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Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing

and cognitive function: a cross-sectional study of 91 105 participants in the UK Biobank

cohort

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Background: Disruption of sleep and circadian rhythmicity is a core feature of mood disorders

and may be associated with increased vulnerability to such disorders. Previous studies in this

area have used subjective reports of activity and sleep patterns but the availability of

accelerometer-based data in UK Biobank participants permits the derivation and analysis of new,

objectively-ascertained circadian rhythmicity parameters. We aimed to examine associations

between objectively-assessed circadian rhythmicity and mental health and wellbeing

phenotypes, including lifetime history of mood disorder.

Methods: Wrist-worn accelerometry data from 91 105 participants of the UK Biobank cohort

were used to derive a circadian relative amplitude variable, which is a measure of the extent to

which circadian rhythmicity of rest-activity cycles is disrupted. In the same sample, cross-

sectional associations between low relative amplitude and mood disorder, wellbeing and

cognitive variables were examined in a series of regression models.

Findings: A quintile reduction in relative amplitude was associated with increased risk of lifetime

major depressive disorder (MDD) (odds ratio (OR) = 1.06, 95% CI 1.04, 1.08) and lifetime bipolar

disorder (OR = 1.11, 95% CI 1.03, 1.20), as well as with greater mood instability, higher

neuroticism score, more subjective loneliness, lower happiness, lower health satisfaction, and

slower reaction times. These associations were independent of demographic, lifestyle, education

and overall activity confounders.

Interpretation: Circadian disruption is reliably associated with a range of adverse mental health

and wellbeing outcomes, including MDD and BD. Lower relative amplitude may be linked to

greater vulnerability to mood disorders.

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Research in context

Evidence before this study

Although circadian disruption is likely to be a core feature of mood disorders such as major depression and bipolar disorder, studies to date have tended to assess sleep-related factors or subjective reports of circadian preferences (e.g., eveningness/morningness) which may be indirectly related to circadian rhythmicity. We searched Web of Science for studies of objectively-measured circadian rhythmicity and mood disorders published before May 2017, using the search terms "accelerometry"/"actigraphy", "circadian" "amplitude" and "bipolar" or "depression". We identified 17 articles that compared accelerometry-derived measures of circadian amplitude between healthy controls and mood disorder patients or those at risk of mood disorder, or correlated depressive/manic symptoms with amplitude. Most studies reported lower amplitude in depressed and bipolar patients or high-risk individuals compared to controls, but different definitions of circadian amplitude were employed across these studies, sample sizes were almost universally small, and most studies did not control for potential confounders such as lifestyle factors and overall activity levels. Additional searches did not reveal any studies examining objectively-measured circadian rhythmicity and subjective wellbeing.

Added value of this study

This study provides the first large-scale investigation of the association of objectively-measured circadian rhythmicity with a range of mental health, wellbeing, personality and cognitive outcomes, with an unprecedented sample size of over 90 000 participants. Previous studies have typically examined simple group differences adjusting for no or very few confounders, whereas we found that circadian relative amplitude is reliably associated with depression, bipolar and subjective wellbeing, personality and cognitive measures, even after adjusting for a wide range of sociodemographic, lifestyle, education and activity covariates.

Implications of all the available evidence

Circadian disruption is a core feature of the mood disorders depression and bipolar disorder, and is likely also to be associated with risk factors for mood disorder, including impaired subjective wellbeing, neuroticism and mood instability. Accelerometry-derived measures of relative amplitude may be associated with greater vulnerability to mood disorder.

Introduction

Circadian rhythms are variations in physiology and behaviour that occur in cycles with a predominantly 24-hour period. They are ubiquitous in nature and are fundamental for health and homeostasis. Integrity of circadian rhythmicity is critical for mental health and wellbeing, and certain forms of disruption are associated with mood disorders, particularly major depressive disorder (MDD) and bipolar disorder (BD).¹ Although several studies have identified associations between disrupted circadian rhythmicity and adverse mental health outcomes,²,³ much of this work has limitations, which include relatively small or highly selected samples, minimal adjustment for confounders, and subjectively-reported measures of circadian function such as chronotype (preference for evening or morning activity).

