Investigating the relationship between diurnal rest-activity rhythms and mood disorders: a data-driven approach.

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Abstract

Within mental health disorders, mood disorders describe those that have a significant impact on an individual's emotional state. These disorders represent a leading cause of disability worldwide and can have a severe impact on an individual's quality of life, including frequently reported problems with diurnal patterns of rest and activity. As a result, sleep and activity patterns represent a target for future phenotypic markers and therapies, but further investigation is required.

Given the heterogeneity of symptoms, it is helpful to consider rest-activity patterns within sub-groups of mood disorders. Typically, these disorders are grouped into depressive disorders (characterised primarily by low mood or anhedonia) and bipolar disorders (characterised primarily by feeling unusually hyper or irritable, often with depressive episodes). Less acknowledgement has been given to a potential third group, unipolar mania, who experience episodes of mania but not depressive episodes. Within common diagnostic criteria (DSM-5 and ICD-11) unipolar mania is grouped with bipolar-I disorder, yet the limited research available suggests considerable differences in demographics and outcomes. Combining bipolar disorder and unipolar mania groups may be contributing to the variability of research findings in this area.

This thesis investigates the relationship between rest-activity rhythms and mood disorders in a large UK-based population (UK Biobank). Through a combination of statistical and machine learning methods it aims to (a) investigate whether these rhythms can help us validate the nosological status of unipolar mania; (b) characterise rest-activity rhythm differences in these mood disorder groups, including seasonal patterns; (c) determine how accurately mood disorder groups can be differentiated using rest-activity measures; and (d) compare rest-activity measures in criteria-driven vs data-driven mood disorder groupings.

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Publications

The following publication is based directly on the research described in this thesis. To acknowledge the contribution of co-authors, as detailed below, “we” instead of “I” was used in this chapter.

Chapter 3:

Sangha N, Lyall L, Wyse C, Cullen B, Whalley HC, Smith DJ. The nosological status of unipolar mania and hypomania within UK Biobank according to objective and subjective measures of diurnal rest and activity. Bipolar Disord. 2022; 24: 726-738. doi:10.1111/bdi.13237

NS, LL, BC, HW and DS designed the study. CAW derived the rhythmicity variables and NS derived the mood disorder classifications. NS analysed the data, prepared all tables and figures, and drafted the manuscript. All authors contributed to the editing of the manuscript.

Additional Papers

Lyall LM, Sangha N, Wyse C, Hindle E, Haughton D, et al. Accelerometry-assessed sleep duration and timing in late childhood and adolescence in Scottish schoolchildren: A feasibility study. PLOS ONE. 2020; 15(12): e0242080. doi:10.1371/journal.pone.0242080

Cullen B, Gameroff MJ, Ward J, et al. Cognitive Function in People With Familial Risk of Depression. JAMA Psychiatry. 2023; 80(6): 610–620. doi:10.1001/jamapsychiatry.2023.0716

Lyall LM, Sangha N, Zhu X, Lyall DM, Ward J, Strawbridge RJ, Cullen B, Smith DJ. Subjective and objective sleep and circadian parameters as predictors of depression-related outcomes: A machine learning approach in UK Biobank. Journal of Affective Disorders. 2023; 355: 83-94. doi:10.1016/j.jad.2023.04.138.

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Author's Declaration

I declare that, except where explicit reference is made to the work of others, this thesis is composed by myself, and that, as part of a research group, the contribution of others has been acknowledged. I confirm that this thesis has not been submitted for any other degree at the University of Glasgow or any other institution.

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List of Abbreviations

AA	Average Acceleration
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
BD	Bipolar Disorder
BD-I	Bipolar Disorder Type 1
BD-II	Bipolar Disorder Type 2
BMI	Body Mass Index
CI	Confidence Interval
DSM-5	The Diagnostic and Statistical Manual for Mental Disorders, 5th Edition
FDR	False Discovery Rate
GWAS	Genome-Wide Association Study
HiTOP	Hierarchical Taxonomy of Psychopathology
ICD-11	International Classification of Diseases, 11th Edition
IDP	Imaging Derived Phenotype
IS	Interdaily Stability
IV	Intradaily Variability
LAN	Light at Night
MDD	Major Depressive Disorder
MHQ	Mental Health Questionnaire
MRI	Magnetic Resonance Imaging
MVPA	Moderate to Vigorous Physical Activity
OR	Odds Ratio
PMD	Probable Mood Disorder
PRS	Polygenic Risk Score
RA	Relative Amplitude
RDoC	Research Domain Criteria
rMD	Recurrent Major Depressive Disorder
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
sMD	Single-Episode Major Depressive Disorder
SMOTE	Synthetic Minority Over-Sampling Technique

SPT-window	Sleep Period Time Window
UM	Unipolar Hypomania/Mania
UK	United Kingdom

Chapter 1 Introduction.

1.1 Mood disorders

1.1.1 An introduction to mood disorders

Mood disorders describe psychiatric conditions that primarily affect a person's emotional state. Whilst there are many disorders contained within this category, major depressive disorders (MDD) and bipolar disorders (BD) are most prevalent and are therefore of high priority within the mood disorder research community; BD is estimated to affect 1% of the population, whilst depressive disorders are estimated to affect 3.8% making them a leading cause of disability worldwide (Institute of Health Metrics and Evaluation, 2019; McIntyre et al., 2020; Merikangas et al., 2007).

In clinical diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders, MDD is characterised by an extensive period (approximately 2 weeks or more) of low mood, irritability, and/or anhedonia (a lack of pleasure derived from activities that were previously enjoyed). This is accompanied by a range of other psychophysiological symptoms including poor concentration, excessive guilt, hopelessness, suicidal thoughts, sleep disruption, changes in appetite or weight and changes in energy levels. The life course of MDD may take the form of a single acute episode (sMD) or recurring episodes (rMD), with recurrence estimated to affect 40-60% of first episode MDD patients. Whilst little is understood about the factors leading to recurrence, it has been associated with a more severe symptom profile, post-episode residual symptoms, family history of MDD and social avoidance (Fava et al., 2010; Lewinsohn et al., 2000; Lye et al., 2020; Monroe & Harkness, 2022).

BD is differentiated from MDD by the presence of episodes of mania or hypomania and often, but not always, the depressive episodes described above. Manic episodes involve a period of feeling extremely happy/excited or irritable to the extent that it affects a person's ability to perform normal day-to-day activities, and can include symptoms such as increased activity levels, talkativeness, risk-taking, and reduced sleep. Whilst manic episodes are severe and often result in hospital admission, hypomanic episodes are milder and often shorter in duration; this presence of manic or hypomanic episodes is the main differentiator of the BD subtypes type 1 (BD-I) and type 2 (BD-II) respectively (Carvalho

et al., 2020; McIntyre et al., 2020). Despite exhibiting less severe manic symptoms, bipolar-II is associated with frequent depressive episode recurrence and high rates of disability and therefore still represents an important subgroup within BD (Rosa et al., 2010; Vieta et al., 1997).

1.1.2 Mood disorder diagnosis and heterogeneity

Due to the high levels of symptom overlap between rMD, sMD and BD, timely and accurate diagnosis proves difficult for researchers and clinicians. The classification of these disorders (also known as psychiatric nosology) is primarily done with reference to the criteria outlined in The Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5) or International Classification of Diseases, 11th edition (ICD-11). Whilst the BD criteria are identical across both, there is a minor difference in the MDD diagnosis criteria; namely that ICD-11 lists hopelessness about the future as a symptom and DSM-5 does not (First et al., 2021). Despite this high level of cross-diagnostic-criteria agreement, reliability and validity of diagnosis are still questionable and addressing this remains a priority within mood disorder research (Ratheesh et al., 2023; Regier et al., 2013).

A key issue with mood disorder heterogeneity is the vast number of potential symptom profiles that exist within these mood disorder groups. For example, within DSM-5 there are potentially more than 1000 different symptom and severity combinations that would lead to MDD diagnosis, over 100 of which have been observed clinically (Ratheesh et al., 2023). Furthermore, in a wide range of measurements from genetics through to treatment response, analysis has often identified multiple different profiles (or sub-groups) within these mood disorder groups suggesting that current definitions of BD and MDD may actually be capturing a variety of individual disorders (Almeida et al., 2020; Gildengers et al., 2012; Nguyen et al., 2022). Recently, dimensional approaches to the study and classification of psychiatric disorders have been gaining popularity in an effort to address these issues; two proposed frameworks include the Research Domain Criteria (RDoC) framework and the Hierarchical Taxonomy of Psychopathology (HiTOP) framework (Conway et al., 2019; Cuthbert, 2015). These frameworks focus on the underlying biological and behavioural systems leading to psychopathology without the confinement of traditional categorical diagnoses.

1.1.3 Unipolar mania

One under-researched group that may be contributing to the heterogeneity of BD are those with unipolar mania or hypomania (UM). These patients experience manic episodes like their BD counterparts, but not major depressive episodes. Despite this, under current DSM-5 and ICD-11 criteria they are categorised as having bipolar-I disorder (Angst et al., 2020). This is because, for many people presenting with an initial manic episode, this is later followed by one or more major depressive episodes over the lifetime (BD). Some epidemiological studies have suggested that between 0.18% and 3.1% of the population may present with unipolar mania, however these studies are severely limited by insufficient follow-up length and recall bias with respect to mild depression episodes (Angst et al., 2019; Beesdo-baum et al., 2009; Merikangas et al., 2012). Despite this, a review of the limited available evidence suggests that UM diagnosis remains stable for many, and likeliness of a diagnosis change to BD decreases with the number of manic episodes (Angst & Grobler, 2015).

Whilst research featuring UM is limited, there is some evidence to support clinical population differences between UM and BD. Clinical sample size for UM is a recurring problem in the research and this was addressed by Angst et al. (2018) by pooling nine epidemiological studies, resulting in the largest UM study to date (UM(N)=304) (Angst et al., 2019). Results from this, and additional studies, suggest that UM is more frequent in males than females, whilst the proportion of each sex affected in BD is approximately equal (Angst et al., 2019; Baek et al., 2014). UM was also associated with a reduced risk of co-morbid conditions including suicide attempts, anxiety disorders, drug-use disorders and eating disorders when compared to BD. Family history, anxious temperament and onset age did not differ between BD and UM. Hyperthymic temperament did not differ either; however, other findings have found an increased risk of hyperthymic temperament in UM (Perugi et al., 2007).

Additional differences have been identified in smaller studies. UM appears to be more frequent in non-western countries including Nigeria, Ethiopia, South Africa, Tunisia, India and Hong Kong, and as such has been retained as a distinct disorder within the Chinese Classification of Mental Disorders (Angst & Grobler, 2015; Y.-F. Chen, 2002; S. Lee & Yu, 1994). There is some evidence to suggest this may be partly due to increased stigma and

discrimination, resulting in reduced reporting of depression and other mental health concerns (Krendl & Pescosolido, 2020). Manic episodes also appear to be more frequent in UM when compared to BD (Stokes et al., 2020). Treatment response differences are unclear, with some finding no differences and others noting a decreased response to lithium (the widely accepted gold standard for BD treatment) (Stokes et al., 2020; Yazıcı, 2014).

1.1.4 A note on co-morbid anxiety disorders

Whilst not classified as a mood disorder, anxiety disorders are frequently reported to co-occur with mood disorders. A meta-analysis of mood and anxiety disorder comorbidity estimates that having either anxiety disorder or BD increases the probability of developing the other 7.8-fold, whilst having either anxiety or MDD increases the probability 13.8-fold (Saha et al., 2021a). In comparison to having just one, comorbid mood and anxiety disorders are linked to a more severe illness trajectory, increased suicidal risk, substance use, and treatment resistance (Gaudiano & Miller, 2005; Melton et al., 2016; Rohde et al., 2001; Saha et al., 2021b). Anxiety disorders are not the focus of this thesis, but the role of co-morbid anxiety is further explored in chapter 6.

1.2 Circadian disruption & mood disorders

1.2.1 Chronobiological underpinnings of mood disorders

No single mechanism exists to explain mood disorders, but one promising area of research involves the role of circadian disruption. In mammals (including humans), the molecular clock network regulates the 24-hour rhythm through a variety of clock genes which are expressed in most cells throughout the body (Takahashi, 2015). These genes can sustain their own autonomous rhythms but are synced throughout the body by a ‘master clock’, the suprachiasmatic nucleus (SCN) located within the anterior hypothalamus. The SCN and other regional clocks throughout the nervous system take cues from the environment, so called ‘external zeitgebers’ that keep the 24-hour rhythm in line with the surrounding natural environment. The most impactful external zeitgeber for the SCN is light, but regional areas may rely more on others including food intake, exercise, and temperature, which can lead to desynchrony between these central and peripheral clocks (Heyde &

Oster, 2019). Chronobiological theories of mood disorders suggest that de-regulation of either the master clock or regional clocks results in disturbances to clock-regulated outputs including dopamine, serotonin, cortisol, melatonin and inflammation; and this in turn contributes to the biological, physiological and behavioural changes identified in mood disorders (McCarthy et al., 2022). These theories are supported by evidence that mood disorder symptoms improve following circadian rhythm stabilisation, for example through the use of bright light therapy which can be used to advance or delay circadian timing (McClung, 2007). Notably, there is some evidence suggesting that this relationship may be bi-directional as mood disorder symptoms have been linked to increased risk of future circadian disruption (Doane et al., 2015).

The sleep-wake cycle is closely linked to the circadian rhythm and is widely accepted to consist of two processes: regulation by the circadian clock as described above, and homeostatic sleep pressure (Borbély, 1982). Homeostatic sleep pressure builds exponentially throughout time spent awake and decreases exponentially when asleep (Wirz-Justice, 2006). Whilst the circadian clock and homeostatic sleep pressure are independent processes, there is evidence that they influence each other. For example, when homeostatic sleep pressure is high, external zeitgebers such as light may have less influence on the circadian clock (Deboer, 2018).

1.2.2 Measurement of circadian disruption: self-report measures

There has long been a link between circadian disruption and mood disorders in humans which can be observed at every level from genetics to behaviour. The importance of this relationship is highlighted by its inclusion within the RDoC framework as part of the arousal and regulatory systems domain, consisting of three related sub-units: arousal, circadian rhythms, and sleep-wakefulness (Feld & Feige, 2021). Whilst understanding these three sub-units at all levels is necessary to build a complete understanding of circadian disruption in mood disorders, behavioural and self-report measurements are an attractive option as they are often cost effective and minimally invasive for participants.

1.2.2.1 Self-report measures

A popular self-reported phenotype for circadian timing is chronotype which describes the timing of an individual's sleep-wake cycle. Whilst the exact categorisation differs depending on measurement technique, this phenotype involves identifying individuals with a preference for morning activity (so-called 'larks') and those with a preference for evening activity ('owls'). Well established chronotype questionnaires include the Munich Chronotype Questionnaire which focuses on actual sleep and activity timing (Roenneberg et al., 2003), and the Horne-Östberg Morningness-Eveningness Score which is more concerned with preferential sleep and activity timing (Horne & Östberg, 1976), both of which have shown high levels of correlation with each other (Zavada et al., 2005). Whilst chronotype determines when a person prefers to sleep and when they are at their cognitive and physical peak, this is rarely accounted for in natural environments which can lead to a social jet-lag effect (Fárková et al., 2021). This social jet-lag is thought to be a contributing factor in the association between late chronotype and poor health outcomes, including higher levels of fatigue (Fárková et al., 2021); higher body mass index (Arora & Taheri, 2015); increased nicotine, alcohol and caffeine consumption (Hasler et al., 2013; Wittmann et al., 2010); poorer exam performance (Zerbini et al., 2017); and increased risk of type-2 diabetes when compared to earlier chronotypes (Tan et al., 2020).

Notably, late chronotype has repeatedly been associated with increased risk of mood disorders, though the direction of this effect is still unclear. This includes a spectrum of depression symptoms, from increased depressive symptom severity in healthy subjects to clinical cases of MDD (Antypa et al., 2016; Au & Reece, 2017; Bauducco et al., 2020; Kivelä et al., 2018). Many findings also report increased propensity for late chronotype in BD, however these reports are mixed. Some evidence suggests that late chronotype may be associated with increased risk of depressive episodes and not (hypo)manic episodes, yet others have found that BD-I and BD-II are both equally likely to have late chronotype compared to matched control participants (Melo et al., 2017; Romo-Nava et al., 2020; Wood et al., 2009). Two published studies have investigated chronotype in a UM group and found increased morningness in the UM group when compared to a BD group (Chang et al., 2023; Mittal et al., 2013). These findings point towards a relationship between polarity and chronotype in BD, but further research is required.

There are some limitations to consider with the use of chronotype and other self-report measures of rest-activity rhythms. Most methods do not account for variable rhythms, including workday and weekend differences in sleep timing and seasonal changes. They may also be affected by reporting bias. Despite this, they have shown strong correlation with objective measures of rest-activity rhythms and show good stability over 2-year periods (Murray et al., 2020).

1.2.2.2 Behavioural measures

Objective behavioural measures address some of the limitations of self-report measurements such as chronotype. In diurnal rest-activity measurement, actigraphy is commonly utilised due to its ability to track sleep and activity in naturalistic conditions with relatively low impact on the wearer (Murray et al., 2020). This usually involves a participant wearing a research-grade accelerometer on their wrist to measure acceleration, frequency, and direction of movement; however, the increasing public use of personal activity trackers is prompting research into the viability of using these devices too (Cho et al., 2020; Van Til et al., 2020). Summary statistics are then derived from this information, providing objective measures of sleep (sleep timing, duration and efficiency), activity (average acceleration, moderate and vigorous physical activity), rhythm variability (relative amplitude, interdaily stability, intradaily variability) and circadian rhythm parameters (phase, amplitude) (Nelson, 1979; Van Someren et al., 1999). These measures and their derivations are described in further detail in the methods chapter (chapter 2).

As with the self-reported measures above, actigraphy studies have also identified associations between rest-activity disruption and mood disorders. Less differentiation between active and inactive periods within a day (as measured by relative amplitude) have been found in both MDD and BD groups when compared to healthy control groups, suggesting they exhibit low activity levels throughout the day and/or disrupted sleep (Lyall et al., 2019). These differences are also related to increased symptom severity in MDD (Difrancesco et al., 2022). A recent systematic review and meta-analysis of actigraphy for mood disorder categorisation found that, when compared to healthy control groups, BD was associated with significant differences in sleep measures including sleep onset, duration, and efficiency, and that this persisted in euthymic states (Tazawa et al., 2019). In contrast, these pervasive sleep differences were not found in MDD groups (with the exception of decreased sleep efficiency) suggesting that actigraphy-measured rest-activity

profiles may be able to differentiate between mood disorders. This relationship is further supported by the many studies that have found improvements in rest-activity rhythm following treatment for mood disorders, including increased levels of daytime activity and sleep efficiency (Burton et al., 2013). No published studies have assessed rest-activity rhythms via actigraphy in UM; however, sleep duration, quality and activity level differences have been observed during manic episodes in BD (Lahti et al., 2009; Ortiz et al., 2021). Sleep reduction has been theorised as a key pathway to mania with evidence that manic episodes can be triggered by enforcing reduced sleep, but the relationship between sleep duration and UM requires further research (Wehr, 1992).

Whilst actigraphy can provide an objective measure of diurnal rest-activity rhythms, this methodology also comes with limitations. Measurement length is limited by battery life and researchers must balance this with measurement resolution (Murray et al., 2020). User error, discomfort or technical problems can result in poor quality data, and so appropriate quality-control checks are necessary. Objective measures may also overlook an important aspect of rest-activity rhythm disruption in mood disorders; an actigraphy study that included self-report questions found that lower physical activity and later phase were more common in MDD when compared to controls, but only in the actigraph measures. Conversely, significant sleep differences were found in MDD, but only in self-report measures (Difrancesco et al., 2019). This highlights the benefits of including both objective and subjective measures of activity and sleep.

1.2.3 Incorporating seasonality

Seasonal changes are strongly implicated in both mood disorder and circadian research. In geographic areas with changeable climates, both sleep and activity are influenced by seasonal and environmental factors including daylight hours, temperature, and weather (Ferguson et al., 2023; Friborg et al., 2012; Tucker & Gilliland, 2007). Mood disorder symptoms and episodes also appear to have a seasonal element, with major depressive episodes peaking in winter months and manic episodes peaking in non-winter months (Akhter et al., 2013; Medici et al., 2016; Patten et al., 2017). One published study has assessed seasonality in UM using the Seasonal Pattern Assessment Questionnaire, a questionnaire designed to quantify seasonal mood and behavioural changes (Mittal et al.,

2013). UM participants were found to exhibit lower levels of seasonality when compared to a BD group, but further research is required to confirm this finding.

Table 1-1 Key circadian terms used within this thesis.

Term	Description
Chronobiology	*The study of biological rhythms.*
Circadian rhythm	*The daily cycle of processes within the (human) body that occur approximately every 24 hours.*
Sleep-wake cycle	*Closely related to the circadian rhythm, this describes the resulting cycles of alertness and sleepiness that occur approximately every 24 hours.*
Diurnal rest-activity	*Like sleep-wake cycles this refers to cycles of alertness and sleepiness that occur approximately every 24 hours, but specifically for organisms where alertness is highest during the daytime and sleepiness is highest during the night.*
Chronotype	*This describes the timing preference for a person's activity and sleep and can be a behavioural phenotype for circadian rhythm timing.*
Social jet-lag	*Irregular rest-activity patterns as a result of a person's daily schedule not being adequately aligned to their chronotype.*
Actigraphy/accelerometery	*A popular method for measuring naturalistic rest-activity rhythms in humans. An actigraph (accelerometer) is worn by the participant and continuously measures movement.*

1.3 Key gaps in the literature

The heterogeneity of symptom profiles within mood disorders is a key focus within the psychiatric research community as reducing this could potentially improve the timing and accuracy of diagnosis, treatment selection, and identification of relevant biomarkers and behavioural phenotypes. UM is currently included within BD in DSM-5 and ICD-11, and

as a result we have insufficient knowledge of UM within the context of other mood disorder groups (rMD, sMD and BD) and healthy controls. Existing studies focused on UM are often clinic-based, have small sample sizes, and have not been replicated.

Circadian disruption is repeatedly observed in mood disorders and increasing our understanding of this relationship may lead to the development of better therapies and identification of biomarkers and behavioural phenotypes. However, we currently have a limited understanding of these rhythm differences in rMD, sMD and BD, and no reliable understanding of rest-activity rhythm differences in UM. Furthermore, differences in methodology make comparisons between studies difficult.

Both mood disorders and diurnal rest-activity rhythms are associated with seasonal factors. Whilst the season of measurement is often accounted for in mood disorder and circadian research, few studies set out to specifically describe or quantify these seasonal patterns, nor to incorporate wider seasonal measures such as meteorological factors. Differences in seasonal and meteorological conditions at the time of measurement may be contributing to the mixed findings in the literature.

1.4 Thesis aims and contributions

Increasing our understanding of circadian disruption in mood disorders may contribute to the development of targeted treatment and diagnostic tools, increasing quality of life for those affected. Unfortunately, mood disorder research is currently hindered by the heterogeneity problem and this thesis aims to address that as follows:

1. This thesis aims to investigate the nosological status of UM using behavioural and self-report phenotypes of circadian rhythms in a large population-based dataset (chapter 3).

2. It aims to characterise rest-activity rhythms in rMD, sMD, BD and UM, and any associated seasonal patterns (chapter 4).

3. It aims to investigate the extent to which any rest-activity and seasonal differences are unique to a specific mood disorder group and potential discriminatory value (chapter 5).

4. Finally, it assesses remaining mood disorder heterogeneity by comparing rest-activity rhythms in (a) mood disorders groups based upon established DSM-5 criteria and (b) data-driven mood disorder groups based upon reported symptom profiles (chapter 6).

Addressing these aims provides novel findings that will contribute significantly to our very limited understanding of UM and its role in mood disorder heterogeneity.

Chapter 2 Data description and key methods.

2.1 Overview

The following provides a detailed description of the datasets used in this thesis; UK Biobank and HadUK-Grid. It also describes the methodology used to identify probable mood disorder groups and measurements of rest-activity rhythms, both of which are key features in subsequent analysis chapters. Additional analysis-specific methodologies are described within each relevant chapter.

2.2 UK Biobank

2.2.1 Dataset description

UK Biobank is a large-scale data resource containing a wide range of detailed health and biomedical data for approximately 500,000 volunteers. Participants were UK residents and aged 37-73 years old at the time of recruitment. Data collection began in 2006 and covers a wide range of questionnaires and physical assessments including, but not limited to, lifestyle and demographic questionnaires, mental health questionnaires, physical activity monitoring, brain imaging, cognitive testing, and genetics. Baseline assessments and subsequent in-person assessments were administered at one of 22 assessment centres throughout the UK, apart from brain imaging which was administered at one of 4 assessment centres. Some follow-up assessments were administered online/remotely.

