MET hours per week)	52.88 ± 57.93	46.59 ± 45.22	F = 20.53, p < 0.001*	0.12
Physical activity group (% low/moderate/vigorous)	17.3 / 38.0 / 44.7	15.7 / 40.9 / 43.4	χ^2 = 4.23, p = 0.120	0.008
Mentally passive sedentary behaviour (TV viewing hours per day)	2.49 ± 1.61	2.61 ± 1.43	F = 7.39, p = 0.007*	-0.08
Mentally active sedentary behaviour (non-occupational computer use hours per day)	1.14 ± 1.04	1.01 ± 0.92	F = 20.14, p < 0.001*	0.13

BD = bipolar disorder; HC = healthy control; MET = metabolic equivalent of task
[a] Cohen's d effect size is reported for continuous variables, ϕ for categorical variables with 2 groups, and Cramer's V for categorical variables with > 2 groups.
---- Data not applicable
Data are expressed as mean ± SD.

Table 2. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
Mentally passive sedentary behaviour					
Diagnostic group	-0.17	0.06	0.0043*	-0.28	-0.05
Age	-0.06	0.001	<0.0001*	-0.06	-0.06
Mentally passive sedentary behaviour	-0.03	0.006	<0.0001*	-0.04	-0.02
Mentally passive behaviour*diagnostic group	0.02	0.04	0.5296	-0.05	0.09
Mentally passive sedentary behaviour*age	-0.0001	0.0007	0.8895	-0.001	0.001
Mentally passive sedentary behaviour* age*diagnostic group	0.008	0.004	0.0744	-0.001	0.02
Mentally active sedentary behaviour					
Diagnostic group	-0.17	0.06	0.004*	-0.28	-0.06
Age	-0.06	0.001	<0.0001*	-0.06	-0.06
Mentally active sedentary behaviour	0.13	0.008	<0.0001*	0.12	0.15
Mentally active sedentary behaviour*diagnostic group	0.11	0.05	0.04*	0.005	0.22

Table 2. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
Mentally active sedentary behaviour*age	0.01	0.001	<0.0001*	0.008	0.01
Mentally active sedentary behaviour* age*diagnostic group	0.009	0.007	0.2010	-0.005	0.02
Physical activity					
Diagnostic group	-0.15	0.06	0.0123*	-0.26	-0.03
Age	-0.06	0.001	<0.0001*	-0.06	-0.06
Physical activity	-0.003	0.0002	<0.0001*	-0.003	-0.003
Physical activity*diagnostic group	-0.003	0.001	0.0078*	-0.005	-0.0007
Physical activity*age	0.00	0.00	0.2980	-0.0001	0.00
Physical activity*age*diagnostic group	-0.0001	0.0001	0.5238	-0.0003	0.0002

*Significant at $p < .05$ after Benjamini-Hochberg FDR correction for multiple comparisons.
[a] Unstandardised regression coefficient
[b] Lower-limit confidence interval
[c] Upper-limit confidence interval