The objective assessment of patterns of rest and activity using accelerometry in over 90 000 participants of the UK Biobank cohort represents an unprecedented opportunity to test the association between disrupted circadian rhythmicity and a range of mental health disorders.^{4,5} The depth and breadth of data collected as part of the UK Biobank project also make it possible to control for a wide range of potential confounders within multivariable models.

Here we report the first large-scale population cohort assessment of the relationship between circadian function and mood disorders, both MDD and BD. We employed a commonly-used metric: relative amplitude (RA), which reflects the relative difference between the most active 10-hour period (M10) and the least active 5-hour period (L5) in an average 24-hour period.⁶ In secondary analyses, we also assessed for association between circadian rhythmicity and several phenotypes that are known to be related to mood disorders, including neuroticism, mood instability, subjective wellbeing and cognitive function (assessed via reaction time).

Methods

Participants and ethical approval

Over 502 000 United Kingdom (UK) residents aged 37-73 years were recruited to the UK Biobank, a general population cohort, from 2006-2010. At any one of 22 assessment centres across the UK, participants completed a range of lifestyle, demographic, health, mood, cognitive and physical assessments and questionnaires.⁴ Accelerometry data were collected from a subset of more than 100 000 participants in 2013-2015, and around 160 000 participants completed an online Mental Health Questionnaire (MHQ) in 2016-2017. Here, we used data from the 91 105 participants who provided accelerometry data that passed quality control (details below) and who had data on all covariates in base models and on at least one dependent variable, after exclusion of participants self-reporting sleep apnoea or insomnia (n=343). Characteristics of participants with low RA of

>2 standard deviations (SD) below the sample mean, and those with higher RA, are presented in Table 1. Characteristics of participants meeting criteria for lifetime MDD, lifetime BD and controls are shown in Table S1. Participants provided informed consent, and UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (11/NW/03820). The current analyses were conducted under UK Biobank application number 26209 (PI Wyse).

Measurement of predictors

Accelerometry data collection and pre-processing

In 2013, 240 000 UK Biobank participants were invited to wear an accelerometer for seven days as part of a physical activity monitoring investigation. Of these, 103 720 (43%) accepted, and returned the accelerometer to UK Biobank after use. Participants who accepted the invitation received a wrist-worn Axivity AX3 triaxial accelerometer in the post and were asked to wear the device on their dominant wrist continuously for seven days, while continuing with their normal activities. The start of accelerometry data collection was on average 5.70 years (SD = 1.13) after the initial baseline assessment. At the end of the seven-day period, participants were instructed to return the accelerometer to UK Biobank using a prepaid envelope.

Data pre-processing was conducted by the UK Biobank accelerometer expert working group: for details see ref. ⁵ and http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=131600. An overall acceleration average in milli-gravity (mg) units (UK Biobank field ID 90012) was calculated by the working group and was used in partially and fully adjusted models to control for overall activity levels.

Circadian relative amplitude measure

RA is the relative difference between the most active continuous 10-hour period (M10) and the least active continuous 5-hour period (L5) in an average 24-hour period,⁶ and is a common non-parametric measure of the amplitude of rest-activity rhythms.³ RA was calculated from physical activity intensity data (average vector magnitude; m*g*) in 5 s epochs (UK Biobank field ID 90004), using Clocklab (Actimetrics) and the following formula:

$$RA = \frac{(M10 - L5)}{(M10 + L5)}$$

M10 and L5 are the average activity during the continuous 10- or 5-hour period containing the maximum or minimum, respectively, overall activity counts in each 24-hour recording period (midnight to midnight). Data were first averaged by minute. Onset times of the M10 and L5 periods were identified by moving a 10- or 5-hour window in steps of 1 minute to identify the continuous overlapping period containing either the 10 most or 5 least active hours (on

average).⁷ The mean M10 and L5 activity values across all included 24-hour periods were used to calculate each individual's RA value.

RA ranges from 0 to 1, with higher values reflecting clearer distinction between activity levels during the most and least active periods of the day. Lower values result from reduced daytime activity and/or increased night-time activity. Accelerometry-derived activity measures have demonstrated good validity and reliability.⁸ Mean RA was 0.87 (SD=0.06; range 0.121-0.997), similar to previously reported values in healthy populations.³ RA values were however negatively skewed (see Figure S1).