All participants who opted to join UK Biobank provided written, informed consent, and had the option of being removed from this study at any time. UK Biobank has generic ethical approval from the Northwest Multi-centre Research Ethics Committee (ref 11/NW/03820). The analyses in this thesis were performed under UK Biobank project approvals 6553 (PI Smith), 26209 (PI Wyse), 54772 (PI Lyall) and 17689 (PI Lyall).

2.2.2 Identifying probable mood disorders in UK Biobank

2.2.2.1 Probable mood disorder criteria

For the analysis in this thesis, it was necessary to identify participants with a probable mood disorder; unipolar mania (UM), bipolar disorder (BD), recurrent major depression (rMD) and single episode major depression (sMD). Potential sources included questionnaires in which participants answered a variety of questions related to mental health, self-reported diagnosis provided during the interview section of each assessment centre, and linked hospital records which included primary or secondary diagnosis for hospital in-patients. The questionnaires were chosen as they encapsulated a wider pool of participants, including those that may not have sought formal diagnosis or those with sub-threshold mania symptoms (hypomania).

Two mental health questionnaires (MHQ) are available within UK Biobank, both of which contain information on depressive and manic symptoms. The touchscreen MHQ was administered to a subset of participants at baseline (2006 onwards, 231,287 participants) and at subsequent in-person follow up sessions (up to 3 follow-up sessions at the time of writing). A separate sample of 172,966 participants voluntarily took part in a more comprehensive MHQ in 2016 which was completed remotely online. Both the touchscreen and online MHQs contained questions related to depression and mania, however the following differences existed:

1) Possible mania symptoms in the touchscreen questionnaire included: being more active than usual, more talkative than usual, less sleep required than usual and more creative than usual. The online questionnaire had a more extensive list of possible mania symptoms which included those listed above and additionally: more restless than usual, racing thoughts, easily distracted, and more confident than usual.
2) Mania/hypomania duration within the touchscreen questionnaire included: less than a week, less than a week but more than two days, a week or more. In the online questionnaire the options were less than 24 hours, more than one day but less than one week, and a week or more.
3) Within the touchscreen questionnaire participants could only report the key depressive symptoms which are feelings of depression or anhedonia (unenthusiastic or disinterested in things that are usually enjoyed). In the online questionnaire participants could report depression and anhedonia, but also weight changes, sleep

changes, feeling of worthlessness, difficulty concentrating, and an increase in thoughts related to death.

4) During the touchscreen questionnaire, the full depression questionnaire was only available to participants that answered 'yes' to experiencing feelings of depression or anhedonia for 1+ week, whereas the depression section of the online questionnaire required participants to have experienced feelings of depression or anhedonia for 2+ weeks.
5) Within the touchscreen questionnaire participants were asked if they had "ever seen a general practitioner (GP) for nerves, anxiety, tension or depression", whereas in the online questionnaire they were asked if they had "told a professional about these problems (medical doctor, psychologist, social worker, counsellor, nurse, clergy, or other helping professional)".

As the questions within the online MHQ are more extensive than those of the touchscreen MHQ, the online MHQ was the preferred source when identifying probable mood disorder. However, the touchscreen MHQ has been used to identify probable mood disorder elsewhere and contains an acceptable level of detail (Smith et al., 2013). Therefore, where the online MHQ had been completed this was used to identify probable mood disorder, and where it had not been completed the most recent completed touchscreen questionnaire was used in its place.

Figure 2.1 provides a detailed summary of the criteria for each probable mood disorder. In short, the questionnaires were used to identify participants that had experienced probable episodes of (hypo)mania or depression, and probable mood disorder was categorised based on the combination and recurrence of these episodes; UM for 1+ episodes of mania or hypomania and no depression episodes; BD for 1+ episodes of mania or hypomania and 1+ episodes of major depression; rMD for 2+ episodes of depression and no episodes of mania or hypomania; sMD for 1+ episodes of depression and no episodes of mania or hypomania. This criteria approximates the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria for these diagnoses as closely as possible within the confines of the available questions.

A) Probable mood disorder episode(s) criteria

	Online Questionnaire (Primary source)	Touchscreen Questionnaire (Secondary source)
Probable mania episode(s)	• Has felt hyper/manic or argumentative/irritable for 1+ weeks • 3 or more symptoms* • Symptoms caused problems with daily activities	• Has felt hyper/manic or argumentative/irritable for 1+ weeks • 3 or more symptoms* • Symptoms caused problems with daily activities
Probable hypomania episode(s)	• Has felt hyper/manic or argumentative/irritable for 2+ days • 3 or more symptoms*	• Has felt hyper/manic or argumentative/irritable for 2+ days • 3 or more symptoms*
Probable no (hypo)mania episode(s)	• Never felt hyper/manic or argumentative/irritable for 2+ days	• Never felt hyper/manic or argumentative/irritable for 2+ days
Probable single major depressive episode	• Had feelings of depression and/or anhedonia for 2+ weeks • Reported 1 period of depression and/or anhedonia for 2+ weeks • 5 or more symptoms* • Professional informed about symptoms	• Had feelings of depression and/or anhedonia for 1 week • Reported 1 period of depression and/or anhedonia for 1+ weeks • Longest period of depression/anhedonia lasted 2+ weeks • GP or psychiatrist seen for nerves/anxiety/tension/depression
Probable recurring major depressive episodes	• Had feelings of depression and/or anhedonia for 2+ weeks • Reported multiple periods of depression and/or anhedonia for 2+ weeks • 5 or more symptoms* • Professional informed about symptoms	• Had feelings of depression and/or anhedonia for 1 week • Reported multiple periods of depression and/or anhedonia for 1+ weeks • Longest period of depression/anhedonia lasted 2+ weeks • GP or psychiatrist seen for nerves/anxiety/tension/depression
Probable no major depressive episode(s)	• Never had feelings of depression and/or anhedonia for 2+ weeks	• Never had feelings of depression and/or anhedonia for 1 week

** Mania and depression symptoms for the online questionnaire and touchscreen questionnaire are listed in section 2.2.2.1*

B) Probable mood disorder criteria

		Criteria	Online Questionnaire N	Touchscreen Questionnaire N	*Total N*
Probable unipolar mania (UM)	✓	Probable mania episode(s) OR probable hypomania episode(s)	1,234	336	*1,570*
	×	Probable single major depressive episode OR probable recurring major depressive episodes			
Probable bipolar disorder (BD)	✓	Probable single major depressive episode OR probable recurring major depressive episode AND Probable mania episode(s) OR probable hypomania episode(s)	5,519	1,195	*6,714*
Probable recurring major depressive disorder (rMD)	✓	Probable recurring major depressive episodes	22,784	16,744	*39,528*
	×	Probable mania episode(s) OR probable hypomania episode(s)			
Probable single episode depressive disorder (sMD)	✓	Probable single major depressive episode	10,987	5,443	*16,430*
	×	Probable mania episode(s) OR probable hypomania episode(s)			
Probable control	✓	Probable no (hypo)mania episode(s) AND probable no major depressive episode(s)	55,020	48,332	*103,352*
Total N		-	*95,544*	*72,050*	*167,594*

Figure 2.1: Criteria for probable mood disorder episodes (A) which are subsequently combined to identify probable mood disorders (B)

2.2.2.2 Exclusions

Participants that met the following criteria were excluded from the analysis in this thesis; severe neurological diagnoses, brain injury, schizophrenia, sleep apnoea or insomnia, or a main job that involved shift-work. Severe neurological diagnoses, brain injury, schizophrenia, sleep apnoea and insomnia were based on illnesses reported by participants during the verbal interview at assessment centres and coded by trained medical professionals (UK Biobank Field ID 20002). This included stroke, transient ischaemic attack, subdural haemorrhage/haematoma, subarachnoid haemorrhage, neurological injury/trauma, infection of nervous system, brain abscess/intracranial abscess, encephalitis, meningitis, chronic/degenerative neurological problem, motor neurone disease, multiple sclerosis, parkinsons disease, dementia/alzheimers/cognitive impairment, epilepsy, head injury, other demyelinating disease (not multiple sclerosis), cerebral aneurysm, cerebral palsy, other neurological problem, brain haemorrhage, spina bifida, ischaemic stroke, fractured skull/head, meningioma/benign meningeal tumour, and benign neuroma. Shift-work was reported by participants during the touchscreen questionnaire at assessment centres (UK Biobank Field ID 826). In total 23,290 participants were excluded (UM(N)=257, BD(N)=1,284, rMD(N)=6,294, sMD(N)=2,360, Control(N)=13,095).

2.2.3 Subjective rest-activity measures

Participants were asked about their sleep characteristics and rest-activity rhythms as part of the assessment centre touchscreen questionnaire. This included information on sleep duration, difficulty getting up in the morning, chronotype, sleeplessness, snoring and napping, however this thesis focused specifically on sleep duration, difficulty getting up, chronotype and sleeplessness for analyses that included subjective rest-activity rhythms (Table 2.1).

Table 2-1: Subjective rest-activity measures featured in each analysis chapter.

	Chapter 3	Chapter 4	Chapter 5	Chapter 6
Sleep duration	✓*	-	✓	✓*
Chronotype	✓*	-	✓	✓*
Difficulty getting up	✓	-	✓	✓*
Sleeplessness	✓	-	-	-

* *measure was refined, as described below.*

Sleep duration was assessed by asking participants to report the approximate number of hours of sleep they get in every 24-hour period, including naps (UK Biobank Field ID 1160). Participants were asked to confirm if they entered low or high values (< 3 hours or > 12 hours), and durations < 1 hour or > 23 hours were excluded by UK Biobank. 3,327 participants answered 'do not know' or 'prefer not to answer' and were subsequently excluded in analyses using this measure. In the analysis for chapter 3 and 6 this measure was further categorised into short (< 7 hours), regular (7-9 hours), and long sleep duration (> 9 hours) (Kyle et al., 2017).

To measure chronotype participants were asked to choose which describes them best: 'definitely a morning person', 'more a morning than evening person', 'more an evening than morning person', or 'definitely an evening person' (UK Biobank Field ID 1180). 63,130 participants answered 'do not know' or 'prefer not to answer' and were subsequently excluded in analysis using this measure. For chapters 3 and 6 participants choosing 'more morning than evening person' and 'more evening than morning person' were combined to create an 'intermediate' group (Taillard et al., 2003).

Participants were asked to report how easy they find it to get up in the morning on an average day: 'not at all easy', 'not very easy', 'fairly easy', or 'very easy' (UK Biobank Field ID 1170). 1,015 participants answered 'do not know' or 'prefer not to answer' and were subsequently excluded in analyses using this measure. In chapter 6 this was dichotomised to a difficult ('not at all easy' and 'not very easy') and not difficult ('fairly easy' and 'very easy') group.

Participants were also asked whether they have difficulty falling asleep (or staying asleep) to measure sleeplessness and insomnia (UK Biobank Field ID 1200). Available options were ‘never/rarely’, ‘sometimes’ or ‘usually’. 612 participants answered ‘prefer not to answer’ and were excluded from analysis using this measure.

Figure 2.2 shows the distribution of time differences between subjective rest-activity measurement and the MHQ used to derive probable mood disorder category. Subjective rest-activity measures were taken from the baseline assessment centre touchscreen questionnaire. There is no time difference for those who only participated in an MHQ during the baseline assessment centre, and the maximum time difference is 16.92 years for those who completed a follow-up touchscreen MHQ or online MHQ.

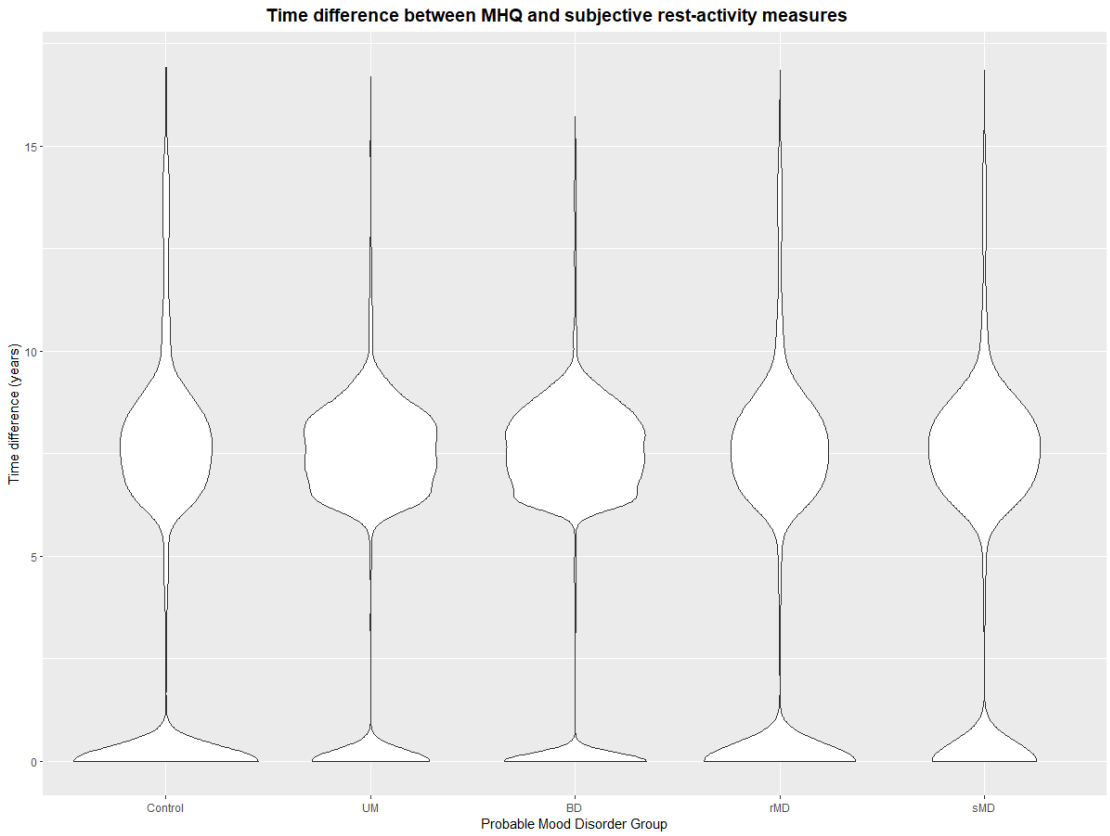

Figure 2.2: Time difference between MHQ and subjective rest-activity measures.

2.2.4 Objective rest-activity measures

2.2.4.1 UK Biobank accelerometer study

An accelerometer is a microelectromechanical system that measures accelerations in relation to the Earth's gravitational field, and outputs a three-dimensional time series of accelerations (up-down, left-right and back-forward) measured in gravitational units (g) (Karas et al., 2019). Given their small size and ability to capture large amounts of data with limited impact on the user, they are widely used to objectively assess naturalistic physical activity and sleep in population studies (Doherty et al., 2017; Strath et al., 2013).

Between May 2013 and December 2015, 103,720 UK Biobank participants took part in an additional accelerometery study. Participants received an Axivity AX3 wrist-worn triaxial accelerometer by mail, sampled at 94-104Hz with a dynamic range of ±8 g, and were asked to wear this on their dominant wrist for a 7-day period whilst continuing with their normal activities. Upon return of the device, the raw data was processed in line with the processing-plan devised by the UK Biobank Physical Activity Expert Working Group (full information available at https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/PhysicalActivityMonitor.pdf). Briefly, pre-processing included device calibration to local gravity, identification of any recording errors, and resampling to 100Hz. Following this, all three axes were combined to one acceleration measurement (calculated as the Euclidean norm of the 3 axes), machine noise was removed from this value using a Butterworth low pass filter (20Hz cut-off), and this was then summarised to five-second long epochs. Non-wear periods were defined as stationary episodes lasting 60 minutes or more, and participants that had less than 3 days' worth of data were removed.

2.2.4.2 Accelerometer derived rest-activity measures

The analyses in this thesis used summarised rest-activity measures that were derived from the pre-processed 5-second epoch acceleration values (Table 2.2). Mean sleep duration and efficiency were derived by Jones et al. using GGIR Version 1.5-17 in R (Jones, van Hees, et al., 2019); Average acceleration, relative amplitude, interdaily stability, intradaily variability, phase and amplitude were derived by Wyse et al. (2018, unpublished) using Clocklab Version 6 (Actimetrics). Additional 'other' variables were derived as part of the analysis for chapter 5.

Table 2-2: Objective rest-activity measures featured in each analysis chapter.

	Chapter 3	Chapter 4	Chapter 5	Chapter 6
Mean sleep duration	✓*	✓	✓	✓
Mean sleep efficiency	✓	✓	✓	✓
Average acceleration	✓	-	✓	✓
Relative amplitude	✓	✓	✓	✓
Interdaily stability	✓	✓	✓	✓
Intradaily variability	✓	✓	✓	✓
Phase	-	✓	✓	-
Amplitude	-	-	✓	-
Other	-	-	✓	-

* *measure was refined, as described below.*

For sleep duration and efficiency, Jones et al. estimated sleep period time windows (SPT-window) by re-estimating the z-angle (representing the dorsal-ventral direction) from the acceleration data for 5-minute rolling windows across each 24hr measurement period. This allowed them to identify periods of movement and non-movement, with non-movement being defined as periods below the 10th percentile. Periods of non-movement lasting 30 minutes or more, and that were less than 60 minutes apart, were combined to define the start and end of a SPT-window. Within the SPT-window, periods of inactivity that lasted 5 minutes or more and had no z-angle movement greater than 5° were totalled to get a daily sleep duration, and these were averaged across the 7-day measurement period to get mean sleep duration. In chapter 3 sleep duration was modified to 3 groups in line with adult sleep duration recommendations: short (mean sleep duration < 7 hours), regular (mean sleep duration 7-9 hours), and long (mean sleep duration > 9 hours) (Chaput et al., 2018). Sleep efficiency was calculated as the daily sleep duration divided by the daily SPT-window, and this was also averaged across the 7-day measurement period to get mean sleep efficiency (Jones, van Hees, et al., 2019).

Relative amplitude (RA), interdaily stability (IS) and intradaily variability (IV) are non-parametric measures that describe rhythm variability (Van Someren et al., 1999). RA

describes the ratio of activity between the most active 10-hour period (M10) and least active 5-hour period (L5) of a day:

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

RA ranges from 0 to 1 with higher values representing higher levels of distinction between active and rest periods, and lower values possibly indicating lower levels of daytime activity and/or disturbed sleep. In this thesis RA is the mean of the RA values from all measured days.

IS quantifies the stability of rest-activity rhythms across multiple days, where *n* is the total number of acceleration measures, *p* is the number of acceleration measures per day, $\bar{X}_h$ are hourly mean accelerations, $\bar{X}$ is the mean acceleration across all days, and X_i is the acceleration at an individual sampling point:

$$IS = \frac{n \sum_{h=1}^{p} (\overline{X_h} - \bar{X})^2}{p \sum_{i=1}^{n} (X_i - \bar{X})^2}$$

IS ranges from 0 to 1 with higher values representing a more stable rhythm and better coupling to external zeitgebers.

IV describes the fragmentation of the rest-activity rhythm within a given day, where *n* is the total number of acceleration measures, $\bar{X}$ is the mean acceleration across all days, and X_i is the acceleration at an individual sampling point:

$$IV = \frac{n \sum_{i=2}^{n} (X_i - X_{i-1})^2}{(n-1) \sum_{i=1}^{n} (X_i - \bar{X})^2}$$

IV ranges from 0 to 2+, with higher values representing more fragmentation which can signify disturbed sleep or periods of low activity throughout the day. In this thesis IV is the mean of the IV values from all measured days.

Phase and amplitude are calculated using cosinor analysis, a parametric method for estimating characteristics of a circadian rhythm that involves fitting continuous cosine functions to observed data using regression (Suibkitwanchai et al., 2020). Phase describes the timing of peak activity in any 24-hour period (lower values representing earlier

timing), whilst amplitude describes the peak activity level itself (higher values representing higher activity levels).

A range of additional measures were derived from the accelerometer data for chapter 5 including differences between weekday and weekend activity levels, periods of moderate-to-vigorous-activity, and mean acceleration at various times of day. These are described in further detail within chapter 5.

Figure 2.3 shows the distribution of time differences between accelerometery derived rest-activity measures and the MHQ used to derive probable mood disorder category. This ranges from -6.52 years (MHQ was completed before the accelerometery study) to 9.71 years (MHQ was completed after the accelerometery study).

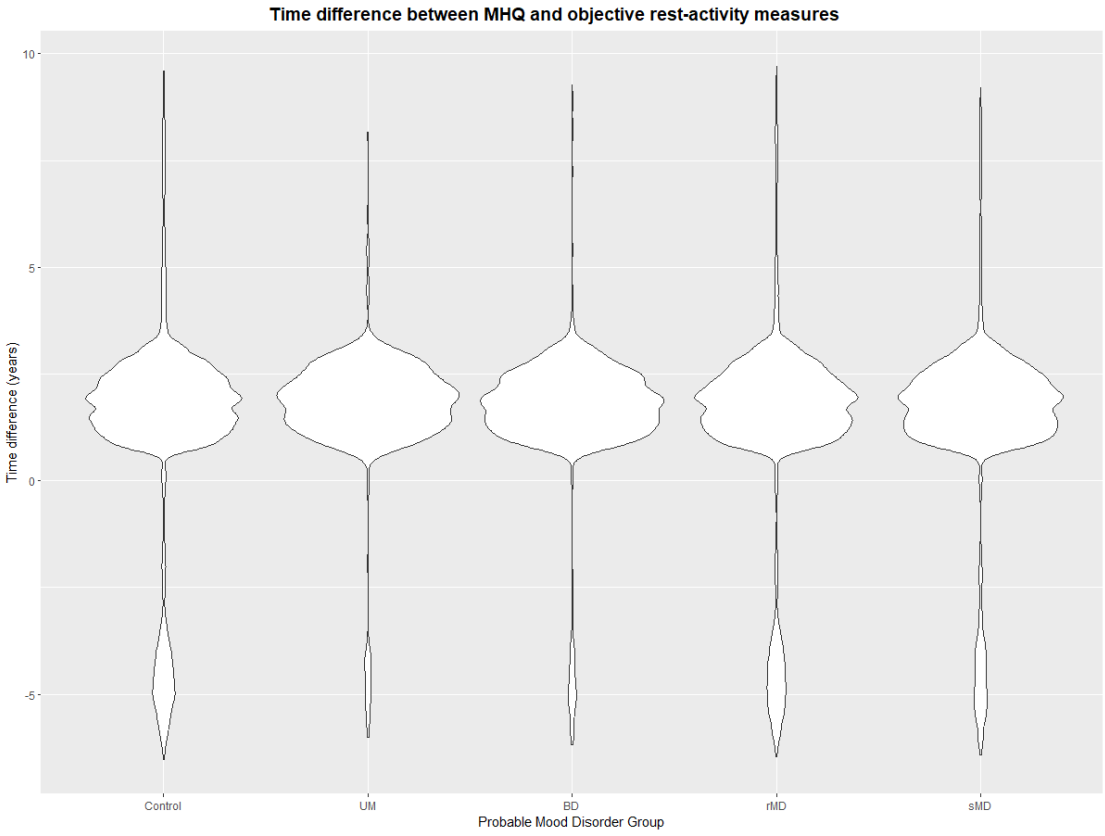

Figure 2.3: Time difference between MHQ and objective rest-activity measures.

The distribution of time differences between subjective and objective measures of rest-activity are shown in Figure 2.4. Participants took part in the accelerometery study between 2.79 and 9.69 years after the baseline assessment centre.