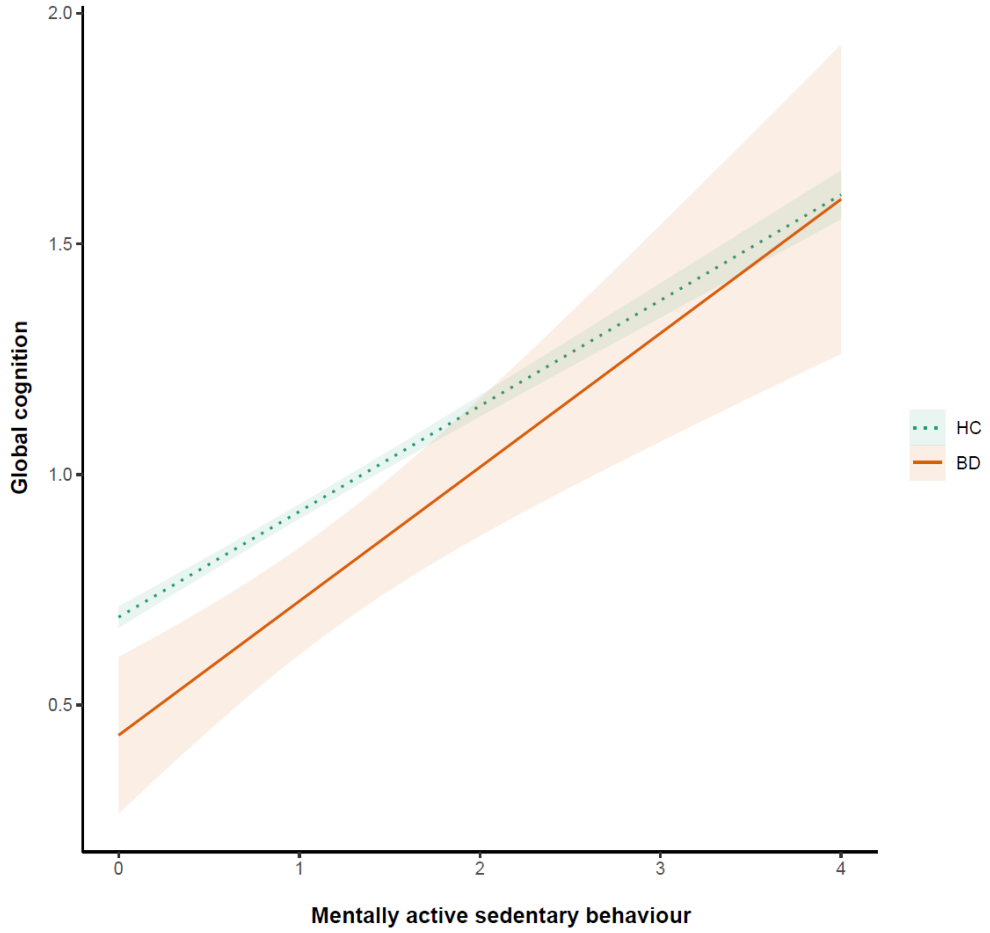

Figure 1. Differences in cognition as a factor of mentally active sedentary behaviour in BD and HC groups. *Mentally active sedentary behaviour reflects hours per day of computer use. Note the association is stronger in the BD groups versus HCs*