Using data quality metrics provided by the UK Biobank accelerometer working group⁵, participants who provided accelerometry data for less than 72 hours or did not provide data for all one-hour periods within the 24-hour cycle were excluded. Participants were also excluded if their data was identified by UK Biobank as having poor calibration, or calibration that, due to insufficient data, was performed using data from the previous or subsequent participant to use the same accelerometer. We excluded participants with data flagged by UK Biobank as unreliable (unexpectedly small or large size) and participants whose wear-time overlapped with a daylight savings change.

Demographic and lifestyle variables

At the baseline assessment, participants provided data on demographic characteristics including age, ethnicity, educational attainment and lifestyle. Townsend social deprivation scores⁹ were derived based on postcode of residence, with negative scores reflecting relatively greater affluence. Smoking status ('never', 'previous', 'current') and frequency of alcohol intake ('never'; regularly ('1-2 times a week'/'3-4 times a week'); occasionally ('1-3 times a month'/'special occasions only'); daily ('daily/almost daily')) were derived from a touchscreen lifestyle questionnaire. For smoking and alcohol variables, 'never' was used as the reference category. BMI was calculated from measurements of height (m) and weight (kg) using weight/height².

During an online MHQ conducted in 2016-2017 (details below), participants completed one item from each of five subscales (emotional abuse; physical abuse; sexual abuse; emotional neglect and physical neglect) of the brief Childhood Trauma Questionnaire.¹⁰ Statements related to each subscale were rated on a 5-point scale from 'never true' to 'very often true'. Using established thresholds,¹¹ participants were categorised as meeting criteria for childhood trauma vs. no/subthreshold childhood trauma.

Measurement of mood, wellbeing and cognitive dependent variables

Primary mental health-related dependent variables were lifetime MDD and lifetime BD: participants were classified as meeting criteria for MDD/BD or not based on responses to the online MHQ. Secondary wellbeing and cognitive dependent variables were self-reported mood instability, neuroticism scores, self-rated happiness and health satisfaction, self-reported loneliness, and reaction time.

In 2016, an average of 7.55 years (SD = 0.93) after the baseline assessment, and 1.85 years (SD = 0.65) years after accelerometry data recordings, 337 799 UK Biobank participants were invited to complete an online MHQ ('Thoughts and Feelings') designed to assess lifetime symptoms of mental disorders. As of May 2017, 157 751 participants had completed the questionnaire.

Participants met criteria for lifetime MDD if they reported ever having had a period of persistent low mood or anhedonia (at least two weeks, lasting at least most of the day, almost every day) which interfered with everyday life or activities and involved at least five symptoms from: low mood, anhedonia, fatigue, weight change, sleep changes, difficulty concentrating, feeling worthless, thinking about death. Participants were categorised into the control (no lifetime depression) group if they responded 'No' to ever having had a period of low mood or anhedonia lasting at least two weeks, or if they reported a period of low mood or anhedonia which involved less than five symptoms from the above list. Participants were excluded from the control group if they self-reported a diagnosis of depression, if they had missing data for at least one depressive symptom question or if they reported recent (past two weeks) depressive symptoms lasting at least several days. Questions within the MHQ were derived from the Composite International Diagnostic Interview – Short Form.¹²

Participants who completed the MHQ were classified as having lifetime BD if they reported a period of intense irritability or feeling 'high', 'hyper' or 'excited' that lasted at least a week and which was associated with at least four features from: 'more active', 'more talkative', 'needed less sleep', 'more creative/more ideas', 'more restless', 'more confident', 'thoughts were racing', 'easily distracted'. Participants were categorised as controls (no lifetime BD) if a) they reported never having experienced a period of irritability or feeling 'high', or b) if they did report such a period but it lasted less than a week; or fewer than four of the above manic features were reported. Participants were excluded from the control group if they met criteria for probable BD based on the baseline mental health questionnaire (2006-2010), 13 or if they self-reported a diagnosis of mania, hypomania, BD or manic depression. Participants who met criteria for both MDD and BD were categorised into the lifetime BD group.