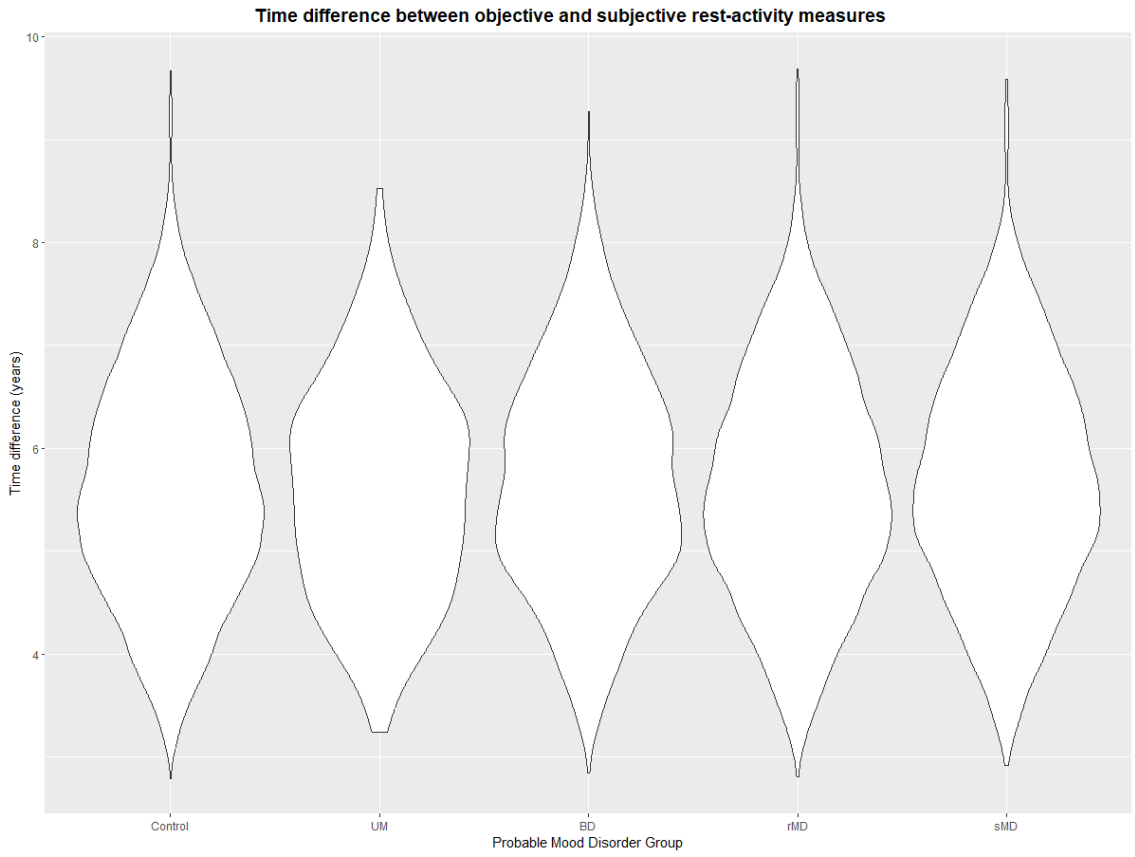

Figure 2.4: Time difference between objective and subjective rest-activity measures.

2.2.5 UK Biobank strengths and limitations

UK Biobank provides the unique opportunity to assess a wide variety of objective and subjective rest-activity rhythm outcomes in a large sample of UK adults. The inclusion of high-quality accelerometer data and comprehensive questionnaire data covering mental health, subjective sleep and activity, and lifestyle preferences allows for novel investigations into the relationships between these factors. However, there are some limitations; the UK Biobank cohort are not adequately representative of the UK adult population as they are older, healthier, and more highly affluent. As described in sections 2.2.3 and 2.2.4, there are varying time differences between rest-activity measures and the criteria used to determine probable mood disorder category. Additionally, it is not possible to assess mood state for probable mood disorder groups at the time of rest-activity

measurement in this dataset. Finally, whilst the range of questions included within the mental health questionnaires allowed for criteria that approximates clinical diagnostic criteria (section 2.2.2), these questionnaires were not administered by a professional and are therefore of limited clinical validity.

2.3 HadUK-Grid

2.3.1 Dataset description

HadUK-Grid (version 1.1.0.0) was made available in 2018 by the Met Office Centre for Environmental Data Analysis and provides meteorological information dating from 1862 to the present day. This information is collected from up to 600 weather stations across the UK, however this varies by time and measure. Regression and interpolation were applied to this station data to generate meteorological values for 1km x 1km grid areas across the UK, accounting for latitude, longitude, altitude, terrain shape, coastal proximity, and urban land use. This is described in further detail here: https://www.metoffice.gov.uk/binaries/content/assets/metofficegovuk/pdf/weather/learn-about/uk-past-events/papers/monthly_gridded_datasets_uk.pdf.

Grids are provided on daily, monthly, seasonal, and annual timescales and include precipitation, air temperature, sunshine, sea level pressure, wind speed, humidity, vapour pressure, lying snow and ground frost.

2.3.2 Data linkage and measures

Meteorological data files were downloaded for each measure of interest, and each year of accelerometery wear (2013, 2014 and 2015). Each file contained a 3-dimensional array of meteorological measurements; the x and y axes represented 1km easting and northing grid points (900x1450), and z-axis represented time (e.g. 12 for a monthly resolution). Figure 2.2 shows the x and y axes of the sunlight-hours measure plotted for a specific z-axis ‘slice’ (January 2013).

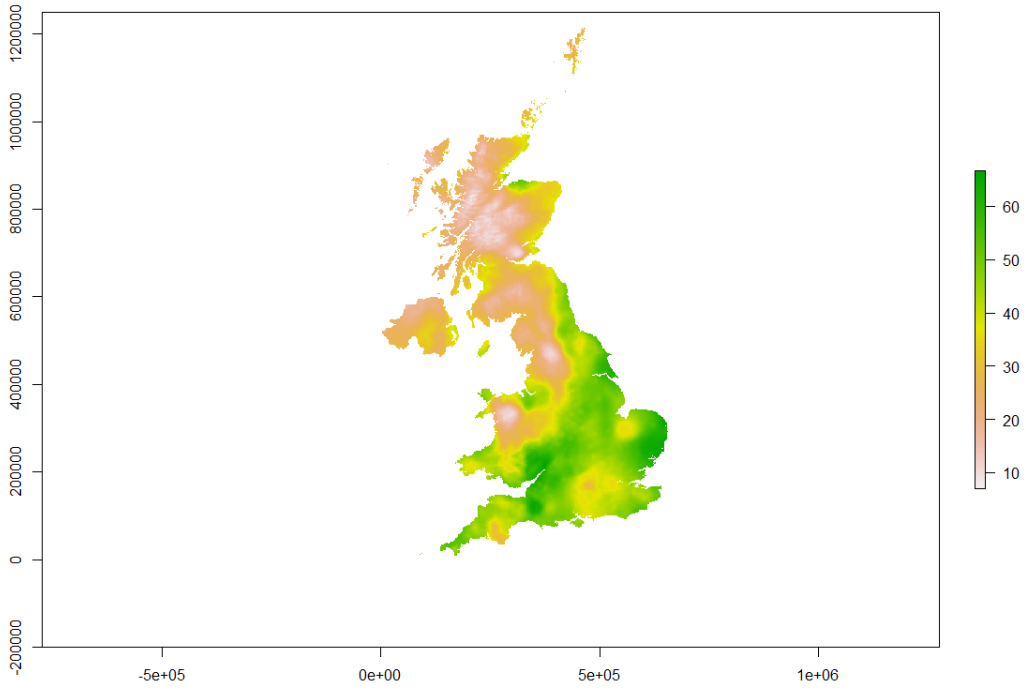

Figure 2.5: Sunshine hours from HadUK-Grid for January 2013.

For meteorological measures of interest (hours of sunshine, days of ground frost and precipitation), the HadUK-Grid data was linked to the UK Biobank data based on the approximate latitude and longitude of the participants' home address (converted to easting and northing) and the start date of accelerometer wear, using the 'sp' (version 1.6-0) and 'raster' (version 3.6-20) packages in R.

Precipitation (mean rainfall, mm) was the highest resolution meteorological measure, with daily data available. This was averaged over the 7-days of accelerometer wear, and a lag variable was also calculated for the 7-days prior to accelerometer wear. Sunshine (mean hours) and ground frost (mean days) were provided on a monthly basis. The monthly average corresponding to the month in which accelerometer wear was started was used, and a lag variable for the prior month was also included.

Chapter 3 The nosological status of unipolar mania and hypomania within UK Biobank according to objective and subjective measures of diurnal rest and activity.

3.1 Introduction

There is longstanding debate about whether individuals who experience episodes of mania or hypomania in the absence of depressive episodes (so-called unipolar mania, UM) should be considered as nosologically distinct from individuals with bipolar disorder (BD). Currently, both DSM-5 and ICD-11 incorporate UM as part of bipolar-I disorder (Angst et al., 2020). It has been suggested that including UM within BD hinders research on the pathophysiology of mania and increases heterogeneity within BD research (Angst, 2015).

Studies comparing characteristics of UM groups to BD groups are relatively rare, but some work suggests that there may be differences in both demographic and lifestyle factors, as well as mental health outcomes. For example, the sex distribution in BD is approximately equal but UM may be more common in males (Angst et al., 2019; Baek et al., 2014). Individuals with UM tend to experience more manic episodes than those with BD but have similar treatment and self-harm characteristics (Stokes et al., 2020). People with UM may also have less social disability and higher scores for hyperthymic temperament (Perugi et al., 2007). In contrast, some studies have found UM groups to be at higher risk of hospitalisation, greater use of medications and worse overall functioning compared to BD (Andrade-Nascimento et al., 2011). BD tends to be associated with a higher risk of comorbid Attention Deficit Hyperactivity Disorder (ADHD) and anxiety disorders than UM (Andrade-Nascimento et al., 2011; Baek et al., 2014). Overall, low participant numbers in these studies make it difficult to identify consistent and objective biological and/or phenotypic markers that might differentiate between UM and BD.

One area that may provide new insights on biological or phenotypic markers is sleep and circadian rhythm function. A large body of research has highlighted associations between disturbed circadian rhythms and mood disorders, particularly BD (Benard et al., 2019; H.-J. Lee et al., 2013; Lewis et al., 2017; McClung, 2013). Morningness-eveningness preference (chronotype) is a behavioural phenotype for circadian rhythm timing which has good reproducibility over time (Kantermann & Eastman, 2018; Murray et al., 2020), although subjective measures such as chronotype are more prone to reporting bias than objective measures such as actigraphy. Although findings are mixed overall, multiple studies have identified chronotype differences between BD and control groups, with later chronotype (a preference for evening activity) more commonly observed in people with

BD, even before the onset of illness (Alloy et al., 2017; Seleem et al., 2015). The relationship between chronotype and UM has not yet been investigated in detail, but one study found no difference in chronotype preference between participants with sub-threshold mania and controls (Giglio et al., 2010). Mania is more typically examined in the context of BD where published findings have shown that chronotype differences exist regardless of polarity or mood state in BD (Alloy et al., 2017), and that late chronotype is associated with a more depressive course of BD (Vidafar et al., 2021).

Actigraphy can provide an objective and naturalistic approach to measuring diurnal patterns of rest and activity. A small activity monitor, usually worn on a wrist, measures acceleration, frequency and direction of movement (Murray et al., 2020). Actigraph studies have identified aberrant rhythms of rest and activity in BD (Alloy et al., 2017; Melo et al., 2017). This includes lower activity levels throughout the day, longer sleep duration (but more disturbed sleep), and a less stable daily rhythm compared to controls. No studies to date have explicitly compared actigraphy measures in UM versus BD, but there is inconsistent evidence of associations between manic episodes and changes in objectively measured sleep duration, sleep quality and activity levels (both increases and decreases have been reported) (Beiwinkel et al., 2016; De Crescenzo et al., 2017; Lahti et al., 2009; Ortiz et al., 2021; Torous & Powell, 2015).

We set out to test for similarities and differences between UM, BD, and a non-mood disordered comparison group within the large UK Biobank cohort, making use of a broad range of demographic, lifestyle and mental health outcomes and with a particular focus on objective and subjective measures of diurnal patterns of activity and sleep. Our primary hypothesis was that individuals with UM would have a different profile of sleep and timing of diurnal rest/activity compared to individuals with BD.

3.2 Methods

3.2.1 Participants

We used data from UK Biobank which comprises of a range of data on health, lifestyle, demographics and physical characteristics from over 502,000 UK residents. These tests and questionnaires were administered at testing centres across the UK from 2006 onwards and included questionnaires relating to mental health, and (for a subset of participants, N=103,617) data from wrist-worn accelerometers. Participants who self-reported severe neurological diagnoses, brain cancer/injury, personality disorder, psychosis, schizophrenia, sleep apnoea/insomnia, or a main job that involved shift-work were excluded from the analysis (N=29,522).

3.2.2 Probable mood disorder criteria

Participants were provided with a touchscreen mental health questionnaire within which there were five mania specific questions (this questionnaire was introduced part way through UK Biobank recruitment and so was only administered to a subset of participants, N=214,576). Two of these questions identified whether a participant had a period of elevated mood or irritability lasting at least two days, and participants only answered the remaining mania questions if they answered yes to one of these questions. The remaining three questions assessed symptoms experienced during this time, duration of the episode, and how problematic the episode was. This questionnaire also assessed depressed mood, firstly by identifying whether the participant had experienced depressed feelings or anhedonia lasting 2+ weeks and, if yes, assessing additional symptoms, number of episodes and how problematic the episode had been. In our analysis, participants were identified as having probable UM if they answered yes to being irritable or ‘hyper’ for two days or more *and* had experienced 3 or more manic symptoms. Participants were considered to have probable BD if they met UM criteria and additionally met criteria for single or recurring major depression (yes to 2 or more weeks of depressed feelings or anhedonia, 5 or more depressive symptoms and a health professional had been consulted about these symptoms). These criteria resemble the DSM-5 criteria as closely as possible within the limitations of the questions available within the UK Biobank cohort.

A subset of UK Biobank participants opted in for completion of a specific mental health follow-up questionnaire completed online in 2016-2017 (N=157,317). The mania section of this questionnaire was structured similarly to the baseline touchscreen mental health questionnaire, although the multiple-choice options for symptoms and duration questions were slightly different. The online symptoms assessment had eight symptoms whereas the touchscreen version only had four symptoms. The duration options included 'less than 24 hours', 'more than one day but less than a week', and 'a week or more' (the touchscreen duration included 'less than a week', 'less than a week but more than two days', and 'a week or more'). Due to the additional level of detail, if a participant had completed this more comprehensive online questionnaire, the mood disorder criteria were applied from this assessment rather than from the touchscreen questionnaire.

3.2.3 Measurement of activity and sleep outcomes

Participants who opted into the UK Biobank accelerometer sub-study were provided with an AX3 triaxial accelerometer (Axivity, Newcastle upon Tyne, UK) and asked to wear this on their dominant wrist for 7 days. Data collection took place from 2013 to 2016. The UK Biobank Accelerometer Expert Working Group conducted data pre-processing and provided acceleration averages which were then used to calculate the following variables (further details are available at http://biobank.ctsu.ox.ac.uk/crystal/docs/PhysicalActivityMonitor.pdf).

Average Acceleration (AA) is the average level of activity over the full measurement period (Doherty et al., 2017). *Relative Amplitude (RA)* is the relative difference between the most active 10-hour period and least active 5-hour period of a given day, calculated as an average across all days of available data. Lower RA values suggest disturbed sleep and/or lower levels of daytime activity. *Interdaily Stability (IS)* indicates the level of coupling of activity levels to 24-hour daily patterns. Higher values suggest a regular daily rhythm whereas lower values indicate more variation in wake-up times or activity levels across various days. *Intradaily Variability (IV)* quantifies how fragmented the daily rhythm is, with higher values suggesting disturbed sleep or periods of inactivity during the daytime. Further information on the calculation of RA, IS and IV can be found here (Van Someren et al., 1999). *Mean Sleep Duration* is the number of hours spent sleeping within the sleep window (i.e. between going to bed and getting out of bed), averaged across all days of

wear. *Mean Sleep Efficiency* quantifies the amount of time spent sleeping as a proportion of the total sleep window, with higher values suggesting less disturbed sleep. Further information on the calculation of mean sleep duration and mean sleep efficiency can be found here (Jones, Lane, et al., 2019). In total 25,388 participants had complete accelerometer data which passed quality control and met the criteria for either probable BD, probable UM, or no mood disorder.

As well as the above objective measures, participants at recruitment completed questionnaires that included questions relating to sleep. This included self-reported average sleep duration, level of difficulty getting up in the morning (lower values indicated more difficulty), sleeplessness (higher values indicated more sleeplessness), and chronotype (higher values indicated more eveningness).

3.2.4 Measurement of mental health and psychological outcomes

The mental health follow-up questionnaire included questions relating to happiness, of which two were considered: ‘In general how happy are you?’ and ‘In general how happy are you with your health?’, both of which had options of extremely, very or moderately happy/unhappy. Within this questionnaire participants also reported whether they had ever self-harmed and if they had ever experienced anxiety (“a period lasting one month or longer when most of the time you felt worried, tense, or anxious”).

Within the touchscreen mental health questionnaire, participants reported whether they considered themselves to be risk-takers. A neuroticism score was also calculated based upon the answers to twelve questions that cover domains of neurotic behaviour (Smith et al., 2013).

3.2.5 Additional measures

During the baseline assessment visits participants provided demographic and lifestyle information including age, sex, ethnicity, educational attainment, smoking status and alcohol intake. Postcode of residence at the time of the assessment was used to derive

Townsend deprivation scores. Body-mass index (BMI) was calculated from measurements of height and weight taken at the time of assessment. Regular prescription medication was recorded by a trained nurse during the verbal interview section at the assessment centre and this was summarised into a categorical variable representing psychotropic medication use if the medication was any of those listed in Supplementary Figure S3.1.

3.2.6 Statistical analysis

Group differences for each variable of interest across each of the mental health groups (BD, UM, controls) were examined using individual multivariable logistic regression models. Three group comparisons were performed for each variable of interest: BD vs UM; UM vs control; and BD vs control.

Continuous relative amplitude, interdaily stability, average acceleration and sleep efficiency were inverted so that an increased score reflected a more negative outcome, for consistency with all other comparisons. These continuous variables, along with intradaily variability, were divided into quintiles due to their narrow ranges.

Both objective and subjective sleep duration were categorised into short (less than 7 hours), regular (between 7 and 9 hours) and long (more than 9 hours), with regular as the reference category (Kyle et al., 2017). Chronotype was condensed into three categories: early (‘definitely a morning person’), intermediate (‘more morning than evening’ and ‘more evening than morning’) and late (‘definitely an evening person’), with intermediate as the reference category. Participants who chose not to answer or answered ‘do not know’ were excluded.

Objective and subjective sleep duration were compared in a follow-up analysis to assess whether there were group differences in overestimating or underestimating sleep duration. These measures are not directly comparable as participants were asked to include daytime napping in the subjective sleep duration question, but napping is not included within the objective sleep duration estimate. For this reason participants who reported regular napping in the multiple-choice questionnaire were excluded. For the remaining participants

subjective sleep duration was subtracted from objective sleep duration (rounded to the nearest hour) to estimate the objective/subjective sleep duration difference. If the sleep duration difference was 0 this was categorised as ‘accurate’. If the difference was greater than 0 this was categorised as an ‘overestimation’, and less than 0 was categorised as an ‘underestimation’.

General happiness and happiness with health were both condensed into two categories: happy (‘extremely happy’, ‘very happy’, ‘moderately happy’) and unhappy (‘extremely unhappy’, ‘very unhappy’, ‘moderately unhappy’). Getting up in the morning was also condensed into a binary category of not difficult (‘fairly easy’ and ‘very easy’) and difficult (‘not at all easy’ and ‘not very easy’) with not difficult as the reference category. Participants who chose not to answer or answered ‘Do not know’ were excluded.

For each of these comparisons the multivariable logistic regression model was both partly adjusted and fully adjusted. The partly adjusted models included age, sex, Townsend deprivation score, education level and ethnicity as covariates. The season in which the accelerometer was worn as a covariate was also included in the partly adjusted model for objectively measured variables of interest. The fully adjusted models additionally included BMI, smoking status, alcohol status and psychotropic medication status. Group comparisons for lifestyle and demographic variables were assessed with one-way ANOVA for continuous numeric variables and Pearson’s chi-squared test for categorical variables. All statistical analyses were performed using R version 3.6.1 (R Core Team 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.). False Discovery Rate (FDR) correction was applied to the probability values of the fully adjusted models. The acceptable FDR was defined as < 0.05.

3.3 Results

3.3.1 Demographic/lifestyle comparisons

All assessed demographic variables varied significantly between groups (Table 3.1), confirming their importance as covariates within the subsequent models. UM participants were on average younger than control participants but older than the BD group. The UM group had a higher proportion of male participants, whereas the BD group had more female participants. The control group had significantly lower Townsend deprivation scores (indicating greater affluence) and the UM group were more affluent than the BD group. The BD group were more likely to have a higher BMI than both the UM and control groups, with the UM group having a higher BMI than the control group. Both the UM and BD groups had a higher rate of current or past smoking compared to the control group, with the BD group twice as likely to be current smokers as the UM group. The BD group were more likely to have given up drinking alcohol than the UM and control groups.

Table 3-1: Descriptive statistics of demographic and lifestyle variables.

	Mean (SD) / Percentage (N)			Test Statistic	p value	Effect Size
	BD	**UM**	**Control**			
Age	52.11 (7.31)	54.05 (7.76)	57.06 (7.56)	1030	<0.001	0.031
Sex	-	-	-	437.99	<0.001	0.083
Female	61.66 (2,978)	39.12 (470)	46.65 (27,166)	-	-	-
Male	38.34 (1,852)	60.83 (730)	53.35 (31,072)	-	-	-
Townsend Score	-1.02 (3.16)	-1.71 (2.82)	-2.00 (2.67)	297.6	<0.001	0.009
Education	-	-	-	87.63	<0.001	0.026
Incomplete	6.15 (295)	3.60 (43)	8.16 (4,703)	-	-	-
Compulsory	15.05 (722)	12.13 (145)	14.45 (8,336)	-	-	-
Continued	7.36 (353)	6.95 (83)	6.07 (3,498)	-	-	-
College	29.14 (1,398)	28.28 (338)	27.07 (15,612)	-	-	-
University	42.31 (2,030)	49.04 (586)	44.25 (25,521)	-	-	-
Ethnicity	-	-	-	77.01	<0.001	0.025

White	96.30 (4,637)	95.82 (1,146)	97.06 (56,374)	-	-	-
Mixed	1.14 (55)	0.59 (7)	0.37 (214)	-	-	-
Asian or Asian British	0.98 (47)	1.42 (17)	0.98 (569)	-	-	-
Black or Black British	0.85 (41)	0.92 (11)	0.84 (489)	-	-	-
Chinese	0.17 (8)	0.17 (2)	0.27 (159)	-	-	-
Other Ethnic Group	0.56 (27)	1.09 (13)	0.48 (277)	-	-	-
BMI	27.81 (5.19)	27.25 (4.36)	26.53 (4.14)	217.3	<0.001	0.007
BMI (>=18.5 & <30)	*25.33 (2.68)*	*25.58 (2.57)*	*25.16 (2.59)*	*18.21*	*<0.001*	*0.001*
Smoking Status	-	-	-	764.26	<0.001	0.077
Never	48.18 (2,321)	55.63 (667)	61.46 (35,714)	-	-	-
Previous	37.16 (1,790)	37.03 (444)	33.05 (19,206)	-	-	-
Current	14.66 (706)	7.34 (88)	5.50 (3,194)	-	-	-
Alcohol Status	-	-	-	287.36	<0.001	0.047
Never	2.45 (118)	2.08 (25)	3.01 (1,753)	-	-	-
Previous	5.59 (270)	2.58 (31)	1.91 (1,114)	-	-	-
Current	91.96 (4,438)	95.33 (1,144)	95.07 (55,330)	-	-	-
Any Psychotropic Medication	-	-	-	906.47	<0.001	0.119
Yes	3.77 (182)	0.33 (4)	0.33 (191)	-	-	-
No	96.23 (4,648)	99.67 (1,196)	99.67 (58,047)	-	-	-

3.3.2 Mental health and psychological comparisons

As expected, both mood disorder groups had poor mental health/psychological outcomes compared to the control group (Figure 3.1; Table 3.2). This included greater levels of reported anxiety (BD vs Control OR=47.97, 95% CI=44.03, 52.30; UM vs Control OR=3.01, 95% CI=2.54, 3.56; BD vs UM OR=15.47, 95% CI=12.93, 18.59). The anxiety results are not included within Figure 3.1 due to scale differences - the ORs were very high due to much higher proportions of BD and UM reporting anxiety compared to controls (Table 3.2). For most measures, the BD group were more likely to report a negative

outcome, followed by the UM group. The only exception to this was risk-taking behaviour, where both the UM and BD groups were more likely to declare themselves risk-takers than controls (but were not different from each other).