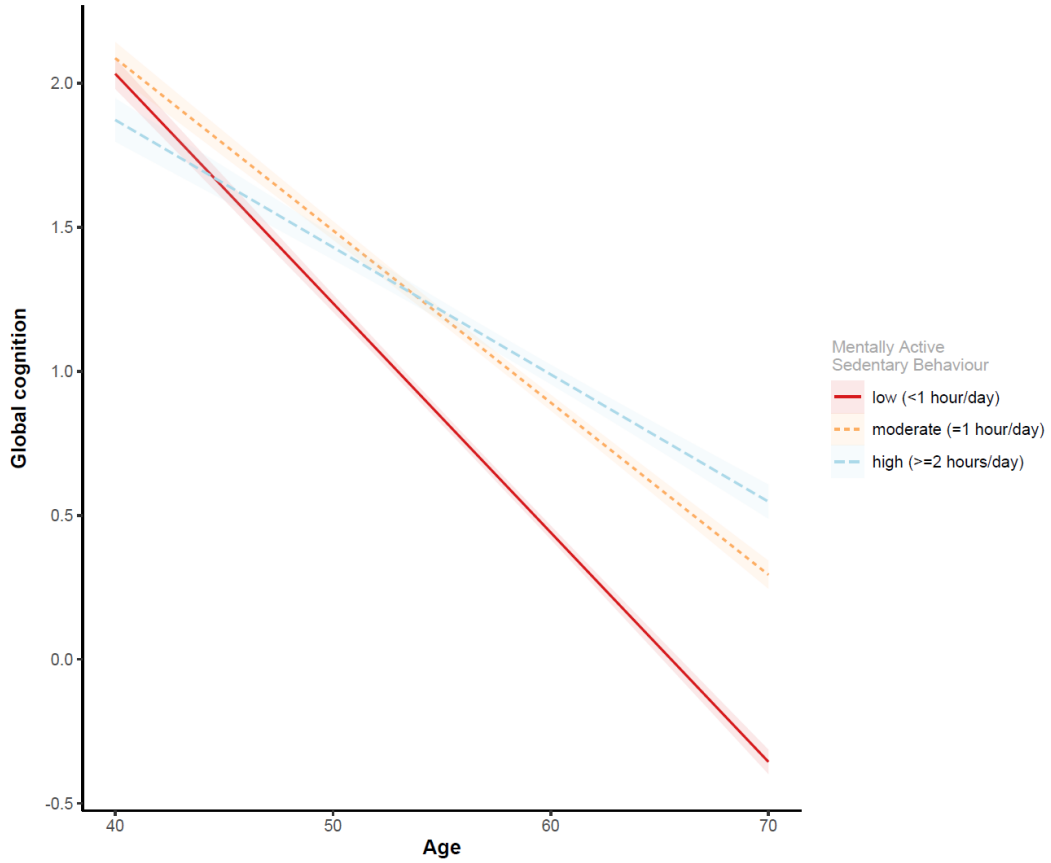

Figure 2. Age-related differences in cognition in subgroups of low moderate or high mentally active sedentary behaviour irrespective of diagnosis. *Mentally active sedentary behaviour reflects hours per day of computer use.*

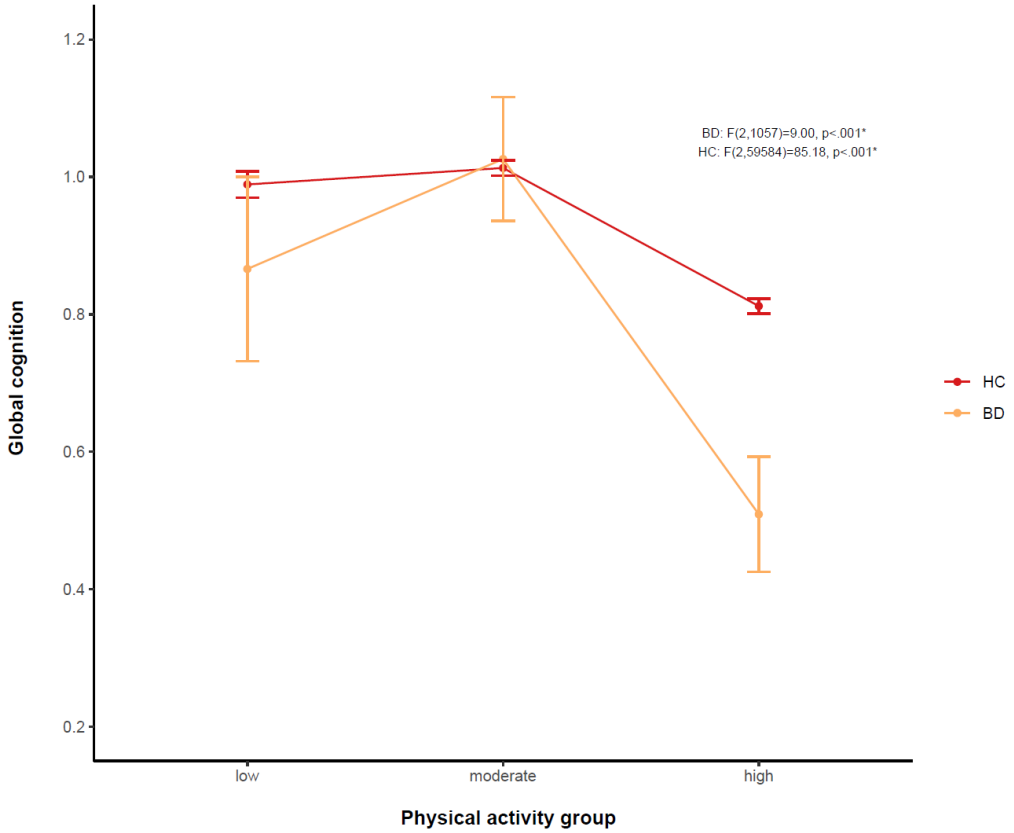

Figure 3. Differences in global cognition by high, moderate, and low physical activity subgroups. *Values reflect estimated marginal means based on diagnosis stratified ANCOVAs. Errors bars reflect standard error. In the HC sample significant differences were evident between the low and high PA groups, and moderate and high PA groups. In the BD sample, a significant difference was evident between moderate and high PA groups.*

SUPPLEMENTARY MATERIAL

Differential Associations of Mentally-Active and Passive Sedentary Behaviours and Physical Activity with Putative Cognitive Decline in Healthy Individuals and those with Bipolar Disorder: Findings from the UK Biobank Cohort

Table of Contents

Supplementary Methods

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, 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 and pressed a button when the cards matched. The outcome of interest was the mean response time (milliseconds). Higher scores indicate worse performance.