Further MHQ questions asked participants to rate their subjective happiness (In general how happy are you?') and health satisfaction (In general how satisfied are you with your health?') from 1 ('extremely happy') to 6 ('extremely unhappy'). For ease of interpretation, happiness and health satisfaction scores were reversed so that higher scores reflected greater satisfaction.

At baseline (2006-2010), participants were asked 'Do you often feel lonely?'. 'Yes'/'no' responses were examined as a further wellbeing (loneliness) dependent variable. An aggregate neuroticism score was calculated for participants who completed all 12 questions from the Eysenck Personality Questionnaire Revised (Short Form; EPQ-R-S) Neuroticism Scale at baseline.¹⁴ The score represents the number of questions answered in the affirmative (range 0-12). One of the neuroticism questions concerned mood instability ('Does your mood often go up and down?'), and 'yes'/'no' responses on this question were examined as a separate dependent variable.

Participants completed several brief cognitive tests via a touchscreen interface at the baseline assessment. Here we focussed on the reaction time task as this was administered throughout the baseline assessment period. Participants viewed 12 'rounds' of 12 pairs of images of cards, and pressed a button when the two cards matched, similar to the game 'Snap'. Response times of under 50 ms or over 2000 ms were excluded and for each participant a mean reaction time was calculated across all correct responses, after excluding the first two rounds. Due to positive skew, analyses were conducted both on raw and log-transformed reaction times: as results were equivalent, raw reaction time results are reported for ease of interpretation.

Statistical analyses

Associations between the RA predictor and each mental health, wellbeing and cognitive dependent variable (lifetime MDD, lifetime BD, mood instability, neuroticism, self-rated happiness, health satisfaction, loneliness and reaction time) were examined in three separate regression models, each adjusting for progressively more potential confounders.

Continuous RA scores were first inverted by multiplying by -1, orienting the association estimates towards the influence of lower RA on dependent variables. As a one-unit change in RA would reflect the difference between the extreme lower and upper ends of the range, scores were divided into quintiles, and regression models examine the effects of RA quintile (higher quintiles reflect lower RA) on dependent variables. Continuous effects of standardised RA scores were also examined after first normalising the distribution by raising scores to the fourth power: results were equivalent to the quintile method and so for ease of interpretation, results using the quintile method are reported.

Associations between RA quintile and binary measures of lifetime MDD, BD, mood instability and loneliness were examined using logistic regression, and ordinal logistic regression was employed for the self-rated happiness and health satisfaction variables: odds ratios (OR) are reported. Linear regression was employed for reaction time (linear regression coefficients reported). Negative binomial regression was employed for models examining neuroticism, as this count-based variable had a skewed distribution, and incidence rate ratios (IRR) are reported. Robust standard errors were employed for all models.

Base models ('Model 1') examined associations between RA quintile and dependent variables, adjusting for age and season at the time of commencing accelerometry (spring = Mar-May; summer = Jun-Aug; autumn = Sep-Nov; winter = Dec-Feb; UK Meteorological Office definitions), sex, ethnicity (white or non-white) and Townsend score. 'Model 2' adjusted for these covariates in addition to lifestyle and activity factors: smoking status, alcohol intake, educational attainment (degree or no degree), overall mean acceleration recorded by accelerometry (UK Biobank field ID 90012), which represents mean activity levels, and BMI, due to suggestions that high BMI may be causally linked to depression.¹5 Model 3 adjusted for all Model 2 covariates in addition to a binary measure of childhood trauma. Childhood trauma is an important risk factor for mood disorder and poorer wellbeing,¹¹¹ but as trauma data were available for only a subset of participants (n= 64 272), this was examined in a separate model to allow maximising of sample size in Model 2. Sociodemographic and lifestyle covariates were selected on the basis of prior associations with circadian disruption and/or mental health-related variables. To maximise sample sizes, available-case analyses were employed: sample sizes for each model are reported in results tables. Reporting of analyses and results followed TRIPOD guidelines where applicable.¹6

Role of the funding source

The funders of the study played no role in study design, data collection, analysis and interpretation, or the writing of the report. The corresponding author had full access to the study data and had final responsibility for the decision to submit for publication.