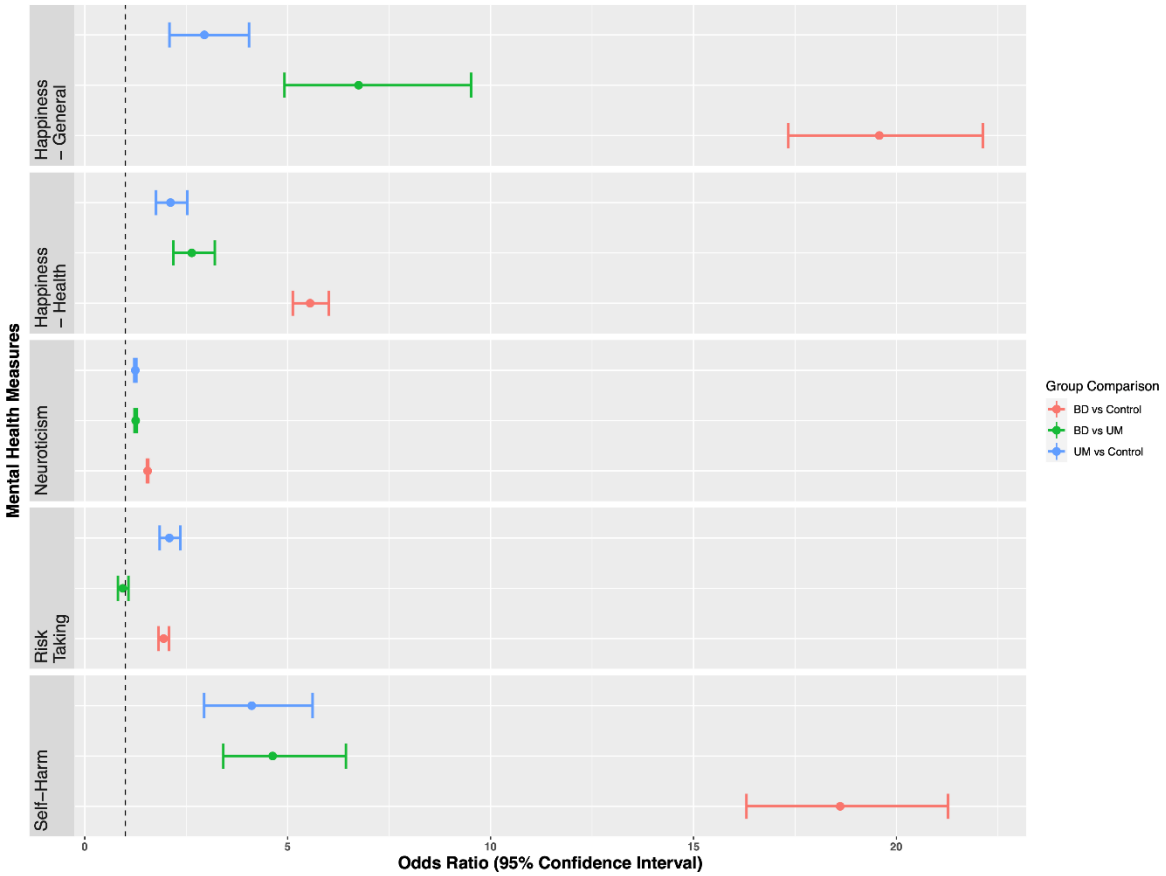

Figure 3.1: Group comparisons of mental health and psychological variables.

Odds Ratios and their 95% Confidence Intervals for measures related to mental health and psychological outcomes. Anxiety is not included in this figure due to the difference in scale. Higher odds ratios reflect a more negative outcome.

Table 3-2: Descriptive statistics of mental health, sleep, and activity.

Measure	BD		UM		Control	
	Sample Size	Mean (SD) / % (N)	Sample Size	Mean (SD) / % (N)	Sample Size	Mean (SD) / % (N)
General Happiness	4632	80.03% (3707)	1151	96.52% (1111)	51651	98.95% (51109)
Happiness with Health	4691	70.33% (3299)	1150	87.22% (1003)	51667	93.97% (48552)
Neuroticism	3989	6.95 (3.27)	1038	4.35 (3.13)	49685	2.54 (2.55)
Risk Taking	4629	39.34% (1821)	1158	43.52% (504)	55974	24.65% (13798)
Self-Harm	4674	17.86% (835)	1151	3.82% (44)	51685	0.79% (406)
Anxiety	4210	74.16% (3122)	1123	15.41% (173)	51100	5.71% (2917)
Relative Amplitude (RA)	1889	0.86 (0.07)	495	0.86 (0.07)	23004	0.87 (0.06)
Average Acceleration (AA)	1889	28.40 (8.72)	495	29.29 (8.22)	23004	28.32 (8.23)
Interdaily Stability (IS)	1889	0.53 (0.13)	495	0.53 (0.14)	23004	0.54 (0.13)
Intradaily Variability (IV)	1889	0.92 (0.24)	495	0.92 (0.27)	23004	0.93 (0.25)
Sleep Efficiency	1889	0.76 (0.08)	495	0.75 (0.08)	23004	0.76 (0.07)
Objective Sleep Duration	1889	-	495	-	23004	-
< 7 hours (Short)	-	36.95% (698)	-	42.42% (210)	-	33.45% (7695)
7 - 9 hours (Normal)	-	61.04% (1153)	-	57.17% (283)	-	65.05% (14964)

> 9 hours (Long)	-	2.01% (38)	-	0.40% (2)	-	1.50% (345)
Subjective Sleep Duration	4771	-	1189	-	57443	-
< 7 hours (Short)	-	29.78% (1421)	-	24.81% (295)	-	19.27% (11068)
7 - 9 hours (Normal)	-	68.06% (3247)	-	74.26% (883)	-	80.01% (45960)
> 9 hours (Long)	-	2.16% (103)	-	0.93% (11)	-	0.72% (415)
Sleeplessness	4775	2.20 (0.69)	1191	2.02 (0.71)	57486	1.89 (0.72)
Difficulty Getting Up	4773	29.54% (1410)	1191	15.45% (184)	57498	10.84% (6233)
Chronotype	4429	-	1105	-	50918	-
Early	-	24.43% (1082)	-	29.86% (330)	-	26.91% (13704)
Intermediate	-	61.14% (2708)	-	59.46% (657)	-	65.76% (33483)
Late	-	14.43% (639)	-	10.68% (118)	-	7.33% (3731)

3.3.3 Objective activity and sleep assessments

Figure 3.2 shows the odds ratios and confidence intervals for the objective measures of activity and sleep (AA, IS, IV, RA, and Sleep Efficiency quintiles). IS did not differ in any of the comparisons, suggesting that all three groups had a similar level of rhythm stability across the seven measured days. Both mood disorder groups had more defined activity and rest periods within each day compared to the control group, as shown by IV, however this effect was only significant for the UM group. Despite better IV, the BD group had lower RA than both the control and UM groups, suggesting less differentiation between periods of sleep and activity in this group. Comparison of AA shows that the BD group had lower overall levels of activity than the control group, whilst the UM group had higher levels of

activity than the control group. Both mood disorder groups also exhibited lower sleep efficiency (more disturbance during the sleep period) compared to the control group, although this difference was only significant for the BD group.

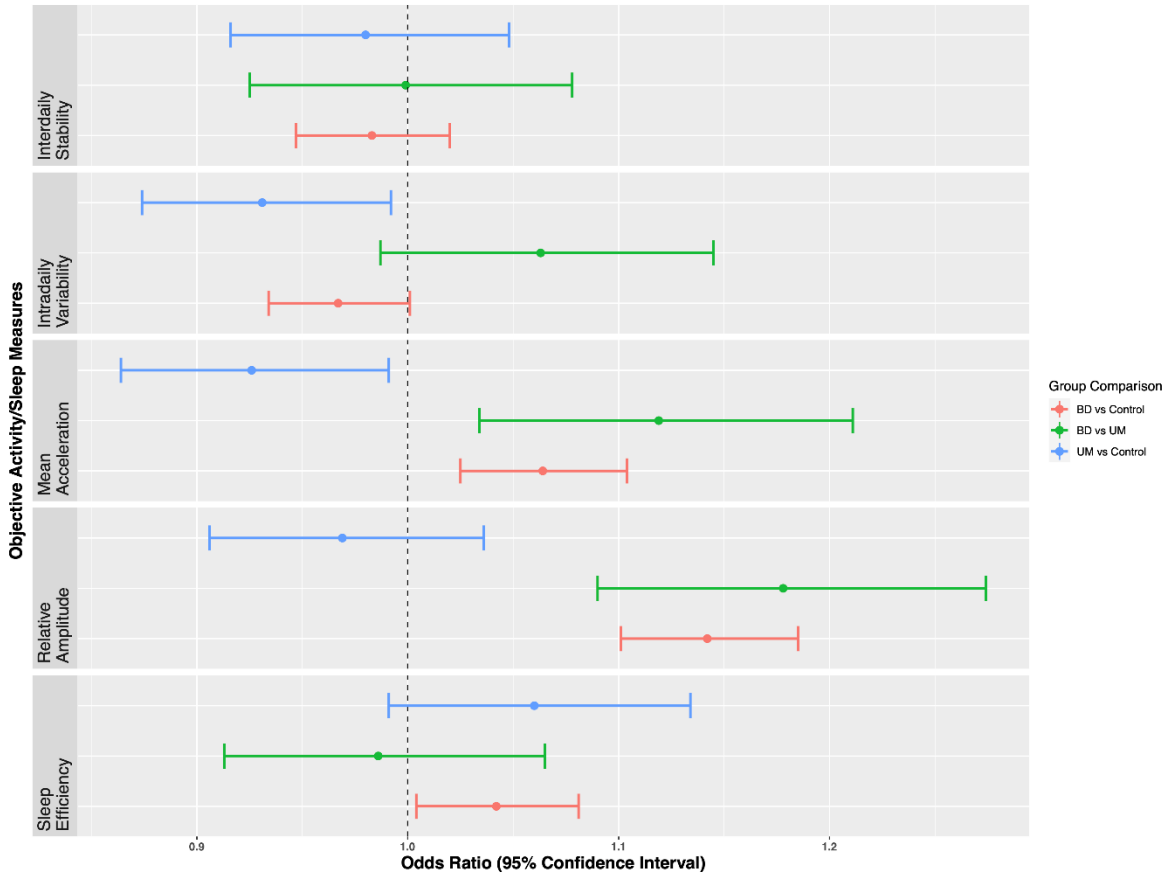

Figure 3.2: Group comparisons of objective measures of rest and activity.

Odds Ratios and their 95% Confidence Intervals for objectively measured sleep and activity variable quintiles.

3.3.4 Objective and subjective sleep duration

Figures 3.3 and 3.4 show the logistic regression results for objective and subjectively measured sleep duration. A very small number of participants in the UM group met criteria for long sleep duration (> 9 hours; objective sleep duration N=2, subjective sleep duration N=11), so Fishers Exact Test was used for those group comparisons instead of logistic regression (Supplementary Table S3.1).

Having a long sleep duration, as derived from the 7-day accelerometer data, was more likely in the BD group than both UM and control groups. The UM group were more likely to have a shorter average sleep period (< 7 hours) than the control group.

As with the objective measure, BD was associated with longer subjective sleep duration. However, although only UM was associated with short sleep duration on the objective measure, both UM and BD were associated with short subjective sleep duration compared to controls. It is worth noting that these findings are not directly comparable as they were derived from different (but overlapping) populations.

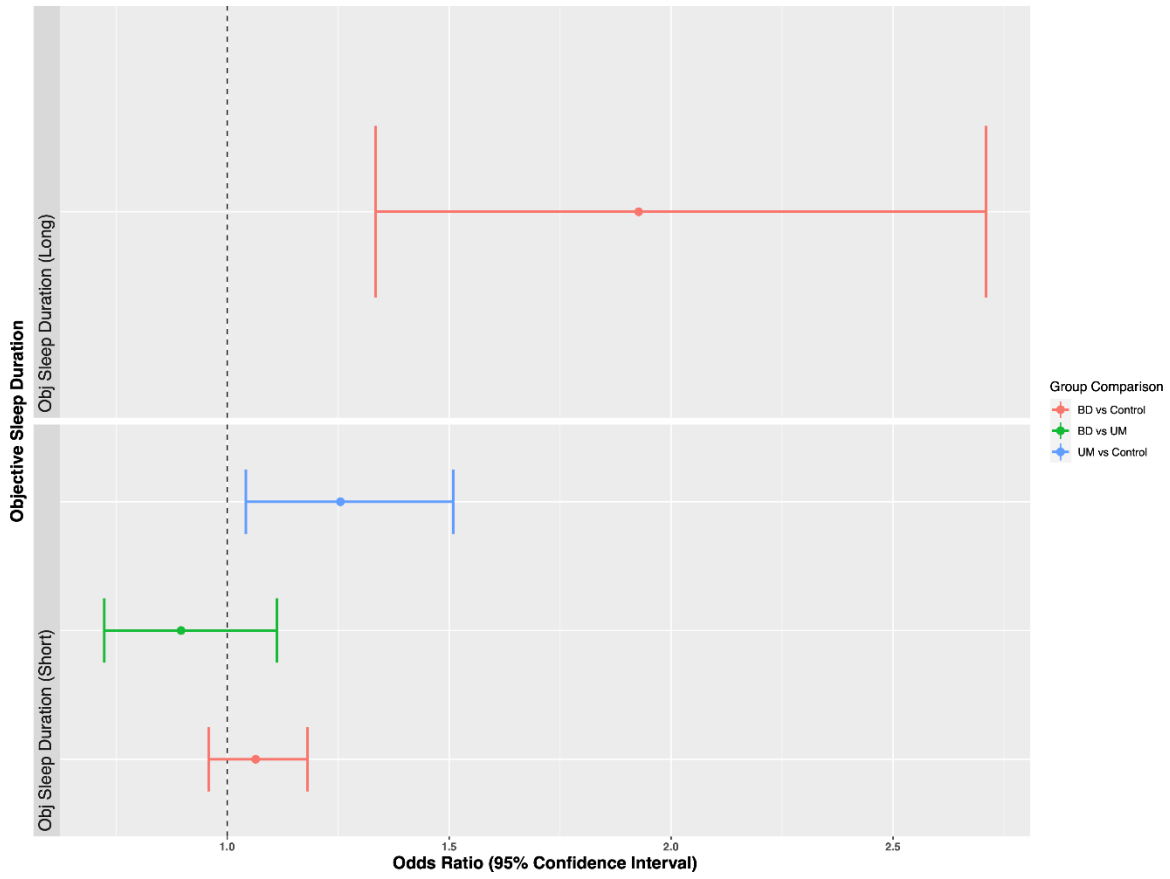

Figure 3.3: Group comparisons of objective sleep duration.

Odds Ratios and their 95% Confidence Intervals for objectively measured sleep duration. Short sleep duration is defined as < 7 hours and long sleep duration is defined as > 9 hours. Groups are compared to a reference group that averaged 7-9 hours of sleep over the period of accelerometer wear. Long sleep comparisons involving the UM group are not included due to small group numbers.

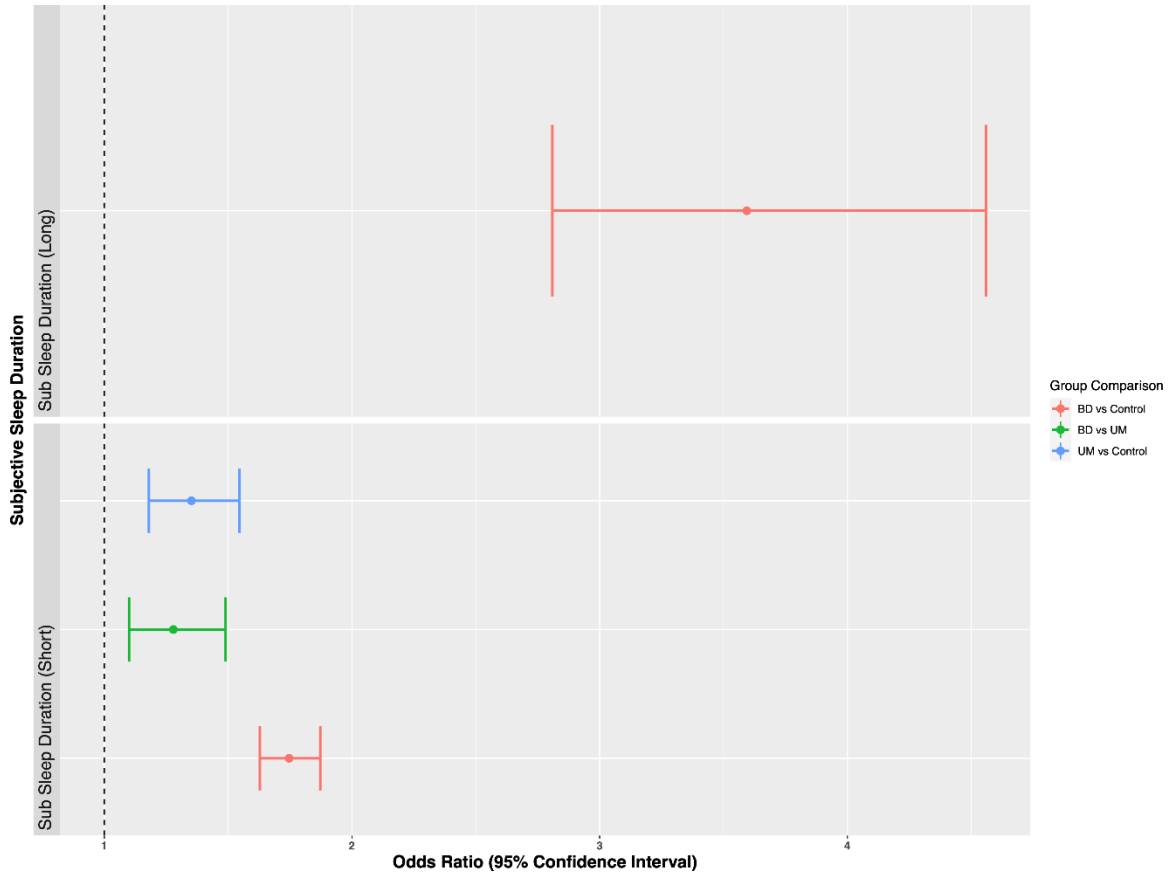

Figure 3.4: Group comparisons of subjective sleep duration.

Odds Ratios and their 95% Confidence Intervals for subjectively measured sleep duration. Short sleep duration is defined as < 7 hours and long sleep duration is defined as > 9 hours. Groups are compared to a reference group that reported 7-9 hours of sleep. Long sleep comparisons involving the UM group are not included due to small group numbers.

In a follow-up analysis, group differences in the accuracy of reported sleep duration were assessed. Table 3.3 summarises the differences in observed and subjectively estimated sleep duration within the UM, BD and control groups. The UM group were most likely to overestimate sleep duration and the BD group were most likely to underestimate sleep duration. As shown in the multinomial logistic regression analysis (Supplementary Table S3.2), the UM group had an increased likelihood of incorrect estimation (both under- and overestimation) compared to the control group, whereas the BD group only exhibited an increased risk of underestimation compared to controls.

Table 3-3: Group comparisons of the difference between objective and subjective sleep duration.

Test statistics are paired samples t-values comparing the mean difference between objectively and subjectively measured sleep duration for each group. Subjective estimations are classed as "accurate" if they are equal to the objective sleep duration (derived from accelerometer wear data, rounded to the nearest hour).

	UM	BD	Control
Mean Difference (Minutes)	5.8	17.3	7.2
Test statistic	1.332	6.666	12.165
p value	0.184	< 0.001	< 0.001
r^2	0.219	0.090	0.156
Underestimated (%)	40.19	43.36	36.51
Accurate (%)	30.23	32.72	37.76
Overestimated (%)	29.58	23.92	25.73

3.3.5 Subjective activity and sleep comparisons

The mood disorder groups reported more difficulties with sleep than the control group. As seen in Figure 3.5, both the BD and UM group were more likely to report disturbed sleep and difficulty getting up, but the BD group reported this to a greater extent than the UM group. This was also true for late chronotype, however early chronotype (a preference for activity in the morning) was reported more often in the UM group compared to both control and BD groups.

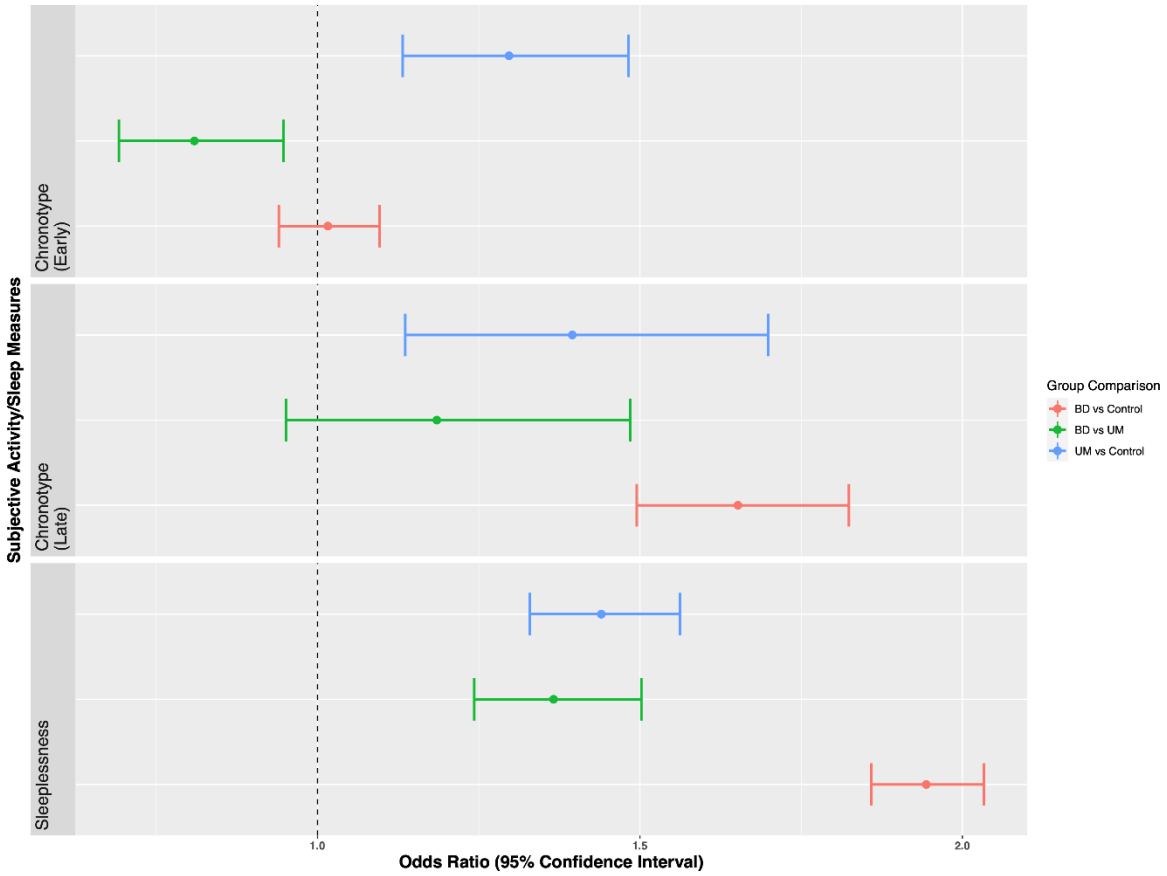

Figure 3.5: Group comparisons of the difference between subjective measures of activity and sleep.

Odds Ratios and their 95% Confidence Intervals for self-report measures of sleep and activity.

3.4 Discussion

Categorical classifications are useful in clinical settings and account for a small number of changes to rest and activity rhythms when classifying bipolar disorders. However, the significant overlap between bipolar disorder categories and high heterogeneity within these groups has inspired interest in dimensional approaches to understanding these groups (Phillips & Kupfer, 2013). Approaches such as the Hierarchical Taxonomy of Psychopathology (HiTOP) and Research Domain Criteria Initiative (RDoC) aim to address this issue by encouraging research into underlying biological and behavioural systems of psychopathology (Conway et al., 2019; Cuthbert, 2015). RDoC specifically identify 'sleep-wakefulness' as of interest in psychiatric illness, and the findings above consider behavioural and self-report aspects of this domain.

Overall, several of the findings described above are of interest with respect to similarities and differences between UM and BD in terms of mental health, wellbeing, sleep and activity characteristics. The UM group had a higher proportion of males than the BD group, in keeping with other reports (Angst et al., 2019; Baek et al., 2014). It is well established that depression affects more females than males, however it is also possible that the UM group may have experienced some sub-threshold depressive symptoms (Angst et al., 2004). Other demographic characteristics also support previous findings, including higher levels of educational attainment in the UM group. Although a limitation of UK Biobank is the low heterogeneity in reported ethnicity, there was a greater proportion of 'Asian or Asian British' ethnicity reported within the UM group. This may be consistent with some reports that rates of UM and mania-predominant BD are higher in South Asia (Angst & Grobler, 2015; Subramanian et al., 2017).

Across all mental health and wellbeing measures, both BD and UM groups reported more negative outcomes compared to controls. Although the BD group generally had worse outcomes than the UM group, this was not true for risk-taking where UM and BD groups were comparable.