3. Fluid intelligence (reasoning): participants were asked to solve a number of numeric and verbal logic problems in 2 minutes. The outcome of interest was the number of correct problems solved. 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. The outcome of interest was a dichotomous measure stating whether participants acted correctly or incorrectly in response to the instruction.

IPAQ scoring guidelines.

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.

Exploratory medication analysis

Given the possibility of confounding effects of psychotropic medication on cognition in the BD group, additional analyses were run to determine whether group differences in cognitive scores were evident between medicated and un-medicated individuals. Psychotropic medications were grouped into medication classes based on previous research (Cullen et al., 2015). A univariate ANCOVA was run with global cognition as the dependent variable, and psychotropic medication classes as the independent variables. Covariates remained the same as those used in the primary analyses.

Post-hoc analyses

To further explore the significant two-way interaction of age with mentally active sedentary behaviour, mentally active subgroups were defined (Computer use; < 1, = 1, and ≥ 2 hours/day) and the age-related cognitive slopes of each of these subgroups were modelled. The primary PROCESS model also revealed a moderating effect of diagnostic group the association of mentally active sedentary behaviour and cognition. To further interpret this, the sample was stratified by diagnostic group and two linear regression models conducted using global cognition as the output and mentally active sedentary behaviour as the independent variable of interest.

Similar post-hoc analyses were run to explore the moderating effect of diagnosis on the physical activity – cognition relationships. The sample was stratified by diagnostic group and two linear regression models conducted with global cognition as the output and physical activity (MET hours per week) as the independent variable of interest. Given the unexpected direction of the physical activity finding, models were then re-run using ANCOVA with *categorical* physical activity (low, moderate, or high IPAQ subgroups)[3] set as the independent variable and global cognition set as the dependent variable in both models.

[3] Given uneven group sizes, these analyses were re-run using tertiles of the continuous MET minutes variables. Results were unchanged and are not provided for brevity.

Supplementary Tables

Table S1. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions (all covariates included)

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
Mentally passive sedentary behaviour					
Diagnostic group	-0.17	0.06	0.0043*	-0.28	-0.05
Age	-0.06	0.001	<0.0001*	-0.06	-0.06
Mentally passive sedentary behaviour	-0.03	0.006	<0.0001*	-0.04	-0.02
Mentally passive behaviour*diagnostic group	0.02	0.04	0.5296	-0.05	0.09
Mentally passive sedentary behaviour*age	-0.0001	0.0007	0.8895	-0.001	0.001
Mentally passive sedentary behaviour* age*diagnostic group	0.008	0.004	0.0744	-0.001	0.02
Age*diagnostic group	0.009	0.007	0.2114	-0.005	0.02
Mentally active sedentary behaviour	0.14	0.08	< 0.0001*	0.12	0.16
Physical activity	-0.003	0.0002	< 0.0001*	-0.003	-0.003
Sex	0.24	0.02	< 0.0001*	0.20	0.27

Table S1. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions (all covariates included)

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
SES	-0.07	0.003	< 0.0001*	-0.08	-0.07
Educational level	0.66	0.02	< 0.0001*	0.63	0.69
Waist circumference	0.001	0.0007	0.1476	-0.0003	0.002
Smoking status	-0.11	0.03	0.0001*	-0.17	-0.06
Alcohol use status	0.63	0.03	< 0.0001*	0.56	0.68
Sleep duration	-0.02	0.008	0.0227*	-0.03	-0.002
Mentally active sedentary behaviour					
Diagnostic group	-0.17	0.06	0.004*	-0.28	-0.06
Age	-0.06	0.001	<0.0001*	-0.06	-0.06
Mentally active sedentary behaviour	0.13	0.008	<0.0001*	0.12	0.15
Mentally active sedentary behaviour*diagnostic group	0.11	0.05	0.04*	0.005	0.22
Mentally active sedentary behaviour*age	0.01	0.001	<0.0001*	0.008	0.01