Results

After exclusion of participants with self-reported sleep disorders (sleep apnoea or insomnia), or with poor quality or unreliable accelerometry data, 91 524 participants remained. Of these, 91 105 participants also had complete data on covariates included in base models as well as on at least one of the dependent variables, and formed the study sample. Characteristics of this sample, and numbers with missing data on dependent variables and covariates are displayed in Table 1:

participants showing low RA of >2SD below the sample mean are compared with the remaining participants. The percentage in this group (3·82%) is greater than the 2·28% expected for a normal distribution due to negatively skewed RA scores (Figure S1). In Table S1, characteristics of participants meeting criteria for lifetime MDD and lifetime BD are compared to controls.

Measurement of lifetime MDD, lifetime BD, happiness and health satisfaction variables took place an average of 1.85 years (SD=0.65) after accelerometry recordings. Mood instability, neuroticism, loneliness and reaction time variables were collected an average of 5.70 years (SD=1.10) before accelerometry data. A boxplot of (reversed) raw RA scores is displayed in Figure S2. In fully adjusted regression models (Model 3), lower RA quintile was associated with increased odds of lifetime MDD (Model 3: OR = 1.06, 95% CI 1.04, 1.08), BD (OR = 1.11, 95% CI 1.03, 1.20), mood instability (OR = 1.02, 1.01, 1.04), and with higher neuroticism scores (IRR = 1.01, 95% CI 1.01, 1.02) after adjusting for demographic, lifestyle, education, activity, BMI and childhood trauma covariates (Table 2).

Lower RA was associated with lower subjective ratings of happiness (OR = 0.91, 95% CI 0.90, 0.93) and health satisfaction (OR = 0.90, 95% CI 0.89, 0.91), with higher odds of reporting loneliness (OR = 1.09, 95% CI 1.07, 1.11) and with slower reaction time (coefficient = 1.75, 95% CI 1.05, 2.45) after adjusting for demographic, lifestyle, education and activity covariates and BMI and childhood trauma. All results were comparable in terms of direction and significance, but with larger ORs, for Model 1 (adjusting for sociodemographic covariates) and Model 2 (adjusting for sociodemographic, lifestyle, education, activity and BMI).

To assess whether effects for non-clinical dependent variables were driven by participants with mood disorders, analyses were repeated after excluding 16 916 participants meeting criteria for lifetime MDD or BD based on MHQ responses, or on self-report. Results are shown in Table S2. After exclusion of participants with mood disorders and after adjusting for lifestyle, activity, BMI (Model 2) and trauma (Model 3), the association between RA and mood instability was no longer significant (Model 3: OR = 1.01, 95% CI 1.00, 1.03, p = 0.124). All other results were unchanged: in Models 1-3, lower RA quintile was associated with increased odds of self-reported loneliness (Model 3: OR = 1.11, 95% CI 1.08, 1.14), higher neuroticism scores (IRR = 1.01, 95% CI 1.01, 1.02), slower reaction time (coefficient = 1.54, 95% CI 0.74, 2.34) and lower subjectively-rated happiness (OR = 0.91, 95% CI 0.90, 0.93) and health satisfaction (OR = 0.90, 95% CI 0.88, 0.91).

Discussion

Lower circadian relative amplitude (RA) was associated with greater risk of mood disorder and with poorer subjective wellbeing. Lower RA is a rhythmicity measure reflecting less marked

differences in activity profiles between daily rest and activity periods, and was associated with increased odds of lifetime MDD and BD. Lower RA was also associated with greater odds of mood instability and self-reported feelings of loneliness, with higher neuroticism scores, reduced self-rated happiness, lower health satisfaction and slower reaction time. These associations were independent of a range of demographic, lifestyle, activity and childhood trauma variables, and associations with all wellbeing, personality and cognitive variables (apart from mood instability) remained after exclusion of participants with lifetime history of mood disorder.