Both mood disorder groups reported worse outcomes than controls on sleep and activity. As with the mental health outcomes, the BD group reported the worst outcomes, followed

by the UM group. An exception to this was reported chronotype. Late chronotype (a preference for evening activity) was more likely in BD than healthy controls, consistent with previous findings (Giglio et al., 2010; Kanagarajan et al., 2018; Melo et al., 2017). However, the UM group were more likely to report both early and late chronotypes. The literature suggests that late chronotype may be related to more severe depressive episodes and a reduction in manic episodes (Vidafar et al., 2021), and that episodes of mania are related to an advance in phase (Moon et al., 2016), which broadly supports the relationship between UM and early chronotype. Early chronotype preference may therefore be a useful distinguishing feature of UM.

There were differences in sleep duration between UM and BD. Sleep duration was measured both subjectively as part of a questionnaire, and objectively during the 7-day accelerometer assessment. Findings relating to sleep duration in BD in other studies have been mixed (Geoffroy et al., 2015; Meyer et al., 2020; Ng et al., 2015) and we found that this may be due to measurement method: the BD group were more likely to have a longer sleep duration (more than 9 hours) in both the objective and subjective measures compared to both UM and controls. However, the BD group were also more likely to report a short sleep duration (less than 7 hours) in the subjective measure which was not supported by the objective measure. The BD group also experienced lower levels of sleep efficiency suggesting that they experience overall poor sleep quality. A follow-up analysis comparing the difference between objective and subjective sleep duration across groups found that the UM group were more likely to *overestimate* their sleep duration than the BD or control group. Both mood disorder groups were also more likely to *underestimate* sleep duration compared to controls.

Sleep duration in UM has not been extensively studied, but loss of sleep is an important trigger for mania in BD (Leibenluft et al., 1996), and increased sleep duration can contribute to improvements in manic symptoms (Galynker et al., 2016). We found that short sleep duration was more likely in UM, whether self-reported or objectively assessed. Although the timing of episodes of mania and depression were not known for these group, the subjective measures were not limited to any specific time period, suggesting that chronic sleep disturbances may persist regardless of proximity to an episode of mania and/or depression.

Although objective measures of sleep and activity had a similar pattern of negative outcomes for both mood disorder groups, *average activity levels* may represent a useful differentiator between UM and BD. The UM group demonstrated higher levels of average activity than both BD and controls. A more detailed investigation of temporal daily activity patterns could lead to specific markers of individuals at greater risk of BD or UM and help to target the most appropriate interventions (Krane-Gartiser et al., 2018).

Whilst rest-activity outcomes are usually assessed in relation to depressive or manic episodes, in this analysis the timing of episodes of mania and depression were not known for these groups and the subjective measures were not limited to any specific time-period. This suggests that chronic changes to sleep and activity may persist regardless of proximity to an episode of mania and/or depression which has implications for future study design and disease management.

Dimensional approaches to understanding (hypo)mania in absence of depressive symptoms at a genetic level have suggested that mania and depression represent two distinct pathway (Merikangas et al., 2014), but little is known about UM at a behavioural level. The above findings suggest that negative sleep, activity and mental health outcomes appear to be transdiagnostic across BD and UM, however by analysing a variety of these outcomes in a large non-clinical population we have found evidence of key differences that may support UM being nosologically distinct. This supports further research into dimensional approaches to classification at a behavioural level.

We acknowledge some limitations to this work. The UK Biobank cohort are older, healthier and somewhat more affluent than the general population, so there may be issues relating to representativeness and our method of classifying BD and UM mood disorder categories was based on self-report measures rather than formal clinical assessments. We acknowledge that these groups are not identical to unipolar mania or bipolar disorder as defined in the DSM or ICD classifications. The nature of the large data collections within UK Biobank was such that a formal diagnostic interview was not feasible. Our groups were therefore constructed as pragmatic proxies of diagnoses, making use of all the available self-reported questionnaire data within the dataset.

There are varying levels of time between self-report measures and accelerometer measures, as these were administered separately between 2013 and 2017. Further, the UM sample size was relatively small compared to BD and healthy controls and the UM group mostly satisfied criteria for hypomania rather than mania. However, the strengths of this study include the relatively large samples and the comprehensive phenotyping information that was available, including high quality objective (actigraph) measures of rest/activity rhythmicity.

3.5 Conclusions

We identified negative outcomes in mental health, activity and sleep in both BD and UM groups compared to controls. For most measures, the BD group had worse outcomes, perhaps suggesting that UM is a less severe subgroup of BD. However, there were some key differences between UM and BD groups that provide some support for UM as nosologically distinct, specifically: a much higher proportion of males; an early chronotype preference; significantly shorter objective sleep duration; and increased levels of activity. We conclude that these findings may have implications for the assessment, classification and treatment of patients who do not experience episodes of major depression but who do have a history of hypomania and/or mania.

Chapter 4 Seasonal differences in objective rest-activity profiles across the unipolar-bipolar mood spectrum within the UK Biobank cohort.

4.1 Introduction

Within mental health disorders, mood disorders (or affective disorders) describe those that have a significant impact on an individual's emotional state. These disorders can be grouped into depressive disorders (characterised primarily by low mood or anhedonia), unipolar mania (characterised primarily by feeling unusually hyper or irritable), and bipolar disorders (frequently a combination of both). Mood disorders represent a leading cause of disability worldwide and can have a severe impact on an individual's quality of life (McIntyre et al., 2020).

Mood disorders are frequently linked with changes to daily activity levels and sleep, and so these behaviours represent a promising target for diagnosis and treatment options. Actigraphy involves users wearing a small activity monitor (usually wrist-worn) which tracks acceleration, frequency, and direction of movement, allowing for non-obtrusive and objective measurement of activity and sleep (Murray et al., 2020). In a large-scale UK based study disrupted rest-activity cycles were associated with increased lifetime risk of both major depressive disorder and bipolar disorder (Lyall et al., 2018). Lifetime depression and bipolar disorder have also been linked to a wide range of adverse sleep outcomes, including later bedtime and wake-time, more disturbed sleep, and increased napping (Wainberg et al., 2021). We have previously identified objective activity and sleep differences in participants with probable unipolar mania, including higher levels of activity and shorter sleep duration (chapter 3, Sangha et al., 2022).

In geographic areas that experience seasonal variation in climate, seasonal changes in sleep and activity levels have been established in studies of the general population. In a large-scale study based in Canada winter months have been associated with a decrease in self-reported walking time, whilst self-reported moderate physical activity was higher in summer (McCormack et al., 2010). Smaller studies using objective measures (accelerometers) have found light-intensity physical activity is increased in spring and summer months whilst sedentary behaviour and time in bed is increased in winter (O'Connell et al., 2014). Middle-aged and elderly populations are at particular risk of increased sedentary behaviour, and these groups have been assessed in accelerometer studies including the Rotterdam Study and UK Biobank (Hofman et al., 2015; UK Biobank, 2016). Within the Rotterdam Study (a middle-aged to elderly population, 50+

years old) participants' level of physical activity increased in summer months, but sedentary behaviours remained stable across seasons (Cepeda et al., 2018). In UK Biobank, summer was associated with reduced sleep duration and increased energy expenditure when compared to winter, and spring was associated with a significant increase in walking time (Willetts et al., 2018).

Whilst there is debate about the diagnostic status of seasonal affective disorder as a subtype of major depression (Traffanstedt et al., 2016), there is some evidence to support seasonality in the timing of mood disorder symptoms and episodes. In a large-scale Canadian study participants aged 12-24 exhibited significant seasonality in depression symptom reporting (peaking in winter), whereas the 25+ group only showed seasonal changes in appetite and sleep (also peaking in winter) (Lukmanji et al., 2020). Reported major depressive episodes have also been found to peak in winter months and are at the lowest in summer months (Patten et al., 2017). Seasonality of mania symptoms also exists in the literature, though results are mixed with peaks identified in spring, summer, and autumn (Geoffroy et al., 2014). In a nationwide Danish study mania-related hospital admissions were found to peak in summer months (Medici et al., 2016); a large cohort study in the United States found autumn was associated with increased hypomania in a bipolar disorder group (Akhter et al., 2013); and in the southern hemisphere hospital admissions for mania increased in spring (Parker & Walter, 1982).

In this analysis we set out to identify differences between objective rest-activity measures in control and probable mood disorder groups, within a large UK-based cohort of middle-aged and elderly adults. Furthermore, we aimed to identify whether these differences are season specific. Our primary hypothesis was that depression groups would exhibit increased adverse rest-activity behaviours when compared to the control group in winter, and the rest-activity profile of bipolar/mania groups would differ from the control group in non-winter seasons.

4.2 Methods

4.2.1 Participants

Participants were identified from the UK Biobank in which a wide range of health, lifestyle, demographic and physical characteristics have been collected from over 502,000 UK residents. Baseline measures were collected between 2006 and 2010 at 22 testing centres across Britain, including a mental health questionnaire and demographic data collection. A subset of participants completed a follow-up mental health questionnaire online between 2016 and 2017 (N=~160,000). Approximately 100,000 participants took part in a wrist-worn accelerometer study between 2013 and 2015, providing up to 7 days of data (Doherty et al., 2017).

Participants were excluded from this analysis if they self-reported severe neurological diagnoses, brain cancer/injury, personality disorder, psychosis, schizophrenia, sleep apnoea/insomnia, or a main job that involved shift-work (N=29,522). After exclusions, 40,494 participants had valid accelerometery data and met the criteria for either control or a probable mood disorder based on the criteria specified in section 4.2.2.

4.2.2 Probable mood disorder criteria

Probable mood disorder categorisation was based on answers to the online follow-up mental health questionnaire where available, as this is the most comprehensive mental health questionnaire within UK Biobank. Where participants had not completed the online follow-up, the baseline touchscreen questionnaire was used.

Participants were classified as being in the *probable unipolar mania/hypomania (UM)* group if they answered yes to ever being hyper/manic or irritable/argumentative for 2+ days, reported 3 or more symptoms of (hypo)mania, and answered no to the depression lead question (feeling depressed or anhedonic for 2 or more weeks). To be classified as *probable single episode of major depression (sMD)* participants had to report ever feeling depressed or anhedonic for 2 or more weeks, have 5 or more symptoms, have informed a

professional about their symptoms, and have had only one episode within their lifetime. They also had to have answered no to the mania lead question (feeling hyper/manic or irritable/argumentative for 2+ days). *Probable recurring major depression (rMD)* required the same criteria as sMD with the exception that they had to have reported more than one episode within their lifetime. The *probable bipolar disorder group (BD)* were defined as those that met the criteria for both UM and either sMD or rMD, whilst the probable control group were classified as those that answered no to both the lead mania and lead depression questions (and therefore all subsequent questions). A total of 24,696 participants met the criteria for the control group; 9,135 participant met the criteria for rMD; 4,328 participants met the criteria for sMD; 1,867 met the criteria for BD; and a further 468 met the criteria for UM.

4.2.3 Objective rest-activity measures

Data collection for the UK Biobank accelerometer sub-study took place between 2013 and 2016, during which time over 100,000 participants were provided with an AX3 triaxial accelerometer (Axivity, Newcastle upon Tyne, UK) and asked to wear this on their dominant wrist for 7 days. The UK Biobank Accelerometer Expert Working Group conducted all data pre-processing and provided acceleration averages (further details are available at http://biobank.ctsu.ox.ac.uk/crystal/docs/PhysicalActivityMonitor.pdf).

Non-parametric calculations are used to derive common measures of rest and activity, including relative amplitude, interdaily stability, and intradaily variability (Van Someren et al., 1999). *Relative Amplitude (RA)* describes the ratio between the activity levels during the most active 10-hour period and least active 5-hour period of a given day, averaged across all recorded days. Lower RA indicates lower levels of daytime activity and/or disturbed sleep. *Interdaily Stability (IS)* is a measure of how closely activity levels follow consistent 24-hour daily patterns between days, with higher values suggesting a regular daily rhythm and lower values indicating more variation in wake times or activity levels across recorded days. *Intradaily Variability (IV)* describes how fragmented the daily rhythm is within a given 24-hour period, averaged across all recorded days. Higher values suggest disturbed sleep or periods of inactivity during the daytime. Cosinor analysis was used to derive *Acrophase (Phase)* which describes the timing of peak activity within a 24-hour period, averaged across all recorded days. *Mean Sleep Duration* is the number of

hours spent sleeping within the sleep window, averaged across all wear days, whilst *Mean Sleep Efficiency* is the ratio of time spent sleeping within the sleep window, with higher values suggesting less disturbed sleep. Further information regarding the derivation of mean sleep duration and efficiency can be found in chapter 2.

4.2.4 Lifestyle and demographic measures

Baseline assessment included the collection of demographic and lifestyle measures including age, sex, and easting and northing coordinates of home location (to 1km resolution). Ethnicity was converted into a binary variable of 'white' and 'non-white' due to small numbers of participants with non-white ethnicities (Lyall et al., 2018). Educational attainment was condensed into 5 categories: incomplete ('none of the above'), compulsory ('O levels/GCSEs' or 'CSEs or equivalent'), continued ('A levels/AS levels or equivalent'), college ('NVQ or HND or HNC or equivalent' or 'Other professional qualifications') and university ('College or University degree'). Smoking and alcohol use status were both categorised into never, previous, or current. Townsend deprivation scores were derived from the participants' postcode of residence at the time of the assessment and assigned to quintile group based on the 2011 census analysis (Yousaf & Bonsall, 2017a). Body-mass index (BMI) was calculated from the height and weight measurements that were taken during the baseline assessments.

4.2.5 Statistical analysis

Demographic and lifestyle measures were compared across the 5 participant groups (controls, UM, BD, rMD and sMD) using one-way ANOVA (continuous) or Pearson's chi-squared tests (categorical). Multiple R-squared (continuous) or Cramer's V (categorical) are reported for effect size of each comparison. Correlation coefficients are reported for continuous variables. Median, interquartile range, minimum, maximum and outliers for rest-activity measures were calculated for each participant group, as were mean rest-activity values by season.

Participants were split into season of accelerometer wear based on the date that they started wearing the accelerometer: spring (start date in March, April or May), summer (start date

in June, July or August), autumn (start date in September, October or November), winter (start date in December, January, February). Within each season, group differences for individual rest-activity measures were examined using multivariable logistic regression models, one for each control group and mood disorder group combination (control & UM, control & BD, control & rMD and control & sMD). This resulted in 24 group comparisons for each season (96 comparisons in total). Each multivariable logistic regression model was adjusted for age, sex, Townsend deprivation score, education level, ethnicity, smoking status, alcohol status and easting co-ordinate as covariates. RA, IS and sleep efficiency were inverted so that an increased score reflected a less favourable outcome, for consistency with all other measures.

All statistical analyses were performed using R version 3.6.1 (R Core Team 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.). False Discovery Rate (FDR) correction was subsequently applied to the probability values of the multivariable logistic regression models and the acceptable FDR was defined as < 0.05.

4.3 Results

4.3.1 Demographic comparisons

Statistically significant group differences existed across most demographic measures, but the effect sizes were negligible, except for sex which exhibited a small effect size (Table 4.1). Whilst most mood disorder groups had a higher proportion of female participants when compared to the control group, the UM group had a higher proportion of male participants. The UM group were also more likely to have completed university level education than both other mood disorder groups and the control group. Mood disorder groups were on average younger, had higher Townsend scores, higher BMI scores and were more likely to be current smokers than the control group. BD and rMD groups were more likely to have stopped consuming alcohol than the UM, sMD and control groups.

Season of actigraph wear was distributed similarly for all groups, with a higher proportion of participants taking part in the summer and autumn months and decreased participation in the winter and spring months. There was no difference in north-south distribution of participants across the groups, however the BD group lived further west on average than the other groups. Whilst the Easting and Northing statistics are useful in evaluating this data set, the UK Biobank accelerometer study did exclude the Northwest region for a large part of the project due to potential participant burden, as these participants had been involved in trials for new UK Biobank projects (Doherty et al., 2017). Easting and Northing are therefore not an accurate representation of the true geographical distribution of these groups.

Table 4-1: Descriptive statistics of demographic variables.

	Mean (SD) / Percentage (N)					Test Statistic	p value	Effect Size
	Ctrl	UM	BD	rMD	sMD			
Age	63.68 (7.60)	60.62 (7.95)	58.77 (7.53)	60.71 (7.67)	61.36 (7.51)	418.738	<0.001	0.040
Sex	-	-	-	-	-	2024.866	<0.001	0.224
Female % (N)	48.04 (11,864)	41.03 (192)	62.02 (1,158)	70.99 (6,485)	72.62 (3,143)	-	-	-
Male % (N)	51.96 (12,832)	58.97 (276)	37.98 (709)	29.01 (2,650)	27.38 (1,185)	-	-	-
Townsend Score	-2.04 (2.61)	-1.93 (2.74)	-1.12 (3.10)	-1.35 (2.97)	-1.79 (2.74)	138.100	<0.001	0.014
Education	-	-	-	-	-	108.043	<0.001	0.026
Incomplete % (N)	8.50 (2,100)	3.42 (16)	6.59 (123)	6.58 (601)	5.85 (253)	-	-	-
Compulsory % (N)	14.55 (3,594)	11.75 (55)	14.62 (273)	14.79 (1,351)	14.72 (637)	-	-	-
Continued % (N)	6.10 (1,506)	6.41 (30)	6.32 (118)	6.96 (636)	6.52 (282)	-	-	-
College % (N)	26.20 (6,470)	26.28 (123)	28.44 (531)	24.74 (2,260)	27.66 (1,197)	-	-	-
University % (N)	44.65 (11,026)	52.14 (244)	44.03 (822)	46.93 (4,287)	45.26 (1,959)	-	-	-
Ethnicity	-	-	-	-	-	8.797	0.066	0.015
White % (N)	97.08 (23,975)	95.94 (449)	96.46 (1,801)	97.03 (8,864)	97.60 (4,224)	-	-	-
Non-white % (N)	2.92 (721)	4.06 (19)	3.54 (66)	2.97 (271)	2.40 (104)	-	-	-
BMI	26.35 (4.12)	27.19 (4.09)	27.57 (5.09)	26.91 (4.96)	26.81 (4.76)	57.360	<0.001	0.006
BMI (>=18.5 & <30)	*25.05 (2.60)*	*25.64 (2.53)*	*25.23 (2.69)*	*24.94 (2.71)*	*24.96 (2.67)*	*9.967*	*<0.001*	*0.001*
Smoking Status	-	-	-	-	-	472.680	<0.001	0.076
Never % (N)	61.94 (15,275)	58.71 (273)	49.36 (920)	53.62 (4,892)	55.82 (2,411)	-	-	-

Previous % (N)	33.58 (8,281)	36.34 (169)	37.71 (703)	38.8 (3,540)	37.62 (1,625)	-	-	-
Current % (N)	4.47 (1,103)	4.95 (23)	12.93 (241)	7.57 (691)	6.55 (283)	-	-	-
Alcohol Status	-	-	-	-	-	193.597	<0.001	0.049
Never % (N)	3.14 (776)	2.56 (12)	2.57 (48)	2.93 (268)	2.43 (105)	-	-	-
Previous % (N)	2.22 (548)	2.35 (11)	6.21 (116)	4.48 (409)	3.28 (142)	-	-	-
Current % (N)	94.64 (23,372)	95.09 (445)	91.22 (1,703)	92.59 (8,458)	94.29 (4,081)	-	-	-
Actigraph Season	-	-	-	-	-	31.707	0.002	0.016
Spring % (N)	22.06 (5,448)	21.58 (101)	23.94 (447)	22.16 (2,024)	20.91 (905)	-	-	-
Summer % (N)	27.00 (6,668)	25.00 (117)	26.41 (493)	28.08 (2,565)	28.05 (1,214)	-	-	-
Autumn % (N)	28.12 (6,945)	33.33 (156)	28.39 (530)	28.56 (2,609)	29.97 (1,297)	-	-	-
Winter % (N)	22.82 (5,635)	20.09 (94)	21.26 (397)	21.20 (1,937)	21.07 (912)	-	-	-
Northing	331178 (153208)	319968 (152852)	331913 (150153)	328634 (150887)	332936 (150687)	1.325	0.258	0.000
Easting	422370 (68144)	422581 (67437)	417680 (68809)	423574 (68432)	422727 (66751)	2.940	0.019	0.000

4.3.2 Descriptive analysis

Linear correlations between the continuous numerical measures in this analysis, including the sleep-wake variables of interest and demographic covariates, are shown in Figure 4.1. The highest levels of correlation were between the sleep-wake variables themselves, with sleep efficiency and sleep duration being the most strongly correlated ($r^2 = 0.564$). Increase in sleep efficiency was also correlated with better RA ($r^2 = 0.358$), and better IS with better IV ($r^2 = -0.392$), though the strength of these correlations is low. Increases in age were weakly associated with earlier phase ($r^2 = -0.186$) and better IS ($r^2 = 0.262$), whilst an increased BMI was associated with poorer RA ($r^2 = -0.272$). Correlations between demographic covariates were low except for Northing and Easting ($r^2 = -0.452$) which could adversely affect the stability of a regression model. Given that Northing was not significantly different between groups (Table 4.1), this was removed from the regression models as a covariate.

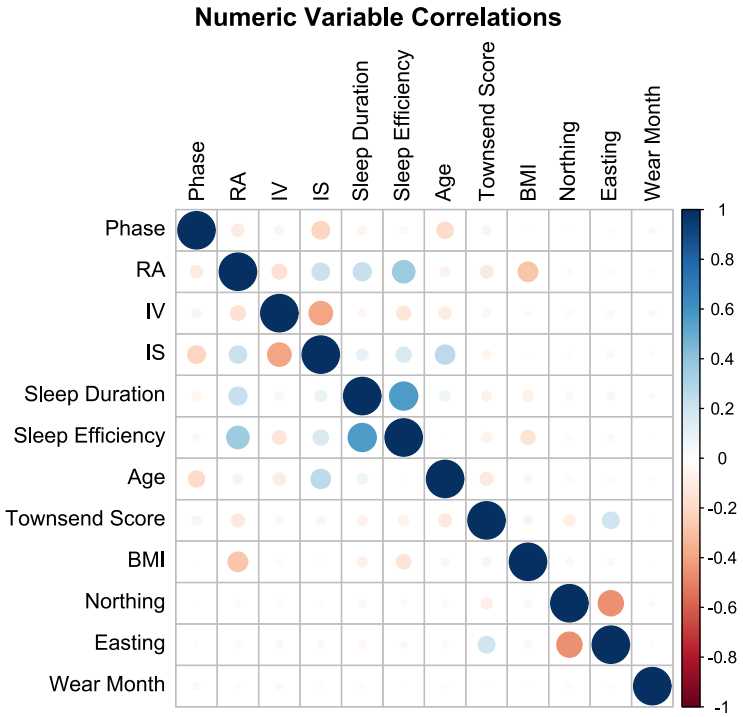

Figure 4.1: Linear correlations between sleep-wake and demographic variables.

Correlations for each combination of the linear sleep-wake and demographic variables are shown. The colour and size of each circle represents the size and magnitude of the correlation coefficient.

Boxplots were used to visually assess the distribution of the rest-activity variables for each mood disorder group (Figure 4.2). For each measure the distributions were broadly similar across all groups, and outliers were common. There was some indication of possible group differences, such as poorer RA and a delayed phase in the BD group; and shorter sleep duration and poorer sleep efficiency in the UM group.