Table S1. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions (all covariates included)

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
Mentally active sedentary behaviour* age*diagnostic group	0.009	0.007	0.2010	-0.005	0.02
Age*diagnostic group	0.005	0.007	0.5082	-0.009	0.02
Mentally passive sedentary behaviour	-0.03	0.006	< 0.0001*	-0.04	-0.02
Physical activity	-0.003	0.0002	< 0.0001*	-0.003	-0.003
Sex	0.23	0.02	< 0.0001*	0.20	0.27
SES	-0.07	0.003	< 0.0001*	-0.08	-0.07
Educational level	0.66	0.02	< 0.0001*	0.63	0.69
Waist circumference	0.001	0.0007	0.1357	-0.0003	0.002
Smoking status	-0.11	0.03	0.0001*	-0.17	-0.06
Alcohol use status	0.62	0.03	< 0.0001*	0.56	0.68
Sleep duration	-0.02	0.008	0.0166*	-0.03	-0.003
Physical activity					

Table S1. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions (all covariates included)

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
Diagnostic group	-0.15	0.06	0.0123*	-0.26	-0.03
Age	-0.06	0.001	<0.0001*	-0.06	-0.06
Physical activity	-0.003	0.0002	<0.0001*	-0.003	-0.003
Physical activity*diagnostic group	-0.003	0.001	0.0078*	-0.005	-0.0007
Physical activity*age	0.00	0.00	0.2980	-0.0001	0.00
Physical activity*age*diagnostic group	-0.0001	0.0001	0.5238	-0.0003	0.0002
Age*diagnostic group	0.007	0.007	0.3006	-0.007	0.02
Mentally passive sedentary behaviour	-0.03	0.006	< 0.0001*	-0.04	-0.02
Mentally active sedentary behaviour	0.14	0.008	<0.0001*	0.12	0.16
Sex	0.23	0.02	< 0.0001*	0.20	0.27
SES	-0.08	0.003	< 0.0001*	-0.08	-0.07
Educational level	0.66	0.02	< 0.0001*	0.63	0.69

Table S1. Models predicting cognition as a function of age, diagnosis, physical activity or sedentary behaviour and their interactions (all covariates included)

	coeff[a]	S.E.	*p*	95% LLCI[b]	95% ULCI[c]
Waist circumference	0.001	0.0007	0.1511	-0.0003	0.002
Smoking status	-0.11	0.03	0.0001*	-0.17	-0.06
Alcohol use status	0.62	0.03	< 0.0001*	0.56	0.68
Sleep duration	-0.02	0.008	0.0113*	-0.03	-0.003

*Significant at p < .05 after Benjamini-Hochberg FDR correction for multiple comparisons.
[a] Unstandardised regression coefficient
[b] Lower-limit confidence interval
[c] Upper-limit confidence interval

Table S2. Associations of mentally active sedentary behaviour with global cognition stratified by diagnostic group

	B	S.E.	*p*	95% Lower Bound CI	95% Upper Bound CI
Diagnostic group: BD					
Mentally active sedentary behaviour	0.20	0.05	<0.001*	0.10	0.31
Diagnostic group: HC					
Mentally active sedentary behaviour	0.14	0.008	<0.001*	0.12	0.16

BD = bipolar disorder, HC =healthy control

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

Table S3. Associations of physical activity with global cognition stratified by diagnostic group

	B	S.E.	*p*	95% Lower Bound CI	95% Upper Bound CI
Diagnostic group: BD					
Physical activity	-0.006	0.001	<0.001*	-0.008	-0.004
Diagnostic group: HC					
Physical activity	-0.003	0.0002	<0.001*	-0.003	-0.002

BD = bipolar disorder, HC =healthy control

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

Table S4. Associations of categorical physical activity with global cognition stratified by diagnostic group