Findings that low RA is associated with increased odds of MDD and BD are consistent with suggestions that circadian rhythm disruption is a core feature of mood disorders and with previous, smaller investigations reporting lower RA in individuals with BD.³ Lower RA reflects reduced distinction, in terms of activity levels, between active and rest periods of the day. This can reflect reduced activity during waking periods, often seen in depressive episodes; increased activity during rest periods, linked to sleep disturbances which are common in mood disorder, or a combination of both. This 'flattening' of the rest-activity cycle is thought to reflect disrupted 24-hour circadian rhythmicity and less entrainment to external zeitgebers.¹⁷

Reduced RA has been reported in healthy individuals scoring highly on mania scales and in healthy relatives of individuals with BD.¹⁸ We provide the first direct evidence of associations between objectively-measured circadian disruption and neuroticism and mood instability, which have both been consistently linked to higher risk of mood disorder. Effect sizes for mood instability and neuroticism were small, so the clinical relevance of these associations is unclear. Furthermore, associations between RA and mood instability were attenuated after exclusion of participants meeting criteria for mood disorder, suggesting the association may have been partly driven by greater mood instability in participants with psychiatric conditions. However, as the association of neuroticism with RA remained after exclusion of participants with probable MDD and BD, this is consistent with suggestions that circadian disruption is associated with increased vulnerability to mood disorders.¹⁸

Associations between low RA and reduced self-rated happiness, health satisfaction and increased subjective loneliness indicate that circadian disruption is more generally associated with impaired subjective wellbeing, particularly as these associations persisted after exclusion of participants reporting lifetime mood disorder. The direction of causality, and indeed the presence of a causal relationship between circadian disruption and wellbeing is however unclear from the current cross-sectional data.

Deficits in memory, reaction time and attention have been reported after sleep deprivation and in shift workers.^{19,20} Our work extends previous findings by demonstrating within a large population-based cohort that objectively-measured circadian disruption is associated with

slower reaction time independent of demographic, lifestyle and activity covariates. Reaction time shows consistent associations with higher general intelligence and white matter integrity and is often considered a general marker of neurocognitive functioning.^{21,22} Our findings support the view that impairments to this functioning are associated with circadian disruption.

Due to the cross-sectional nature of the data, the current findings cannot speak to the issue of causal associations between circadian disruption and poorer mental health and wellbeing outcomes. This is compounded by the temporal separation between recording of baseline demographic and lifestyle variables (2006-2010), accelerometry data (2013-2014) and the MHQ (2016-2017), particularly as reaction time, neuroticism and loneliness data were collected before accelerometry data. Our goal was to assess for evidence of cross-sectional associations rather than to infer causality, but future work following up on the participants with accelerometry data will be useful in elucidating the nature and direction of causality. As the UK Biobank cohort matures, future studies will be able to examine the extent to which low RA can predict new diagnoses of mood disorders (although this possibility may be limited by the age of the UK Biobank cohort) or new depressive/manic episodes in patients with existing mood disorder diagnoses. The collection of further accelerometry data in the same participants would be useful in this regard, as it would allow examination of whether within-participant changes in RA can predict onset of novel episodes and whether stabilisation of objectively-measured rhythmicity is associated with improved mental health, cognitive and wellbeing outcomes. Mendelian Randomisation analysis using alleles associated with circadian disruption may be able to examine evidence for causal associations between circadian disruption and mental health and wellbeing outcomes.23

As rest-activity rhythms differ between younger and older adults, associations between circadian rhythmicity and mental health and wellbeing may differ in cohorts which are younger than UK Biobank. As the circadian system undergoes developmental change during adolescence,²⁴ a common time for onset of mood disorders, longitudinal study of rhythmicity in younger populations and comparison with findings in the UK Biobank may aid understanding of causal mechanisms.

Overall, our findings suggest a reliable association between circadian disruption and both risk of mood disorder and worse subjective wellbeing outcomes. This study also highlights the potential utility of accelerometry-derived relative amplitude in serving as a marker of vulnerability to negative mental health and wellbeing outcomes. RA is relatively cheaply and easily measured, and may be useful in identifying those at greater risk of MDD or BD, or sub-groups of patients who might benefit from therapies aimed at improving circadian rhythmicity.

Contributors

DJS designed the study. CW derived rhythmicity variables and NG derived mental health variables. LL analysed the data and drafted the manuscript. DJS, DL, CW, BC, MB assisted with data analysis strategy, data interpretation and drafting of the manuscript. All authors contributed to editing the manuscript, and have approved the final version.