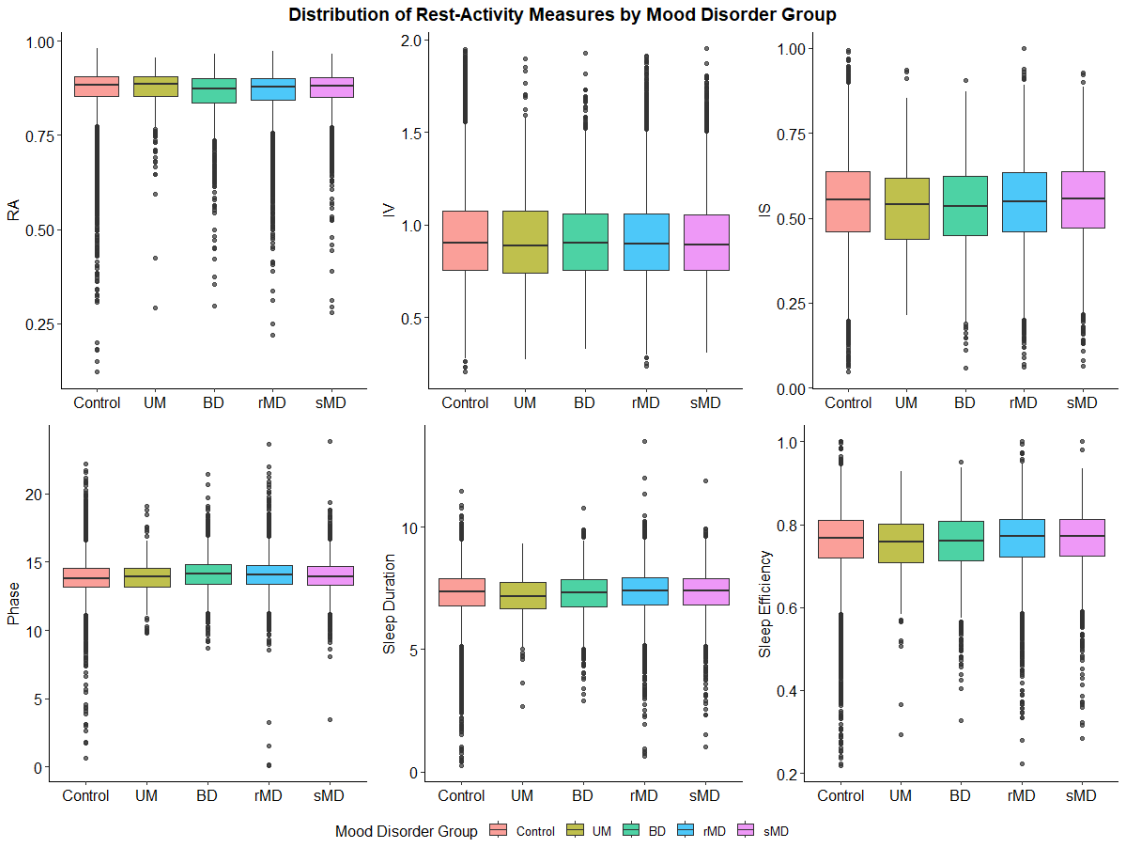

Figure 4.2: Boxplot of rest-activity measures by mood disorder group.

Median, interquartile range, minimum, maximum and outliers are shown for each rest-activity variable, grouped by probable mood disorder.

Seasonal averages for the rest-activity measures suggested some seasonality may exist (Figure 4.3). Both the control and mood disorder groups showed seasonal trends in all measured rest-activity measures, but there were notable diversions from these trends for some season-group combinations. The seasonal pattern of IV was inverted in BD when compared to the other groups. The control group had a more prominent difference in IV in winter than other groups. Groups that include mania (UM and BD) exhibited a delayed phase in winter whilst depression-only groups (rMD and sMD) showed little

phase difference, and the control group had an advanced phase. The UM group demonstrated better sleep efficiency in spring when compared to other groups.

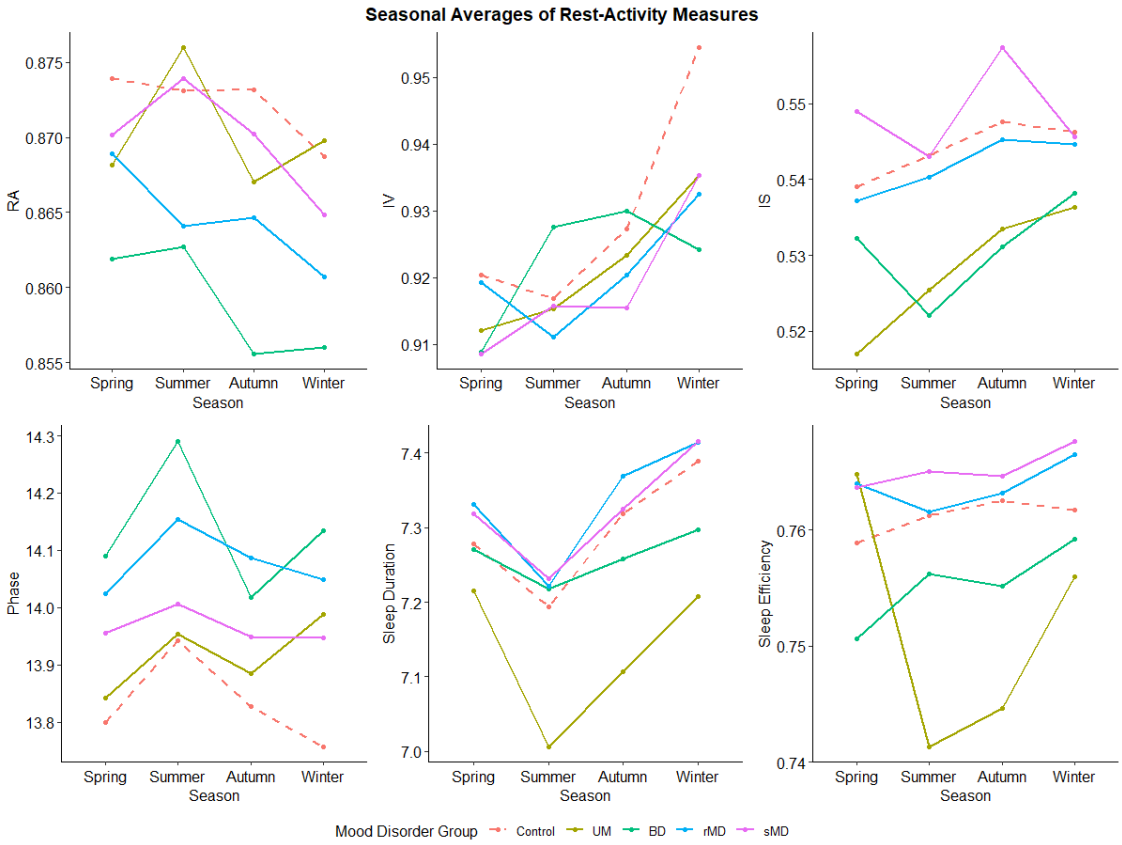

Figure 4.3: Rest-activity averages across seasons.

Mean rest-activity values are shown for each season, with each line/colour representing a single mood disorder group.

4.3.3 Statistical comparisons of rest-activity measures

Multivariable logistic regression models were used to compare rest-activity measures between the control group and each mood disorder group (Figure 4.4; full results in Supplementary Table S4.1). No statistically significant differences were found between the UM group and control group after multiple comparisons corrections, but there was a trend towards better rest-activity rhythms in UM, including better IV. The BD, rMD and sMD groups exhibited significantly different profiles of rest-activity when compared to controls, which was characterised by delayed phase, poorer RA, longer sleep duration and poorer sleep efficiency. However, they did also show better IV and a trend towards better IS.

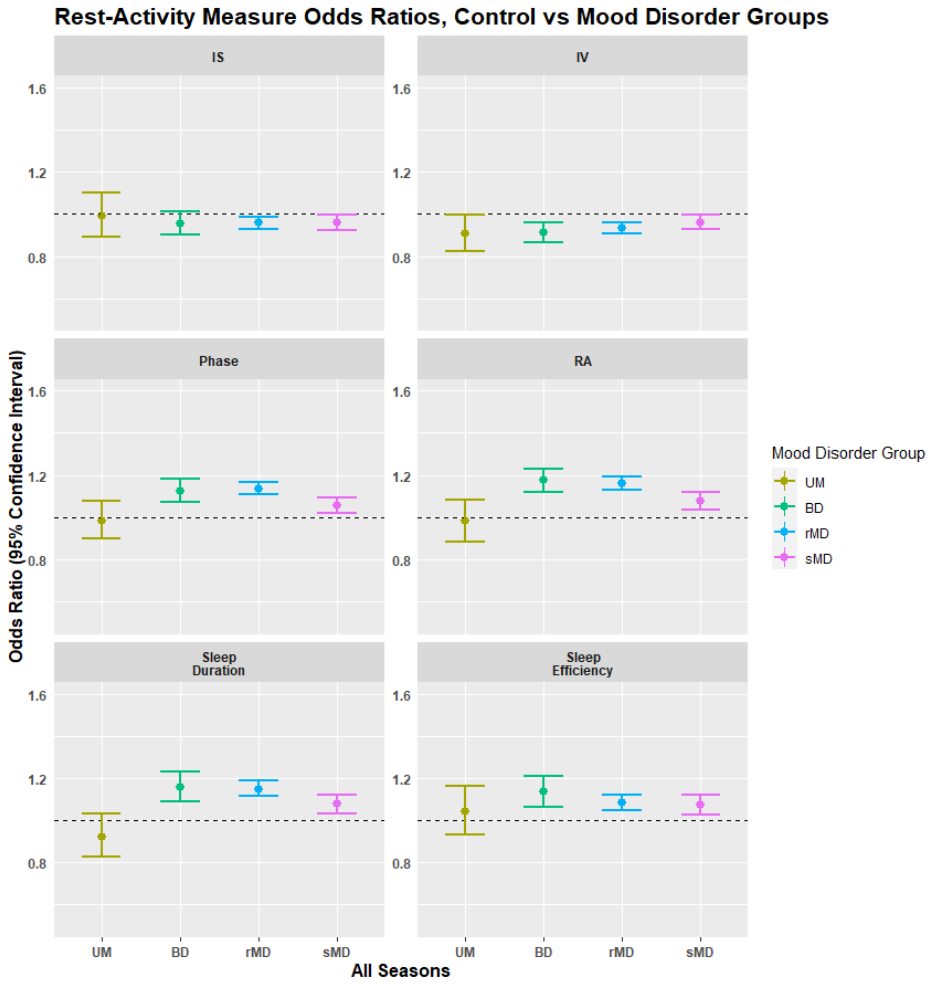

Figure 4.4: Group comparisons of rest-activity measures.

Odds ratios and 95% confidence intervals are shown for each mood disorder group compared to the control group.

As the descriptive analysis highlighted potential seasonal differences in rest-activity measures, these were investigated using further multinomial logistic regression models (Figure 4.5; full results in Supplementary Table S4.1). Rest-activity measures were compared between each mood disorder group and the control group, and this was repeated across each season. After adjusting for demographic covariates and correcting for multiple comparisons, poor IS and IV appeared to have a protective effect in some seasons. Poorer IS in autumn was associated with a reduced risk of being in the sMD group when compared to controls; whilst poorer IV was associated reduced risk of being in the rMD group in summer, and both the rMD and BD groups in winter.

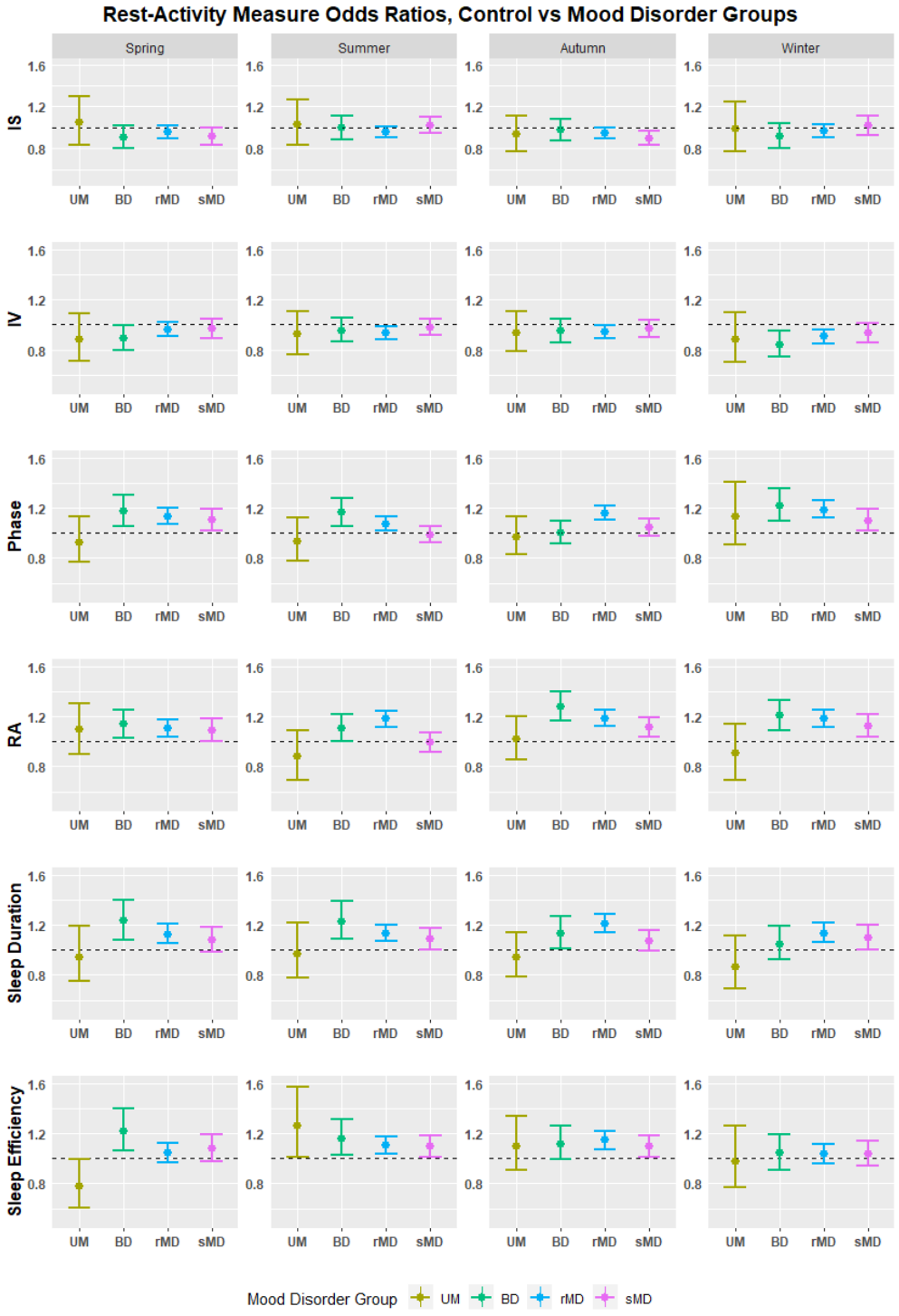

Figure 4.5: Group comparisons of rest-activity measures by season.

Odds ratios and 95% confidence intervals are shown for each mood disorder group compared to the control group. These are shown for each rest-activity measure and split by season of actigraph wear.

A delayed phase was broadly associated with a higher risk of probable mood disorder, but this relationship appears to have some seasonality. Delayed phase was associated with an increased risk of rMD across all seasons, but only in spring for sMD, and

spring, summer, and winter for BD. Similarly, poorer RA was associated with an increased risk of rMD across all seasons, but only in autumn and winter for sMD, and spring, autumn, and winter for BD.

Longer mean sleep duration was associated with increased risk of probable rMD across all seasons but was only associated with an increased risk of probable BD in spring and summer. Poor sleep efficiency appeared to have a seasonal pattern and was associated with increased risk of probable BD in spring. Poor sleep efficiency was also associated with an increased risk of probable rMD in summer and autumn. Probable UM was associated with better sleep efficiency in spring and poor sleep efficiency in summer when compared to the control group, but this finding was not statistically significant after correcting for multiple comparisons, possibly due to this group having a smaller number of participants than other groups.

4.4 Discussion

4.4.1 Summary

After controlling for relevant demographic and lifestyle factors and correcting for multiple comparisons, the UM group did not differ significantly from the control group on any of the rest-activity measures investigated. The remaining mood disorder groups (BD, rMD and sMD) exhibited different profiles of rest-activity when compared to controls. They had a delayed phase, poorer RA, longer sleep duration and poorer sleep efficiency. However, they did also show better IV and a trend towards better IS.

The results of this analysis also highlight the impact that season can have on these rest-activity differences; when models were applied to season-specific subgroups, seasonal differences existed for one or more mood disorder groups in all measured rest-activity variables. This includes the UM group who exhibited sleep efficiency differences in spring and summer; however, these differences were not significant after multiple comparisons corrections, possibly due to small sample size.

We hypothesised that depression groups (BD, rMD and sMD) would have increased adverse rest-activity outcomes in winter. There were more statistically significant differences in total between the depression groups and control group in winter (spring = 8, summer = 7, autumn = 7, winter = 9), but individually the BD group had a peak of differences in spring (5), rMD in summer (5) and sMD in autumn and winter (2). The increase in spring for the BD group does support our second hypothesis; that groups with probable mania symptoms (UM and BD) may have increased rest-activity differences in non-winter months. With larger sample sizes, this could be further supported by the UM group differences that were identified in spring and summer.

4.4.2 Rest-activity profiles

The finding that depression groups show widespread adverse rest-activity differences supports previous research in this area (Germain & Kupfer, 2008; Lyall et al., 2018).

These differences appear to be transdiagnostic in nature, as probable mood disorder group was based on lifetime symptoms and there was a considerable gap between the mental health questionnaire and the accelerometer study (Wainberg et al., 2021). Differences were more frequent and of a greater magnitude for severe depression groups (rMD and BD) in comparison to the less severe depression group (sMD), further supporting the link between circadian desynchrony and depression outcomes (Hasler et al., 2010).

IV (fragmentation of 24-hour rest-activity rhythm within a day) and IS (stability of rest-activity rhythm across days) are typically poorer in depression groups within the literature (Krafty et al., 2019; Luik et al., 2015). An unanticipated finding in this analysis is that IV and IS showed a trend of being more stable in the mood disorder groups when compared to controls. Better IV and IS have previously been associated with schizophrenia, however these results were not replicated in a depression group (Berle et al., 2010). IV quantifies the frequency and extent of transitions between rest and activity periods on an hourly basis, with better IV usually being interpreted as participants having less daytime napping and/or nocturnal activity (Gonçalves et al., 2014). However, RA in the depression groups was also found to be poorer which contradicts this finding by suggesting lower levels of daytime activity and/or nocturnal activity. Furthermore, the reduced sleep efficiency in these groups also supports an increase in nocturnal activity. Given this combination of findings, it is likely that depression groups are exhibiting reduced hour-to-hour variability in activity levels, but that this is comprised of both chronic restless sleeping patterns and low activity levels throughout the day. This is consistent with common depression symptoms including reduced motivation and social withdrawal (Saeb et al., 2015; Vallée et al., 2011). The trend towards better IS in depression groups suggests that this pattern of rest-activity may persist with little day-to-day variation as opposed to the control group that may exhibit more variation in daily routine. Whilst higher IS is typically considered favourable, IS has been found to increase with age as a reflection of a more rigid daily routine and can indicate reduced social interaction and work-related activity which is not necessarily a positive outcome (Li et al., 2021). These results highlight the importance of considering multiple measures in research related to rest-activity rhythms.

Whilst these findings generally support disrupted rest-activity rhythms in mood disorder groups, the UM group exhibited similar rest-activity patterns to the control group in the non-seasonal analysis. There was a trend towards shorter sleep duration and better IV, but neither were statistically significant after correction for multiple comparisons. This finding may be due to the small sample size of the UM group in comparison to other mood disorder groups. Alternatively, as the UM group are primarily comprised of participants that meet the criteria for less severe hypomania, this finding may support the link between circadian desynchrony and symptom severity (Hasler et al., 2010).

4.4.3 Seasonal rest-activity profiles

As hypothesised, seasonal differences in rest-activity rhythms exist in these mood disorder groups. The protective effect of IV was most apparent for the more severe depression groups (rMD and BD) in winter, though the trend persisted during other seasons. In the non-seasonal analysis, better IV coincided with poorer RA and sleep efficiency, suggesting that the reduced hour-to-hour variability was being driven by disturbed sleep and daytime inactivity. However, in the seasonal analysis we found that better IV in winter coincided with poorer RA but not poorer sleep efficiency, suggesting that this is being influenced by reduced daytime activity only. Increased sedentary activity in winter months is pervasive in adult populations, and this finding suggests that individuals with a lifetime history of depression are at increased risk of this seasonal behaviour difference (O'Connell et al., 2014). Whilst IV appears to have a seasonal effect, lower RA in depression groups was pervasive across all seasons. The exception to this was the sMD group who showed no difference from controls in RA during summer, suggesting that people with milder symptom profiles may be at reduced risk of sedentary behaviour during this season.

The phase shift hypothesis associates later onset of morning light with a delayed phase and increase in depressive symptoms (Lewy et al., 2007). Here, accelerometer-derived phase was significantly delayed for winter and spring depression groups (BD, rMD and sMD) when compared to the winter and spring control groups, supporting the relationship between late light onset and phase delay. However, the phase delay also existed in seasons with earlier light onset for the more severe depression groups (rMD

and BD). For rMD, phase delay was persistent across all season groups, whilst the BD group had a normalised phase in autumn and the sMD group had a normalised phase in summer and autumn. This may reflect group differences in chronotype (morningness vs eveningness) which exists independent of season. Mania symptoms are reportedly at their highest in spring, summer, and autumn months and this is hypothesised to be driven by phase advances caused by earlier onset morning light during these seasons (Moon et al., 2016). Whilst not statistically significant, the UM group did trend towards an advanced phase in the spring and summer seasons. Sleep efficiency, however, was significantly better for the spring UM group and this was followed by significantly worse sleep efficiency in the summer UM group. Better sleep efficiency has previously been linked to an increased number of mania symptoms, with the authors hypothesising that excessive goal-orientated behaviour may be causing individuals to leave bed during awakenings (Eidelman et al., 2010).

Disturbances in sleep efficiency and increases in sleep duration are common symptoms in depression and appear to have a seasonal pattern; however, these findings suggest these deficits are less common in winter. The BD group exhibited poor sleep efficiency in spring and summer, whilst the rMD group exhibited poor sleep efficiency in summer and autumn. Sleep duration was longer in the rMD group across all seasons, but only longer during spring, summer, and winter for the BD group. Lack of sleep differences in winter may be due to increased time in bed during winter months within healthy adult populations, as supported by the seasonal rest-activity averages in the exploratory analysis (O'Connell et al., 2014).

4.4.4 Limitations

We acknowledge some limitations to this work. The UK Biobank cohort are not an accurate representation of the UK population as they are older, healthier, more affluent, and less ethnically diverse than the general population. Probable mood disorder categories were based on self-report measures as opposed to formal clinical assessments; while this allows for a larger sample, it also means there is potential recall bias and increased heterogeneity in these groups. Whilst the criteria used to define probable mood disorder groups here are not identical to those defined in the DSM-5 or ICD-11 classifications, the groups were constructed to proxy these as closely as

possible within the limitations of the questionnaire data. The UM group were considerably smaller than other mood disorder groups which may have reduced the ability to detect differences between UM and control groups.

The cross-sectional nature of the UK Biobank means self-report and accelerometer measures were collected at varying times between 2013 and 2017. As the accelerometer data was collected during one season for each participant, seasonal differences may be partly reflecting group differences between participants recruited in different seasons. UK Biobank are currently collecting repeat accelerometer data for a subset of participants in a different season to their initial accelerometer study. When available, future studies may focus on this repeat data to eliminate any between-group differences.

4.5 Conclusions

Here we have characterised rest-activity profiles in probable mood disorder groups as compared to controls, and further characterised seasonal differences between probable mood disorder groups and controls. Probable mood disorder groups with depression symptoms (BD, rMD and sMD) exhibit rest-activity differences when compared to controls. These groups have a delayed phase, poorer RA, longer sleep duration and poorer sleep efficiency. Better IV and a trend towards better IS may be indicative of low daytime activity levels in these groups. Furthermore, we find seasonal rest-activity differences between probable mood disorder and control groups. These seasonal patterns are generally similar across depression groups and are more prevalent during winter, except for sleep measures which align more closely with controls over winter months. The UM group exhibit less rest-activity disruption than depression groups, but seasonal analysis reveals that sleep efficiency differences in spring and summer may be a distinctive pattern within this group. We conclude that these findings may have implications for further research and clinical assessment of these mood disorder groups.

Chapter 5 Come rain or shine: investigating the use of meteorological and rest-activity factors in mood disorder discrimination.

5.1 Introduction

Mood disorders, including depressive and bipolar disorders, are prevalent but are estimated to go undetected in approximately 50% of cases (James et al., 2018; Kohn et al., 2004). These disorders are associated with a reduced quality of life and have been identified as a leading cause of disability worldwide (McIntyre et al., 2020). Early detection is associated with improved outcomes and treatment response, making the removal of barriers to diagnosis a key priority in this research area (Berk et al., 2011). One promising target is the increased public use of wearables which can provide objective measurement of physiological and behavioural measures that are associated with mood disorders.

Mood disorders are frequently associated with disturbances in both subjective and objectively measured rest-activity rhythms. In studies involving objective measures from accelerometers, depression and bipolar disorder have been associated with increased sedentary behaviour, reduced moderate-to-vigorous physical activity (MVPA) and decreased relative amplitude (del Pozo Cruz et al., 2020; Helgadóttir et al., 2015; Ku et al., 2018; Lyall et al., 2018). Sleep differences include increased time-in-bed, changes to sleep efficiency and duration (both increases and decreases have been reported), later bedtime and later wake-time (Husu et al., 2022; Sangha et al., 2022; Wainberg et al., 2021).