Domain	Comparisons	Group	M[a]	SD	Post-Hoc (d)
Diagnostic group: BD					
Physical activity subgroup	F (2, 1057) = 9.00, p < 0.001*	Low	0.87	1.83	Low = mod (0.09)
		Moderate	1.03	1.82	Low > high (-0.19)
		High	0.51	1.84	Mod > high (-0.28)*
Diagnostic group: HC					
Physical activity subgroup	F (2, 59584) = 85.18, p < 0.001*	Low	0.99	1.84	Low = mod (0.01)
		Moderate	1.01	1.72	Low > high (-0.10)*
		High	0.81	1.77	Mod > high (-0.12)*

Note: criteria for categorisation into low, moderate, and high physical activity subgroups can be found on page 2 of this document, BD = bipolar disorder, HC = healthy controls, IPAQ = International Physical Activity Questionnaire

[a]All values are adjusted for sex, educational level, and townsend deprivation index, waist circumference, sleep duration, alcohol use status, smoking status, occupational status, mentally active sedentary behaviour, and mentally passive sedentary behaviour.

d = Cohen's d effect sizes.

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

Table S5. Comparison of low/moderate and high physical activity subgroups in the bipolar disorder and healthy comparison samples

	BD			HC		
Characteristic	Low/moderate physical activity (n=594)	High physical activity (n=480)	Comparison	Low/moderate physical activity (n=33778)	High physical activity (n=25875)	Comparison
Age	54.65 ± 8.06	54.18 ± 7.72	F = 0.92, p = 0.338	56.99 ± 8.03	56.97 ± 8.26	F = 0.11, p = 0.745
Sex (% female)	49.0	48.5	χ^2 = 0.02, p = 0.884	49.3	46.1	χ^2 = 62.48, p < 0.001*
BD subtype (% Type I)	52.4	45.2	χ^2 = 5.43, p = 0.020*	----	----	----
Townsend deprivation index	-0.21 ± 3.22	-0.16 ± 3.25	F = 0.07, p = 0.797	-1.55 ± 2.72	-1.54 ± 2.73	F = 0.05, p = 0.818
Educational level (% attended university)	44.4	34.2	χ^2 = 11.70, p < 0.001*	38.8	34.6	χ^2 = 108.88, p < 0.001*
Alcohol use status (% alcohol users)	87.9	87.7	χ^2 = 0.007, p = 0.932	93.8	94.1	χ^2 = 2.53, p = 0.112
Employment status (% employed/student)	59.6	63.3	χ^2 = 1.56, p = 0.211	61.2	57.0	χ^2 = 109.38, p < 0.001*
Smoking status (% smokers)	19.7	21.5	χ^2 = 0.51, p = 0.477	7.3	6.9	χ^2 = 2.63, p = 0.105
Sleep duration (hours per day)	7.21 ± 1.38	7.04 ± 1.28	F = 4.23, p = 0.040*	7.17 ± 0.98	7.16 ± 0.97	F = 1.08, p = 0.298
Waist circumference	94.08 ± 14.10	89.61 ± 13.37	F = 27.99, p < 0.001*	90.83 ± 13.37	88.37 ± 12.41	F = 529.51, p < 0.001*
Passive sedentary behaviour (hours per day)	2.58 ± 1.65	2.39 ± 1.54	F = 3.71, p = 0.054	2.65 ± 1.45	2.57 ± 1.41	F = 51.94, p < 0.001*
Mentally active sedentary behaviour (hours per day)	1.20 ± 1.06	1.06 ± 1.02	F = 4.47, p = 0.035*	1.04 ± 0.93	0.97 ± 0.89	F = 83.86, p < 0.001*

Note: criteria for categorisation into low, moderate, and high physical activity subgroups can be found on page 2 of this document

Table S6. Associations between psychotropic medication use and global cognitive function in the BD group

Domain	Comparisons	Group	M[a]	SD	Post-Hoc[b]	d[c]
Mood stabilisers	F (1,1056) = 0.30, p = 0.587	NU U	0.42 0.32	9.78 3.87	----	-0.01
Antidepressants	F (1,1056) = 0.20, p = 0.654	NU U	0.40 0.34	9.27 4.56	----	-0.01
First-generation APs	F (1,1056) = 0.54, p = 0.462	NU U	0.18 0.56	6.15 1.93	----	0.08
Second generation APs	F (1,1056) = 6.17, p = 0.013*	NU U	0.68 0.06	9.54 2.99	NU > U	-0.09
Sedatives/hypnotics	F (1,1056) = 2.52, p = 0.113	NU U	0.63 0.10	9.09 2.32	----	-0.08

NU = Non-users, U = users, APs = antipsychotics.