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Declaration of interests

JPP is a member of UK Biobank advisory committee; this had no bearing on the study. The authors have no other competing interests to declare.

Ethical statement

Participants who accepted the invitation to join the UK Biobank cohort provided written, informed consent. UK Biobank has generic ethical approval from the North West Multi-centre Research Ethics Committee (approval letter dated 17th June 2011, ref 11/NW/03820).

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 $Table \ 1. \ Demographic \ characteristics \ of \ participants \ with \ low \ relative \ amplitude \ (RA>2SD \ below \ mean) \ and \ remaining \ participants \ ('Higher \ RA').$

Variable	Low RA (n=3 477; 3.82%)	Higher RA (n=87 628; 96·18%)	Test statistic	р
Age at baseline assessment (years), M (SD); median (IQR)	55·61 (8·33); 56 (48- 63)	56·17 (7·80); 57 (50-62)	4.08	<0.001
Age (years) at accelerometry, M (SD); median (IQR)	61·31 (8·39); 62 (54- 68)	61.87 (7.83); 63 (56-68)	4.13	<0.001
Age (years) at time of MHQ, M (SD); median (IQR)	63·00 (8·21); 64 (56- 70)	63-64 (7-68); 65 (58-70)	3.84	<0.001
Missing data	1245	25 200		
Female, N (%)	1412 (40-61)	50 016 (57.08)	368-92	<0.001
White ethnicity, N (%)	3216 (92·49)	85 014 (97-02)	223-91	<0.001
Townsend deprivation score, M (SD)	-0.61 (3.34)	-1.78 (2.78)	24.06	<0.001
Smoking, N (%)				
Never	1726 (49-64)	50 260 (57.36)		
Previous	1289 (37-07)	31 371 (35·80)		
Current	456 (13·11)	5809 (6.63)		
Missing data	6 (0·17)	188 (0.21)	241.24	< 0.00
Frequency of alcohol intake, N (%)				
Never	390 (11·22)	4756 (5.43)		
Occasionally	965 (27.75)	17 602 (20.09)		
Regularly	1476 (42·45)	45 049 (51-41)		
Daily	645 (18·55)	20 188 (23.04)		
Missing data	1 (0.03)	33 (0.04)	376.97	< 0.001
Season accelerometer worn, N (%)				
Spring	738 (21-23)	19 382 (22·12)		
Summer	941 (27.06)	24 069 (27-47)		
Autumn	1006 (28-93)	24 737 (28-23)		
Winter	792 (22·78)	19 440 (22·18)	2.52	0.471
Degree, N (%)	1332 (38-31)	37 824 (43·16)		
Missing data	19 (0.55)	343 (0.39)	33.42	< 0.00
BMI, M (SD)	29.63 (6.05)	26.57 (4.40)	39.43	<0.001
Missing data	23	167		
Childhood trauma, N (%)	1226 (35·26)	28 857 (32.93)		
Missing data	1265 (36-38)	25 763 (29·40)	138.14	< 0.001
Lifetime MDD, N (%)	554 (15.93)	13 247 (15·12)		
Missing data	1800 (51.77)	36 436 (41.58)	178-63	< 0.001
Lifetime BD, N (%)	29 (0.83)	552 (0.63)		
Missing data	2325 (66·87)	49 131 (56.07)	165.69	< 0.001
Mood instability, N (%)	1622 (46.65)	35 151 (40·11)		
Missing data	70 (2.01)	1465 (1.67)	64.99	< 0.00
Neuroticism score, M (SD)	4.09 (3.34)	3.87 (3.16)	3.50	<0.00
Missing data	690	14 282		
Happiness, M (SD)	4.39 (0.86)	4.60 (0.77)	12.53	<0.00
Missing data	1266	25 505		