Whilst the use of accelerometers can mitigate the potential bias associated with subjective questionnaires, there are limitations with this methodology. For example, accelerometer studies that take place over a short period of time and are only administered once per participant are not robust to environmental factors. In geographic regions with variable seasonal climates (China and Chicago, USA) accelerometer studies that included meteorological measures found that increased sedentary time is associated with increased rainfall and reduced daylight hours (Feinglass et al., 2011; Wen et al., 2019). Ambient air temperature may also affect physical activity in older adults, though there appear to be geographic differences in this relationship; increased sedentary time is associated with temperatures below -7℃ and above 23℃ in Chicago (USA), step count reductions were observed in temperatures above 17℃ in Nakanojo (Japan), but higher temperatures up to 22℃ were associated with an increased step count

in Tayside (Scotland) (Feinglass et al., 2011; Togo et al., 2005; Witham et al., 2014). Non-accelerometer studies have found an increase in reported depressive symptoms for areas with higher wind speed, humidity, snowfall, rainfall, cloud cover and lower atmospheric pressure, whilst protective effects have been found in areas with higher levels of sunshine (Brazienė et al., 2022; O'Hare et al., 2016; Xu et al., 2020). These meteorological differences have been found to impact both reported mood disorder symptoms and objectively measured rest-activity rhythms individually, but little is known about the combined relationship of these measures. The only study, to our knowledge, that included all three factors found that higher minimum daily temperature and longer day length were associated with higher activity levels, and depression status did not modify this relationship (Witham et al., 2014).

This analysis aimed to address this research gap by assessing whether meteorological and accelerometer-derived rest-activity measures can differentiate between mood disorder and control groups with greater accuracy than accelerometer-derived rest-activity measures alone in a large UK-based cohort of middle-aged and elderly adults. As there are many available measures, and we hypothesised that these relationships may be non-linear, this was investigated using a machine learning methodology.

5.2 Methods

5.2.1 Participants

UK Biobank contains data collected from approximately 500,000 volunteers aged 37-73 at recruitment. Participants completed a range of tests and questionnaires which were administered at 22 testing centres across the UK from 2006 onwards. The data includes questionnaires relating to mental health, sleep, and activity, as well as wrist-worn accelerometer measures for a subset of almost 100,000 participants. Further information about the collection protocol is detailed in chapter 2 and elsewhere (UK Biobank, 2007).

5.2.2 Probable mood disorder criteria

Probable mood disorder was determined based on answers to an online mental health questionnaire (MHQ) which was administered to a subset of UK Biobank participants in 2016. For participants who had not taken part in the online MHQ, probable mood disorder was based on answers to the touchscreen MHQ at their most recent assessment centre visit. Both questionnaires are structured similarly; however, in the mania section the online MHQ asks participants to report on 8 mania symptoms whereas the touchscreen MHQ only lists 4 mania symptoms.

Participants were classed as having probable unipolar mania or hypomania (UM) if they reported having experienced at any point in their life a period of elevated mood or irritability lasting at least two days, 3 or more mania related symptoms, an episode duration of 24 hours or more (2 days or more in the touchscreen MHQ) and did not report having experienced depressed feelings or anhedonia lasting 2 or more weeks. They were categorised as probable recurring major depressive disorder (rMD) if they reported depressed feelings or anhedonia lasting 2 or more weeks, 5 or more depression related symptoms, had informed a professional of these symptoms, and reported multiple episodes throughout their lifetime. Alternatively, participants were categorised as having probable single episode major depression (sMD) if they met the criteria for rMD but only reported one episode throughout their lifetime. If a participant met the

criteria for UM (excluding the lack of depression/anhedonia) and either rMD or sMD they were classed as probable bipolar disorder (BD). This criterion mirrors the DSM-5 as closely as possible within the limitations of the questions available. The control group were defined as participants that reported never having a period of elevated mood or irritability lasting at least two days, and never having depressed feelings or anhedonia lasting 2 or more weeks.

5.2.3 Rest-activity outcomes

Subjective measures of rest-activity were obtained at assessment centre visits by multiple-choice questionnaire. Participants reported their average sleep duration, whether they find it difficult to get up in the morning and their chronotype. Objective measures of rest-activity were available for a subset of participants who took part in the accelerometery study. This took place between 2013 and 2016, and participants were provided with an AX3 triaxial accelerometer (Axivity, Newcastle upon Tyne, UK) which was worn on their dominant wrist for up to 7 days. The UK Biobank Accelerometer Expert Working Group conducted data pre-processing and provided acceleration averages in 5-second epochs which are used to derive further rest-activity measures (UK Biobank, 2016). For each day the percentage of acceleration averages that were 50mg or lower, 51mg-100mg, 101mg-150mg, 151mg-200mg and 200mg and above were calculated. The percentage at each activity level was averaged across weekdays and weekends separately, and the variation (standard deviation) was also calculated. At each activity level the difference between weekday average and weekend average was calculated, as well as the difference between weekday and weekend variation. Moderate-and-vigorous-physical activity (MVPA) was defined as a period of 10 minutes where 80% of the acceleration readings were 100mg or above (Sabia et al., 2015). This was calculated for rolling 10-minute windows and the total number of MVPA sessions over the course of the accelerometer wear were calculated (windows that were 10-minutes apart were defined as a new session). Further measures of rest-activity rhythm included relative amplitude, interdaily stability, intradaily variability, mesor, phase, and cosinor amplitude which have previously been derived (chapter 2); and measures of sleep included mean sleep efficiency, mean sleep duration, sleep duration variation, mean sleep midpoint and mean time in bed which have also previously been derived (Jones, van Hees, et al., 2019). In total 39,687 participants had

rest-activity data and met the criteria for a probable mood disorder or control based on the MHQ data.

5.2.4 Seasonal and meteorological measures

Season of accelerometer wear was defined as winter (December, January and February), spring (March, April and May), summer (June, July and August) and autumn (September, October and November) (Trenberth, 1983). Using the HadUK-Grid data from the Centre for Environmental Data Analysis, average rainfall (mm) per week, number of frost days per month and hours of sunshine per month were calculated for participants' home to a resolution of 1 kilometer (Met Office; Hollis, D.; McCarthy, M.; Kendon, M.; Legg, T.; Simpson, 2018). These measures were calculated for the week (or month) of accelerometer wear and the week (or month) prior. Day length was also calculated for each location based on the first day of accelerometer wear. Levels of light at night (LAN) for participants' home were obtained from National Aeronautics and Space Administration satellite data. Additional features targeting the interaction between rest-activity and seasonal measures were also included in seasonal models. The ratio between number of MVPA sessions and each of sun, rain, and frost was calculated, as well as the ratio between average acceleration and sun, rain, and frost.

5.2.5 Demographic measures

Demographic features included age at the time of accelerometer wear, sex, ethnicity, education level, alcohol and smoking status, body mass index (BMI), Townsend deprivation score, and home latitude and longitude. All rest-activity, meteorological and demographic features are listed in Supplementary Table S5.1. Calculated smoking status consisted of smokers, previous smokers, and never smoked, as did alcohol status. Townsend deprivation category was calculated by categorising scores into one of 5 UK-census-calculated quintiles as published here (Yousaf & Bonsall, 2017b). BMI was categorised into <18.5, >=18.5 and <25, >=25 and <30, >=30 and <40, and >=40 based upon Centres for Disease Control and Prevention guidelines; more information can be found here: https://www.cdc.gov/obesity/basics/adult-defining.html.

5.2.6 Machine learning analysis

Participants that had self-reported a severe neuropsychological diagnosis or brain cancer/injury; personality disorder, psychosis, or schizophrenia; sleep apnoea, insomnia or a main job involving shift work were excluded from this analysis. Participants with low quality accelerometery data (flagged by UK Biobank), or accelerometer data that was collected over a daylight savings clock change, were also excluded.

The remaining data (N=29,687) was split into 6 approximately equal groups (N=4,937–4,968), stratified by probable mood disorder category, age (rounded to the nearest 10 years), sex, Townsend deprivation score, season of accelerometer wear, BMI, smoking status and alcohol intake. Of these groups, 5 were used for model training and validation in a 5-fold cross validation design, and 1 was used for model testing and final accuracy reporting. Within the training and validation set, categorical features (sex, alcohol status, smoking status, Townsend deprivation category, BMI category, season of accelerometer wear, LAN status, chronotype, difficulty getting up) were transformed to multiple binary features using one hot encoding. This was then applied to the test data set.

Gradient boosted models are a group of supervised machine learning models in which multiple simple tree-based models are combined iteratively so that new trees reduce the error of the previous trees. As a result, they can handle complex nonlinear relationships and both numerical and categorical data types. Here we use a highly optimised implementation, XGBoost, using the ‘xgboost’ package in R (T. Chen & Guestrin, 2016). XGBoost was used to predict binary outcomes (control vs any mood disorder) using just rest-activity and demographic measures, and then using rest-activity, seasonal and demographic measures to understand whether adding seasonal variables increases model accuracy. Best model parameters were chosen using a grid-search algorithm during the model training and validation stage. Model performance was assessed using the F1 score (the harmonic mean of recall and precision) as this is the most suitable metric for imbalanced classification when false positive and false negative results are of equal importance.

Further individual XGBoost models compared each mood disorder group to controls (UM vs control, BD vs control, rMD vs control and sMD vs control) with and without seasonal and meteorological measures. The model workflow above was repeated for this analysis with an additional step: to account for the large differences in group size between probable mood disorders, the synthetic minority over-sampling technique (SMOTE) algorithm was used to inflate each probable mood disorder group to a sample size matching the control group within the training data sets. This workflow is summarised in Figure 5.1.

All analyses were performed using R version 4.1.1 (R Core Team 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

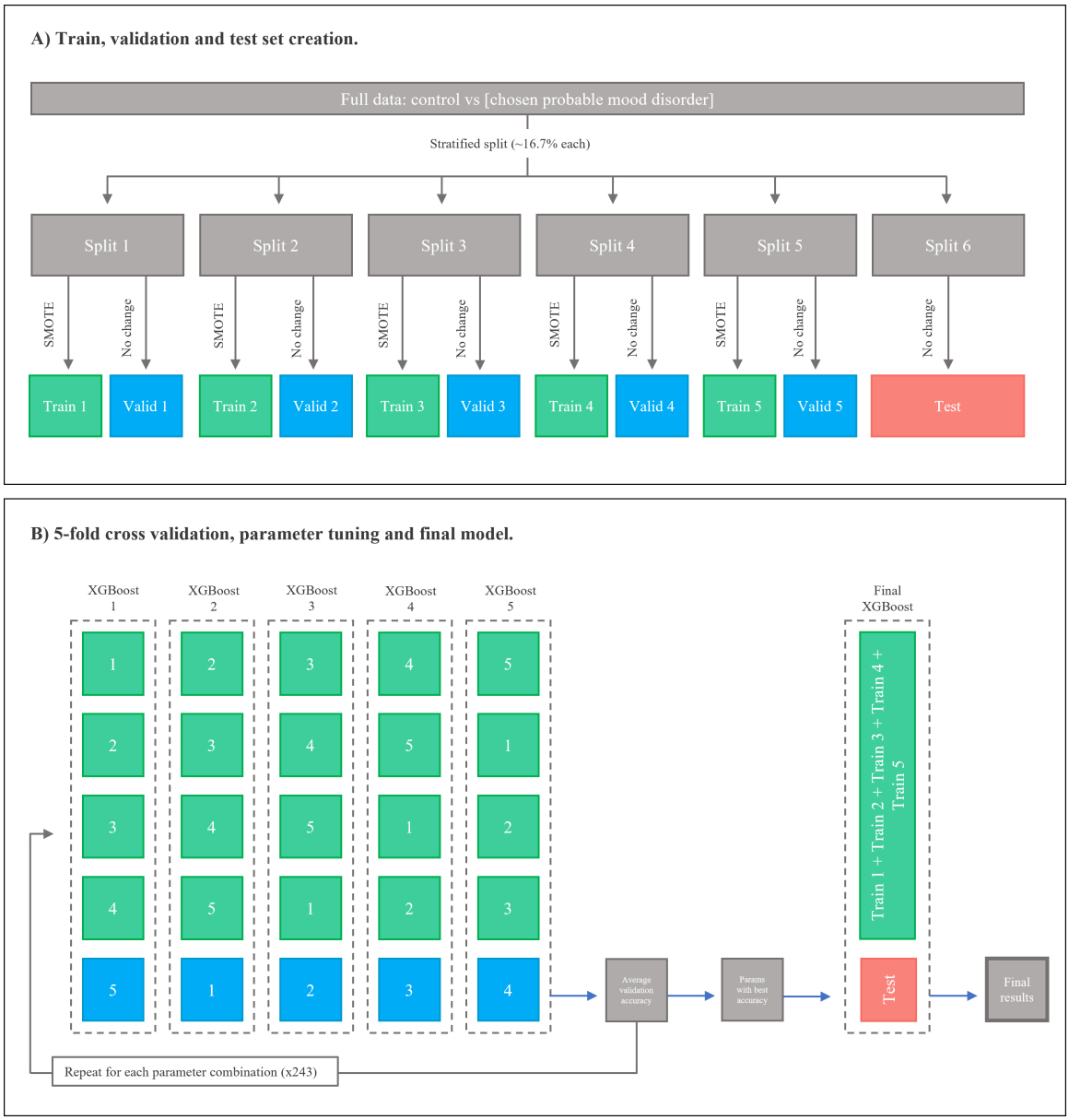

Figure 5.1: Model workflow for individual mood disorder models.

This workflow was repeated with and without seasonal and meteorological data for each mood disorder group: UM, BD, rMD and sMD. The same workflow was used for the 'any mood disorder' analysis except for minority class up-sampling using SMOTE.

5.3 Results

Multiple (N=243) combinations of model hyperparameters were tested using cross-validation for each binary classification XGBoost model and the set of parameters that yielded the lowest mean F1 score was used in the final model. Final model predictions were then applied to each test data set and dichotomised using the standard discrimination cutoff score of 0.5. F1 score and further evaluation metrics were applied to assess model performance (Table 5.1).

5.3.1 All probable mood disorders

The test set accuracy for both the seasonal and non-seasonal model is better than the no information rate (the rate of the largest class; $p < 0.05$), signifying that these are useful models. For both models, approximately 54% of those predicted as being in the mood disorder category were accurate. Of all test-set participants in the mood disorder category, both models accurately identified 63%. Accuracy, precision and F1 score were improved in the seasonal model when compared to the non-seasonal model, but only marginally (accuracy +0.003, precision +0.004, F1 +0.002).

When sub-setting these results by original mood disorder category (UM, BD, rMD and sMD), both the seasonal and non-seasonal model were worse at identifying UM participants compared to all other groups (Figure 5.2). This is likely because UM comprises a small proportion of all probable mood disorder participants (total training and validation sample size: N(UM)=375, N(BD)=1,553, N(rMD)=7,524, N(sMD)=3,557).

Table 5-1: Model parameters and results for the 'all mood disorders' model and 'individual mood disorders' models.

	Model Type	Best Model Parameters	Test Set Mood Disorder N (%)	Test Set Control N (%)	Test Set Accuracy	Test Set Precision	Test Set Recall	Test Set F1
All	Without Seasonal Information	(eta = 0.3, max_depth = 3, colsample_bytree = 1.0, subsample = 0.6, min_child_weight = 10, nrounds = 201)	2,626 (39.6%)	4,000 (60.4%)	0.644	0.544	0.625	0.582
	With Seasonal Information	(eta = 0.3, max_depth = 3, colsample_bytree = 1.0, subsample = 0.6, min_child_weight = 5, nrounds = 154)			0.647	0.548	0.625	0.584
	Difference	-	-	-	*0.003*	*0.004*	*0.000*	*0.002*
UM	Without Seasonal Information	(eta = 0.1, max_depth = 6, colsample_bytree = 1.0, subsample = 1.0, min_child_weight = 10, nrounds = 104)	72 (1.8%)	4,031 (98.2%)	0.876	0.015	0.097	0.027
	With Seasonal Information	(eta = 0.3, max_depth = 3, colsample_bytree = 0.6, subsample = 0.8, min_child_weight = 1, nrounds = 18)			0.766	0.020	0.264	0.038
	Difference	-	-	-	*-0.110*	*0.005*	*0.167*	*0.011*
BD	Without Seasonal Information	(eta = 0.1, max_depth = 3, colsample_bytree = 0.8, subsample = 0.6, min_child_weight = 5, nrounds = 23)	316 (7.3%)	4,009 (92.7%)	0.680	0.142	0.674	0.235

	With Seasonal Information	(eta = 0.1, max_depth = 3, colsample_bytree = 1.0, subsample = 1.0, min_child_weight = 10, nrounds = 52)			0.754	0.157	0.541	0.243
	Difference	-	-	-	*0.074*	*0.015*	*-0.133*	*0.008*
rMD	Without Seasonal Information	(eta = 0.3, max_depth = 3, colsample_bytree = 0.6, subsample = 0.6, min_child_weight = 5, nrounds = 31)	1,492 (27.1%)	4,014 (72.9%)	0.671	0.423	0.589	0.492
	With Seasonal Information	(eta = 0.3, max_depth = 6, colsample_bytree = 0.6, subsample = 0.8, min_child_weight = 5, nrounds = 17)			0.671	0.422	0.579	0.488
	Difference	-	-	-	*0.000*	*-0.001*	*-0.010*	*-0.004*
sMD	Without Seasonal Information	(eta = 0.3, max_depth = 3, colsample_bytree = 1.0, subsample = 0.6, min_child_weight = 5, nrounds = 14)	715 (15.1%)	4,026 (84.9%)	0.671	0.237	0.530	0.327
	With Seasonal Information	(eta = 0.3, max_depth = 3, colsample_bytree = 0.6, subsample = 0.6, min_child_weight = 5, nrounds = 23)			0.697	0.243	0.478	0.322
	Difference	-	-	-	*0.026*	*0.006*	*-0.052*	*-0.005*

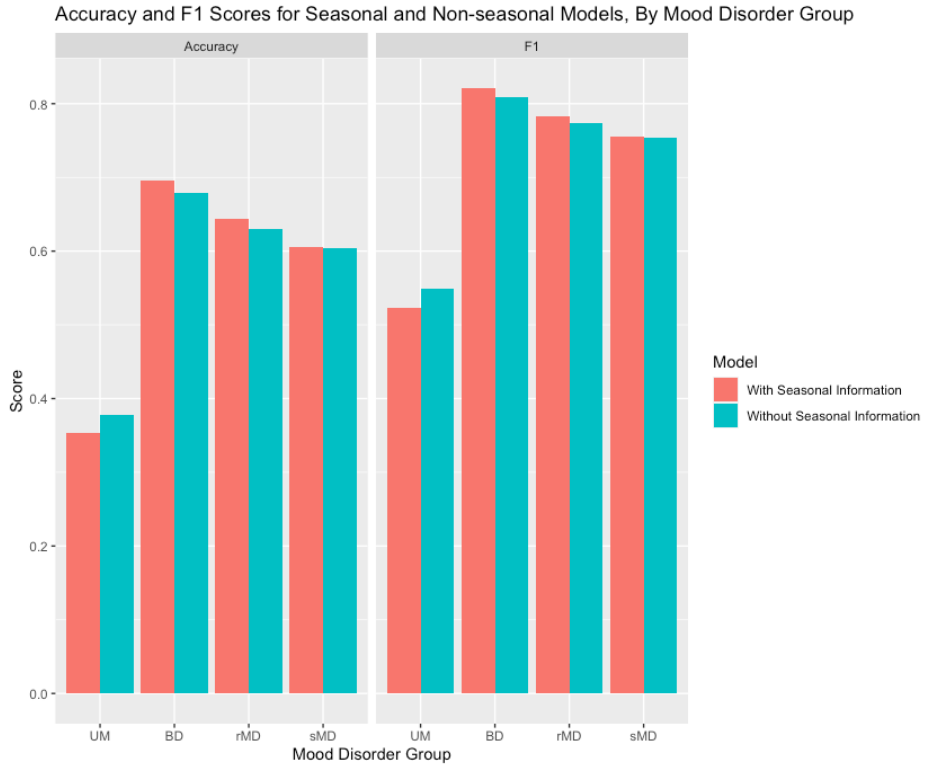

Figure 5.2: Accuracy and F1 scores for seasonal and non-seasonal models, by mood disorder group.

Results from the 'all mood disorder' seasonal and non-seasonal models broken down by underlying mood disorder category (UM, BD, rMD, sMD). The accuracy and F1 scores for UM are visibly much lower than other mood disorder groups.

5.3.2 Individual probable mood disorders

The 'all probable mood disorder' model results suggest model performance can be improved by inclusion of seasonal variables. Individual mood disorder models were used to investigate whether accuracy varies across the mood disorders, and to assess whether the addition of seasonal variables affects accuracy differently for each mood disorder. The addition of seasonal variables resulted in improved F1 scores for the UM and BD groups, but not the rMD and sMD groups (Table 5.1). Test set accuracy does not surpass the no information rate for any individual mood disorder model, and F1 scores are modest. Model performance is poorest in the UM group, further supporting the findings of the 'all probable mood disorder' model.

Feature importance can be assessed within XGBoost using Gain, a metric used to infer a feature's contribution to the model accuracy. Figure 5.3 shows the total gain grouped by variable category (accelerometery, demographic, seasonal and sleep questionnaire) for the individual mood disorder models. The UM model is less dependent on sleep questionnaire and demographic variables, but more dependent on accelerometery and seasonal variables than the other models. The BD and rMD models are similar to each other, however BD uses objective rest-activity measures (accelerometery) more than subjective measures (sleep questionnaire), whilst rMD does the opposite. The sMD model is also similar to the BD model but is more dependent on seasonal measures at the expense of sleep questionnaire measures.

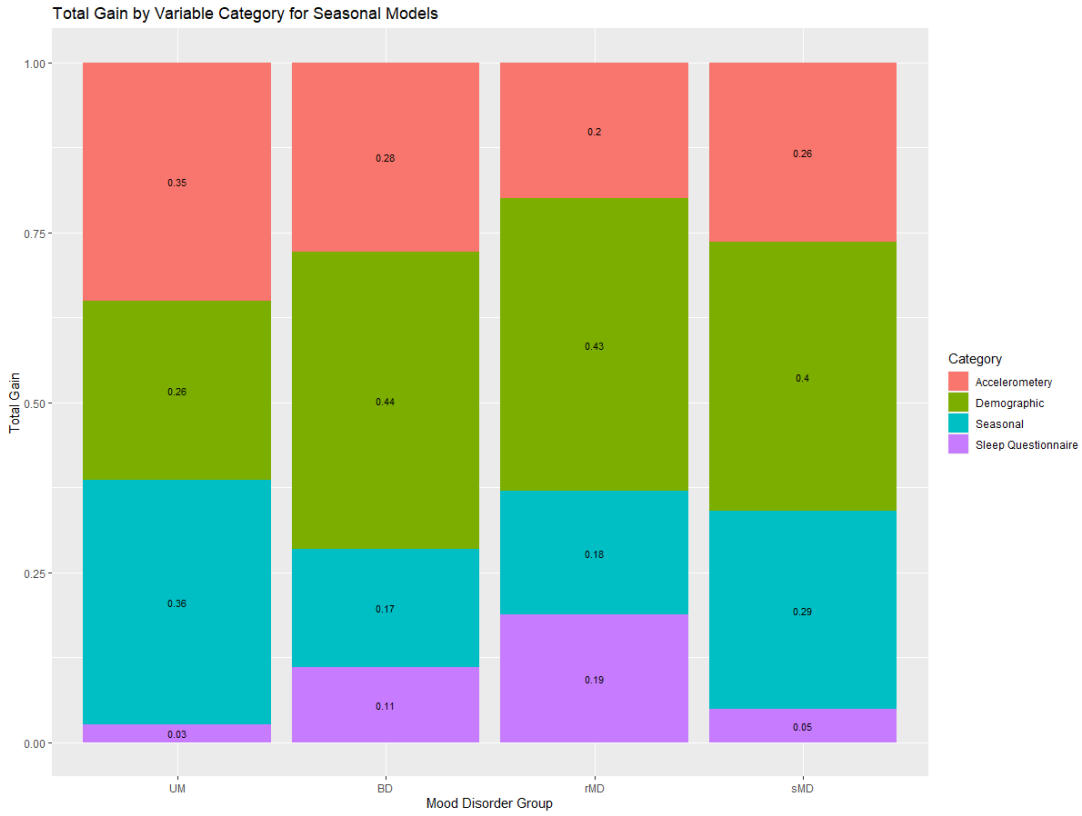

Figure 5.3: Total gain by variable category for seasonal models.