[a]All values are adjusted for age, sex, educational level, townsend deprivation index, waist circumference, sleep duration, alcohol use, smoking status, and occupational status.

[b]If post-hoc relationship is not reported, finding was not significant.

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

*Significant at $p < .05$.

Supplementary Figures

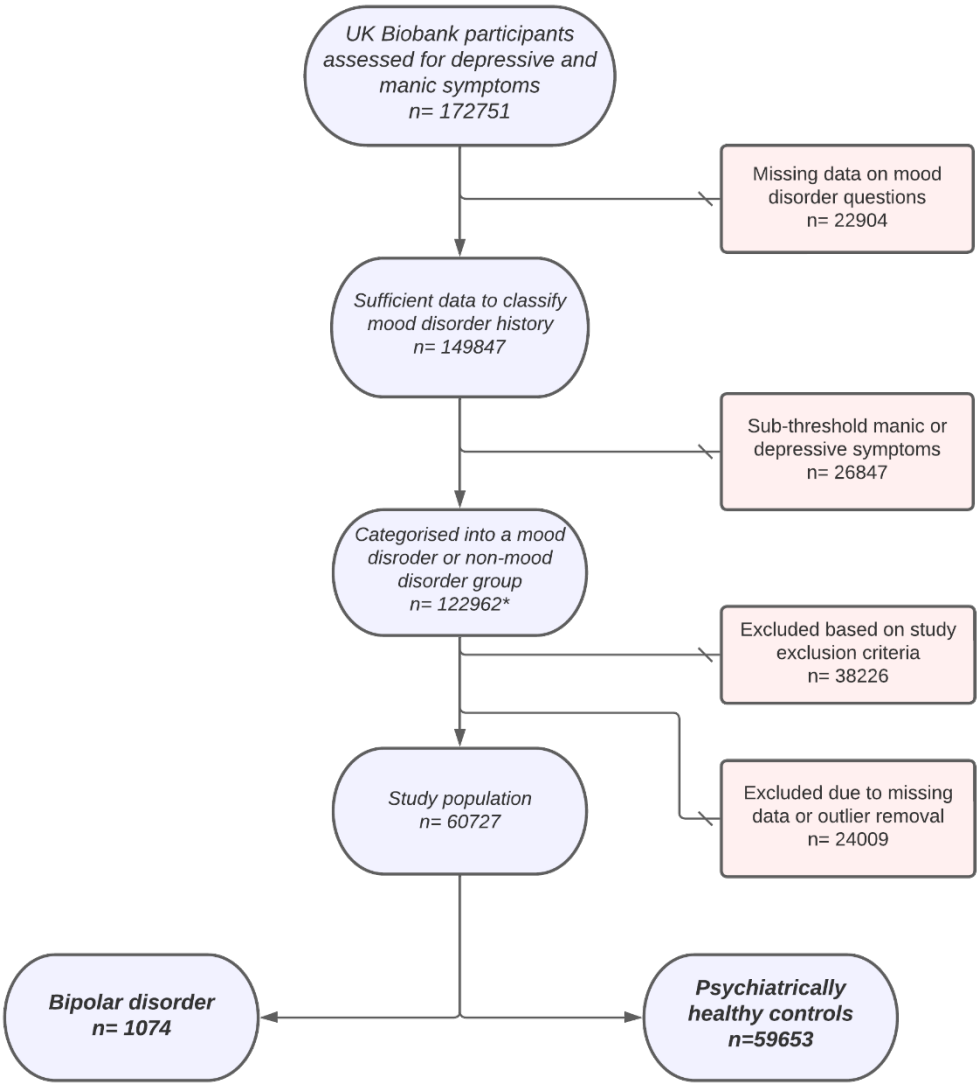

FIGURE S1. Flow chart of participant sampling [a].