Health satisfaction, M (SD)	3.94 (1.13)	4.42 (0.91)	23.75	<0.001
Missing data	1260	25 329		
Loneliness, N (%)	808 (23·24)	13 213 (15.08)		
Missing data	59 (1.70)	1025 (1·17)	182.75	< 0.001
Acceleration average (mg), M (SD)	21.92 (9.22)	28-29 (8-13)	45.08	<0.001
Reaction time (ms), M (SD)	552-92 (112-29)	545.07 (105.06)	4.31	<0.001
Missing data	11	202		
Relative amplitude, M (SD)	0.65 (0.10)	0.87 (0.04)	290.67	<0.001

Test statistics are t values comparing means between low and higher RA for continuous variables, and χ^2 comparing the distribution of values between low and higher RA groups for categorical variables. Numbers with missing data are included where applicable. BD = bipolar disorder, BMI = body mass index, IQR = interquartile range, M = mean, MDD = major depressive disorder, MHQ = mental health questionnaire, SD = standard deviation.

Table 2. Associations between RA quintile and measures of mood disorder, personality/affective traits, subjective wellbeing and cognitive function.

	Model 1				Model 2				Model 3			
Outcome	N (cases; controls)	Coefficient*(95% CI)	р	Model (pseudo) R ²	N (cases; controls)	Coeffiicient* (95% CI)	р	Model (pseudo) R ²	N (cases; controls)	Coeffiicient* (95% CI)	р	Model (pseudo) R ²
Lifetime MDD	13,801; 39,068	1.16 (1.14, 1.17)	<0.001	0.05	13,697; 38,803	1.07 (1.05, 1.09)	<0.001	0.06	13,593; 38,470	1.06 (1.04, 1.08)	<0.001	0.08
Lifetime BD	581; 39,068	1.23 (1.16, 1.31)	< 0.001	0.04	577; 38,803	1.12 (1.04, 1.21)	0.004	0.07	572; 38,470	1.11 (1.03, 1.20)	0.007	0.10
Mood instability	36,773; 52,797	1.07 (1.06, 1.08)	<0.001	0.02	36,437; 52,410	1.02 (1.01, 1.04)	<0.001	0.02	24,936; 37,722	1.02 (1.01, 1.04)	0.004	0.03
Neuroticism score	76,133	1.02 (1.02, 1.03)	<0.001	0.01	75,612	1.02 (1.01, 1.02)	<0.001	0.01	53,624	1.01 (1.01, 1.02)	<0.001	0.01
Happiness	64,334	0.88 (0.87, 0.89)	< 0.001	0.01	63,864	0.91 (0.90, 0.93)	<0.001	0.02	63,322	0.91 (0.90, 0.93)	<0.001	0.03
Health satisfaction	64,516	0.77 (0.76, 0.78)	<0.001	0.02	64,044	0.90 (0.88, 0.91)	<0.001	0.03	63,496	0.90 (0.89, 0.91)	<0.001	0.04
Loneliness	14,021; 76,000	1.14 (1.13, 1.16)	<0.001	0.02	13,874; 75,411	1.09 (1.08, 1.11)	<0.001	0.03	9,526; 53,397	1.09 (1.07, 1.11)	<0.001	0.04
Reaction time	90,892	2.16 (1.69, 2.63)	< 0.001	0.09	90,132	1.91 (1.32, 2.50)	<0.001	0.10	63,502	1.75 (1.05, 2.45)	<0.001	0.09

^{*}Logistic regression was employed for lifetime MDD, lifetime BD, mood instability and loneliness models, and ordinal logistic regression for happiness and health satisfaction models: for these models, coefficients reflect odds ratios (OR). Negative binomial regression was employed for neuroticism scores and so coefficients reflect incident rate ratios (IRR). Linear regression was employed for reaction time: linear regression coefficients are reported. As RA scores were inverted, estimates reflect the influence of lower RA on outcomes. Model 1 adjusted for age and season when commencing accelerometry, sex, ethnicity and Townsend score. Model 2 additionally adjusted for alcohol intake frequency, smoking status, degree, overall mean acceleration and BMI. Model 3 additionally adjusted for childhood trauma. BD = bipolar disorder; CI = confidence interval; MDD = major depressive disorder. N refers to the total sample size, or sample size for cases; controls where applicable (i·e·, where outcomes are binary) McFadden's pseudo R² is reported for all models aside from reaction time, where adjusted R² is reported.