[a]A number of participants asked for their data to be removed from the UK Biobank database following the original mood disorder categorisations (n= 38) and were removed from the flowchart where the asterix is placed.

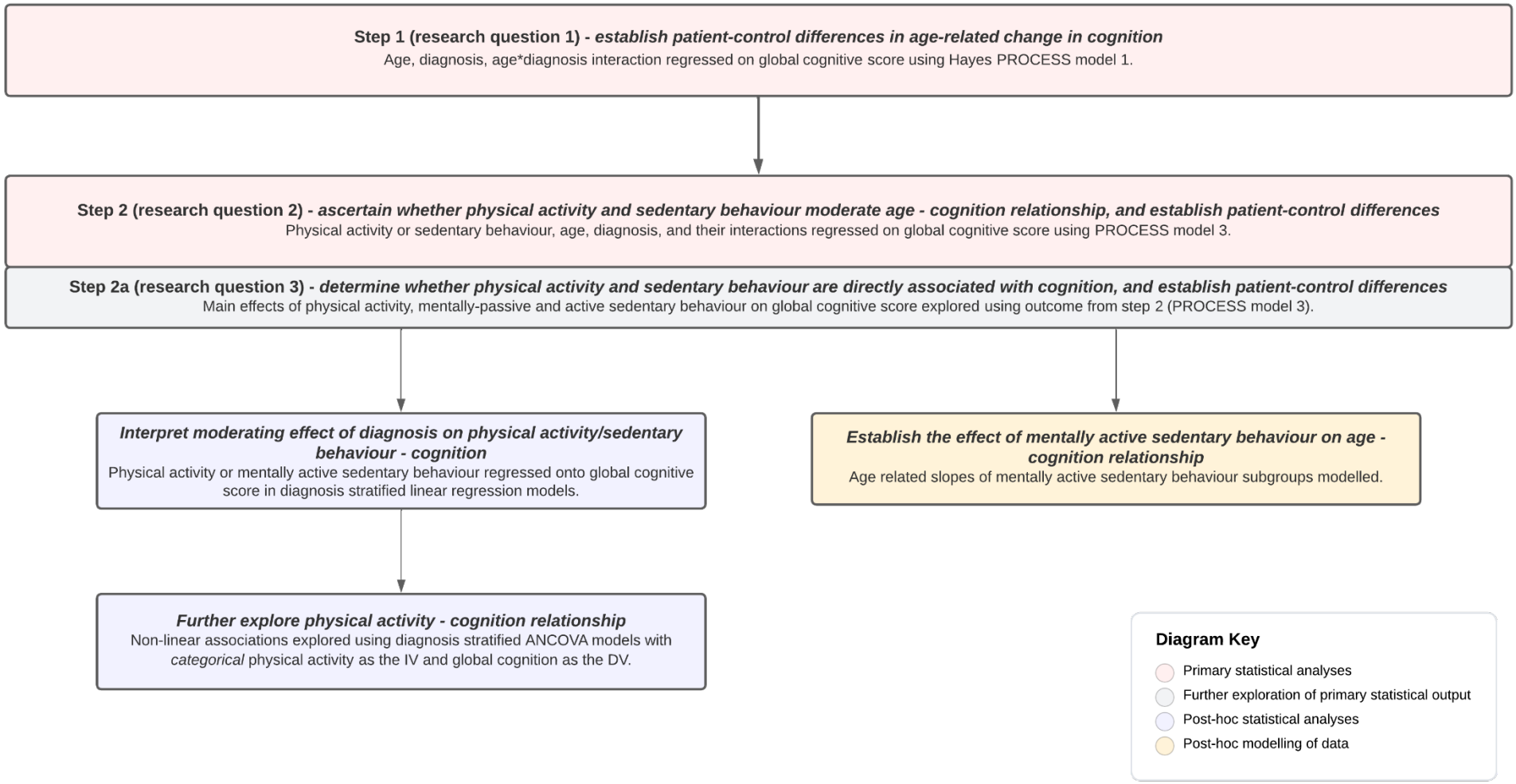

FIGURE S2. Flow chart of statistical analyses.

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