Model gain categorised by variable category for each of the seasonal individual mood disorder models.

Individual variables with high gain scores, and therefore high importance, across multiple models included age, sex, latitude, reported difficulty getting up in the morning, MVPA, MVPA/rainfall ratio, and mean acceleration/rainfall ratio. The UM

model also placed high importance on the average rainfall for the current and previous month. Mood disorder group differences for these variables are reported in Supplementary Table S5.2, however only age, sex, difficulty getting up in the morning, and MVPA periods are statistically significant, and all but sex have a very small effect size (<0.2). This suggests that the role of these measures within the models may be complex, including non-linearity and interactions with other variables.

5.4 Discussion

5.4.1 Discriminatory value

This analysis aimed to assess whether accelerometer-derived rest-activity measures and meteorological measures can be combined to accurately differentiate between mood disorder and control groups. Here, a machine learning model was able to identify probable mood disorder and control participants with better accuracy than a naïve model. The inclusion of seasonal and meteorological measures improved accuracy, precision and F1 score when compared to a model that included only rest-activity measures. Whilst these improvements were small, they highlight the potential of using publicly available data to augment and enhance existing datasets in mood disorder research. Due to unbalanced group sizes, it is difficult to compare model performance with other studies, but similar F1 scores have been reported for depression classification elsewhere (Choi et al., 2021). Better F1 scores have been reported in another accelerometery study of depression; however, this included smaller participant numbers and significantly longer accelerometer recording time, suggesting that longer wear-time may result in better discriminatory ability (Masud et al., 2020).

Discrimination between the probable UM group and control group was lower than all other mood disorder groups in both the ‘all probable mood disorder’ model and the individual mood disorder models. Given the low number of participants in this group, it is unclear whether this is due to lack of available data or a high degree of overlap between UM and control rest-activity behaviours. Previous research in this area suggests that mean acceleration and intradaily variability are higher in UM compared to healthy control groups, but these differences may be too small to discriminate between groups (chapter 3, Sangha et al., 2022). Model performance for probable BD, rMD and sMD is better than UM, suggesting that rest-activity differences may be more pronounced in these groups. This supports the findings that depressive and bipolar disorders are associated with transdiagnostic sleep differences, however the effect sizes of these differences are small which may explain why these models have relatively poor discriminatory performance (Lyall et al., 2018; Wainberg et al., 2021).

5.4.2 Seasonal and meteorological differences

Whilst model performance is not high enough to be of clinical importance, the results do provide insight into the relationship between individual mood disorders, seasonal and meteorological factors, and rest-activity rhythms. Both BD and UM models improved with the addition of seasonal and meteorological variables suggesting that they may be more affected by these factors than the depression groups. This finding could be the result of rest-activity rhythms bring mediated by meteorological factors in BD and UM, or meteorological factors directly contributing to the development of BD and UM symptoms. The latter has been explored within the literature, but the findings are mixed. A recurring finding is that higher ambient air temperatures and increased sunlight exposure may contribute to episode onset in bipolar disorders (Montes et al., 2021). Whilst sunlight related variables were not found to be of high importance in the BD and UM models, it is possible that they were useful within the models. Additionally, sunlight hours are provided monthly within HadUK-Grid and it is therefore possible that the measurement resolution was not high enough to identify a relationship. Investigations into the relationship between major depression and meteorological factors are sparse but there is currently no evidence of an association, and the findings of this analysis partially support this (Huibers et al., 2010).

Analysis of variables with high model importance found that the ratio of average activity levels and rainfall was important for all individual mood disorder models, suggesting that meteorological factors may indeed be contributing to altered rest-activity rhythms in mood disorders. Studies investigating rainfall and mood disorders have not identified any relationship, but they usually focus on severe mood disorder cases involving hospital admissions (Carney et al., 1988; Peck, 1990). Rainfall has been associated with reduced objectively measured activity in healthy older adults, and so further research is required to understand if mood disorder participants show more extreme reductions in activity than control groups, or less extreme due to already having reduced baseline activity levels (Albrecht et al., 2020). Rainfall is measured weekly whilst frost and sunshine are measured monthly in HadUK-Grid, therefore it is unclear if other meteorological-rest-activity relationships exist at this resolution.

Both the identification of this potential behavioural phenotype (ratio of activity level to rainfall) and the indication that meteorological factors are important in BD and UM are novel findings, and further research to increase our understanding of these relationships is desirable.

5.4.3 Limitations

We acknowledge some limitations to this work. The UK Biobank cohort are biased towards an older, healthier, more affluent, and less ethnically diverse sample than the general population. Probable mood disorder categories were based on self-report measures as opposed to formal clinical assessments, which allows for large sample sizes but also increases potential recall bias. This also results in increased heterogeneity in these groups which may be obscuring potential findings. Self-report and accelerometer measures were collected at varying times between 2013 and 2017. Medication status was not included in this analysis.

Whilst it is good practice to address the imbalance between mood disorder and control group numbers using SMOTE, there are some disadvantages to this methodology including potentially obscuring group differences by synthetically producing observations that overlap both groups. It is also difficult to interpret the variable relationships in XGBoost models. Despite these limitations, these findings make a novel contribution to this research area.

5.5 Conclusions

Here we find that accelerometer-derived rest-activity measures and meteorological measures can differentiate between probable mood disorder and control groups better than a naïve model. The inclusion of seasonal and meteorological information marginally increases model performance for UM and BD, suggesting that they are affected by seasonal changes more than rMD and sMD. The UM group were the most difficult to differentiate from the control group, highlighting the importance of group size when investigating heterogenous mood disorder populations. The results suggest that the relationship between rainfall and average activity levels may be altered in mood disorders compared to control groups, and further research would be beneficial to better understand this relationship. We conclude that future research considering rest-activity rhythms in mood disorders may benefit from the inclusion of seasonal and meteorological measures.

Chapter 6 Multidomain comparisons across symptom-derived mood disorder clusters in UK Biobank.

6.1 Introduction

'Mood disorders' describe a range of psychiatric disorders that have a depressive component (feelings of sadness or anhedonia), a mania component (feeling unusually excited or irritable), or both. These include major depressive disorder (MDD) in which people experience one or more periods of depression symptoms, and bipolar disorders (BD) in which most experience both periods of depression symptoms and periods of mania symptoms. There is also some evidence to support a third category, unipolar mania (UM), in which people experience periods of mania symptoms but no depression symptoms (Angst & Grobler, 2015; Sangha et al., 2022). These categories are well embedded in leading psychiatric classification systems (DSM-5 and ICD-11) but have high levels of symptom overlap (Allsopp et al., 2019). They also exhibit similar comorbidities, with MDD and BD both being associated with increased risk of anxiety disorders, self-harm and psychosis related symptoms (Dilsaver et al., 1997; Schaffer et al., 2012). The overlap between these disorders makes diagnosis of discrete categories difficult for clinicians and researchers, ultimately affecting patients and their treatment.

From a research perspective, the heterogeneity of these groups has resulted in pervasive mixed findings across many domains when attempting to find distinguishing biomarkers or phenotypes. One possible explanation is that the current mood disorder groups are not valid representations, and these disorders would be better explained by dimensional and symptom-based models (Conway et al., 2019; Cuthbert, 2015). One study investigating the symptom profiles of a large group of depressed outpatients found 1,030 unique profiles, most of which contained five or less participants, highlighting the extent of differences within the depression population (Fried & Nesse, 2015). Recently, network analysis studies have provided some insight into the relationship between different psychopathologies at the symptom level by including a wide range of symptoms rather than focusing on common symptoms of a specific disorder. These results suggest that depression and mania symptoms may be related via specific "bridge" symptoms (Weintraub et al., 2020), and that there are pathways linking psychosis to depression, and suicidality to depression (van Rooijen et al., 2017). Furthermore, findings suggest depression and anxiety symptoms are highly related and do not form distinct clusters (McElroy et al., 2018). These findings suggest that anxiety, psychosis, and suicidal thoughts may be important co-occurring symptoms to consider when assessing mood disorders. A limitation of network analysis is that it is not well

optimised for ordinal data use, which is common in psychiatric questionnaire data, resulting in information loss as these variables are transformed to alternative data types (Borsboom et al., 2021).

Unsupervised machine learning approaches are useful for finding relationships and structure within data where the 'real' outcome is unknown. Hierarchical clustering is one commonly used technique within this category. In agglomerative hierarchical clustering, each observation begins as its own cluster and then clusters are joined together based on how similar they are. This process is repeated until a hierarchy of clusters is formed. This method therefore allows for both identification of clusters within the data, but also the ability to identify clusters at various levels of the hierarchy (Murtagh & Contreras, 2012). Hierarchical clustering has successfully been used on mood disorder symptom data to validate the sensitivity of the Bipolar Depression Rating Scale (Chang et al., 2009), assess symptom clusters in the Hamilton Rating Scale for Depression (Wang et al., 2021), and to find subtypes of depression (Beijers et al., 2019). Whilst these findings were based on single diagnostic categories, hierarchical clustering has also been used on a transdiagnostic sample of people with major depression, posttraumatic stress disorder, panic disorder, and generalised anxiety disorder (Grisanzio et al., 2018). Six clusters were found based upon symptoms, and those six clusters were then found to differ significantly on several cognition measures.

Large datasets such as UK Biobank provide an opportunity to explore relationships between outcomes of interest and measures taken from multiple domains (Sudlow et al., 2015). Factors that persist regardless of mood state are of particular interest in mood disorder research as they may lead to biomarkers and behavioural phenotypes that can distinguish between these disorders. Neuroimaging, cognition, rest-activity rhythms, and genetics are four such promising domains, but few studies have examined these areas concurrently. Brain structures have been implicated in emotion, cognitive processing, and motivation, and are therefore a key target in neuroimaging studies of mood disorders. Replicated evidence of decreased hippocampus volumes have been found in both MDD and BD, as have reductions in thalamus volume in BD (Hibar et al., 2016; Schmaal et al., 2016). There is also some evidence for differences in other subcortical structures including reduced caudate volume in MDD and BD when compared to healthy control groups, and volumetric differences between MDD and BD

in the accumbens and amygdala (Han et al., 2019; Sacchet et al., 2015). Polygenic risk scores provide a method of comparing the genetic loading of an outcome across unrelated samples and have been suggested as a useful addition in discriminatory models (Liebers et al., 2020). Poorer cognitive test performance has been found in mood disorder groups and across a variety of symptom profiles (Lyall et al., 2019; Zhu et al., 2019). Circadian disruption has been indicated in mood disorder groups and has also been linked to reduced cognitive performance (Lyall et al., 2018).

This analysis aims to identify naturally occurring clusters within a large sample of probable mood disorder (PMD) participants from UK Biobank based upon answers to a broad range of mental health questions. Neuroimaging, cognition, circadian and genetic measures will then be compared across both the resulting clusters and original PMD groups to assess whether the clusters provide novel findings.

6.2 Methods

6.2.1 Participants

We used data from UK Biobank which comprises of a range of data on health, lifestyle, demographic, and physical characteristics from over 502,000 UK residents. These tests and questionnaires were administered at testing centres across the UK from 2006 onwards. Between 2016 and 2017 participants were invited to participate in an online follow-up mental health questionnaire. 158,853 participants fully completed this questionnaire which included questions related to depression, mania, anxiety, self-harm behaviours and unusual/psychotic experiences.

Probable patient groups were identified using the online MHQ criteria described in chapter 2, which approximates the DSM-5 criteria as well as possible within the limits of the available questions. 42,210 participants met the criteria for one of the following mood disorders: probable single episode major depression (N=11,086), probable recurrent major depression (N=22,921), probable bipolar disorder (N=4,933), probable mania/hypomania with subthreshold depression (N=2,046) and probable unipolar mania/hypomania (N=1,224). These participants formed the data set for the clustering analysis, with the clustering algorithm being blind to the original mood disorder labels.

6.2.2 Clustering measures

Clusters for the 42,210 participants with probable mood disorders (PMD) were identified based on a wide range of variables selected from the follow-up mental health questionnaire (Supplementary Table S6.1). This included measures relevant to the mood disorder categories (depression and mania) and mental health questions that have high comorbidity with these mood disorders (anxiety, self-harm, unusual/psychotic experiences).

A total of 14 reported depression measures were included in the clustering analysis mostly relating to the worst episode of depression experienced. These were: duration of

worst episode of depression, number of episodes of depression, fraction of day impacted, level of impact on normal roles, hypersomnia, insomnia, early waking, difficulty concentrating, increased tiredness, feelings of worthlessness, and weight changes. Number of episodes was categorised into an ordinal variable with the following levels: none, one-episode, multiple episodes (where a participant reported more than one but not 'too many to count'), and too many to count. Weight change was split into 4 binary variables: no change, weight increased, weight decreased, and weight both increased and decreased.

Similarly, 10 mania measures related to the worst episode of mania were included. This consisted of duration, severity, increased talkativeness, restlessness, racing thoughts, reduced sleep, increased creativity, increased distraction, increased confidence, and being more active.

Measures of anxiety (N=12) included duration, having multiple worries, how often it was difficult to control the worry, how often it was difficult to stop worrying, level of impact on normal roles, increased worry, reduced concentration, increased tiredness, difficulty sleeping, feeling restless, feeling irritable, and having tense/sore muscles. Duration was bucketed into none, seven days or less, more than seven days but less than 32 days, 32 days or more, and life-long anxiety.

Two measures of self-harm were used in this analysis; whether the participant had ever contemplated self-harm and the reported number of times they had self-harmed. Four measures of unusual or psychotic experiences were also included. These were the number of times the participant had believed an un-real conspiracy theory against themselves, believed in un-real communications or signs, heard an un-real voice, and had an un-real vision. For all measures 'prefer not to answer', 'do not know' or non-response were grouped into the 'no symptom' category.

6.2.3 Clustering analysis

Both hierarchical and k-means clustering techniques were initially investigated, but hierarchical clustering was chosen for the final analysis as the structure better represented the complexity and overlap between these mood disorder groups and allowed insight into the relatedness of these clusters to each other. The sample was split into a training group containing 75% of participants (N=31,659), and a test group containing 25% of participants (N=10,551) so that stability of clusters could be assessed. Within the training and test groups Gower's distance metric was calculated for all possible pairs of observations as this metric allows for both binary and ordinal variables (Gower, 1971). Agglomerative hierarchical clustering was then applied to each group using the 'complete linkage' method. The optimal number of clusters and information about cluster validity were obtained numerically using Dunn's distance metric and Silhouette scores. External cluster validation was done by comparing the resulting clusters to the PMD groups. Cluster meanings at various levels of the hierarchical cluster structure were assessed using group comparisons of the individual input variables (mental health questions). This was done using one-way ANOVA for continuous numeric variables and Pearson's chi-squared test for categorical variables.

6.2.4 Multidomain comparisons

UK Biobank contains measures related to a wide range of domains including neuroimaging, cognition, genetics, and rest-activity rhythms. Based on previous literature, measures identified as being of interest in these mood disorder groups were compared across both the resulting clusters and the original PMD groups.

6.2.4.1 Neuroimaging measures

Left and right subcortical volumes (accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus) were derived from T1-weighted structural images acquired by UK Biobank. Further information about the imaging protocol and derivation of the imaging derived phenotypes (IDPs) can be found at https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf. All IDPs were firstly residualised to account for differences in total intracranial volume, table position and head position (x, y and z). Z-Scores were calculated for the resulting residualised

measures across all available imaging data (regardless of mood disorder status, N=39,678). A total of 5,131 participants had valid subcortical volume data and met the criteria for the cluster analysis.

6.2.4.2 Cognitive tests

A battery of cognitive tests was administered at the time of the MRI visit. The seven cognitive tests included in this analysis are described in further detail below. Numerical memory and prospective memory were not included due to poor reliability (Lyall et al., 2019). Z-Scores were calculated for each test across all available cognitive test data. The sample size of those with valid cognitive test and cluster data is reported for each test below.

Matrix Completion: In this 15-item test participants are provided with a grid pattern with a missing piece and then must choose the option that completes the grid. The score is the number of correct answers (N=2,596).

6-Pairs Matching: In this visual memory task participants are shown an arrangement of six pairs of cards. The card values are then hidden, and participants are asked to identify the card pairs. The score is the number of errors (N=4,293). For this analysis the score was inverted (multiplied by -1) so that a higher score reflects better performance.

Reaction Time: In this 12-item test participants were shown sets of two cards on a screen and asked to respond as quickly as possible when the cards match. The score is the mean response time across rounds 5 to 12 (N=4,330). For this analysis the score was inverted (multiplied by -1) so that a higher score reflects better performance.

Verbal/Numerical Reasoning: In this 13-item test participants are asked to answer a range of multiple-choice questions that assess verbal and numerical reasoning. The score is the number of correct answers within 2 minutes (N=4,294). This test is referred to as ‘fluid intelligence’ in UK Biobank but is more accurately described as ‘verbal/numerical reasoning’ (Cox et al., 2019).

Symbol-Digit Substitution: Participants are provided with a key of shapes and their corresponding numbers at the top of the screen. Using the key, they are asked to translate as many shapes to numbers as they can within 60 seconds. The score is the number of correct answers (N=2,600).

Tower Rearranging: In this 18-item task participants were provided with an image of 3 pegs with 3 coloured hoops on them. They were then shown a target arrangement of hoops and asked how many moves would be required to achieve the target. The score is the number of correct answers (N=2,577).

Trail Making (B): In this test the numbers 1-13 and letters A-L are presented in a random arrangement on the screen and participants are asked to select them in the correct order, alternating between numbers and letters (i.e. 1, A, 2, B, 3, C…). The score is the time taken to complete the task (N=2,559). For this analysis the score was inverted (multiplied by -1) so that a higher score reflects better performance.

6.2.4.3 Rest-activity rhythm measures

Sleep and activity were measured subjectively with multiple choice questionnaires during the assessment centre visit, and objectively (for a subset of participants) using accelerometers. Participants who took part in the accelerometer study were provided with an AX3 triaxial accelerometer (Axivity, Newcastle upon Tyne, UK) and asked to wear this on their dominant wrist for 7 days. Data collection took place from 2013 to 2016 and the UK Biobank Accelerometer Expert Working Group conducted data pre-processing (further details are available at http://biobank.ctsu.ox.ac.uk/crystal/docs/PhysicalActivityMonitor.pdf). Measures of sleep and activity were derived from the accelerometery data (Doherty et al., 2017; Jones, van Hees, et al., 2019; Van Someren et al., 1999) and these measures are described below. 12,096 participants were identified as having valid cluster and accelerometery data.

Average Acceleration (AA): describes the average activity level over the measured period. *Relative Amplitude (RA)*: the relative difference between the most active 10-hour period and least active 5-hour period within a day, which is then averaged across all measured days. Values range between 0 and 1 with higher values being preferable and lower values indicating disturbed sleep/lower levels of daytime activity. *Interdaily Stability (IS)*: indicates the level of coupling of activity levels to 24-hour daily patterns. Higher values suggest a regular daily rhythm whereas lower values indicate more variation in wake-up times or activity levels across various days. *Intradaily Variability (IV)*: quantifies the frequency of transitions between active and inactive periods, with higher values suggesting disturbed sleep or periods of inactivity during the daytime. *Mean Sleep Duration*: is the number of hours spent sleeping within the sleep window

(i.e. between going to bed and getting out of bed), averaged across all days of wear. *Mean Sleep Efficiency*: quantifies the amount of time spent sleeping as a proportion of the total sleep window, with higher values suggesting less disturbed sleep.

Subjective measures included chronotype preference which was reduced to three categories: morning (where participants answered 'definitely a morning person'), intermediate ('more morning than evening' and 'more evening than morning') and evening ('definitely an evening person'). Participants were asked to estimate their average sleep duration and this was also reduced to three categories: short (< 7 hours), normal (7-9 hours), and long (> 9 hours). Finally, participants were asked if they have difficulty getting up in the morning and this was dichotomised to yes ('not at all easy' or 'not very easy') and no ('fairly easy', 'very easy'). For all subjective measures there were between 11,410 and 11,480 participants that had answered these questions and had valid cluster data.

6.2.4.4 Polygenic risk scores

Genome-wide association studies (GWAS) test vast numbers of genetic variants across multiple genomes to identify those statistically associated with a specific trait or disease. From this, a polygenic risk score can be calculated to estimate an individual's common genetic liability to that trait or disease (Uffelmann et al., 2021). LDpred (Vilhjálmsson et al., 2015) was used to calculate the schizophrenia, MDD and BD polygenic risk scores. The schizophrenia and BD risk scores were based on summary statistics from a schizophrenia GWAS and a BD GWAS which included an unrelated sample of 33,426 schizophrenia patients, 20,129 BD patients and 54,065 controls (Consortium, 2018). The MDD score was derived from an unrelated MDD GWAS containing 135,458 MDD patients and 344,901 controls (Wray et al., 2018). Participants were excluded if over 10% of genetic data was missing; if self-reported sex and genetic sex did not match; if purported sex chromosome aneuploidy was reported; if the heterozygosity was an outlier and if the score was beyond three standard deviations from the sample mean. Polygenic risk scores were standardised to Z-Scores based on all available PRS data (regardless of mood disorder status, N=423,025). A total of 24,577 participants were included in the cluster analysis and had valid PRS data.

6.2.4.5 Statistical analysis

Multivariable logistic regression models were used to compare variables of interest across clusters or PMD groups. For each of these comparisons the multivariable logistic regression model was adjusted for confounding variables. This included age, sex, Townsend deprivation score, education level (higher education vs no higher education), BMI, smoking status (current smoker vs not), and alcohol status (current alcohol drinker vs not). Ethnicity (white vs non white) was included in the sleep/activity and brain imaging comparisons but not the cognitive test or PRS comparisons as there were not enough non-white participants. The season in which the accelerometer was worn was included as a covariate for the accelerometery comparisons. Psychotropic medication status was not included due to small numbers. False Discovery Rate (FDR) correction was applied to the probability values of the adjusted models and the acceptable FDR was defined as < 0.05. All statistical analyses were performed using R version 4.1.1 (R Core Team 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.).

6.3 Results

6.3.1 Cluster analysis and validation

The results of agglomerative hierarchical clustering with complete linkage are shown in Figure 6.1. This dendrogram shows how observations combine to make each cluster; height (y-axis) describes the level of distance between each cluster (higher values equating to more distance). Visual inspection of the dendrogram suggests that there are two distinct clusters, one of which has two or three more distinct sub-clusters (Figure 6.2). Internal validity scores (the Dunn Index and mean Silhouette Score) suggest that two or three may be the optimal number of total clusters (Figure 6.3).

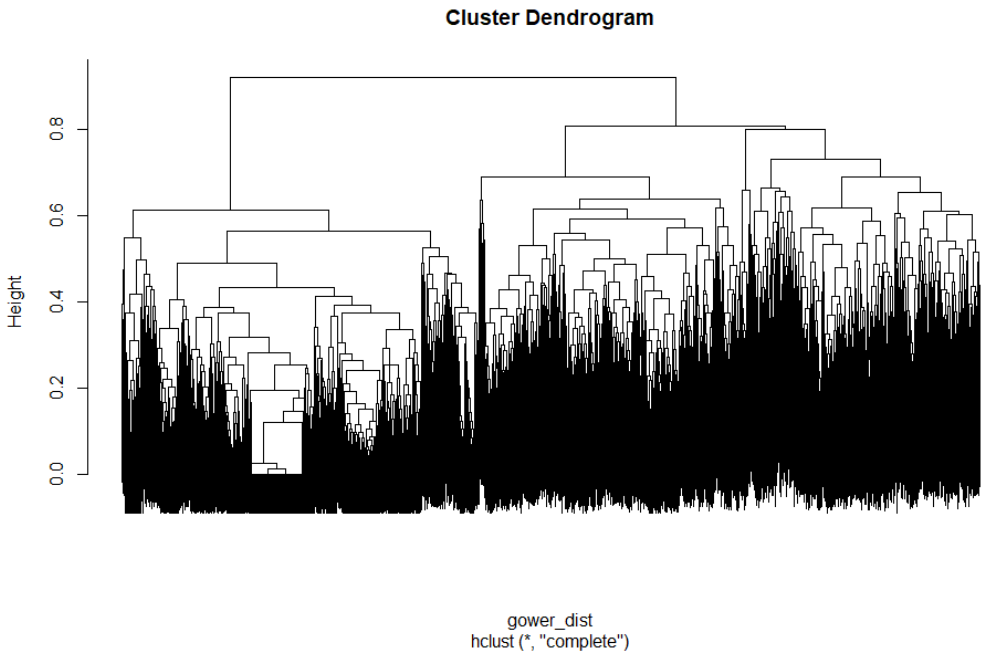

Figure 6.1: Dendrogram of agglomerative hierarchical clustering with complete linkage applied to the training dataset (N=31,659).

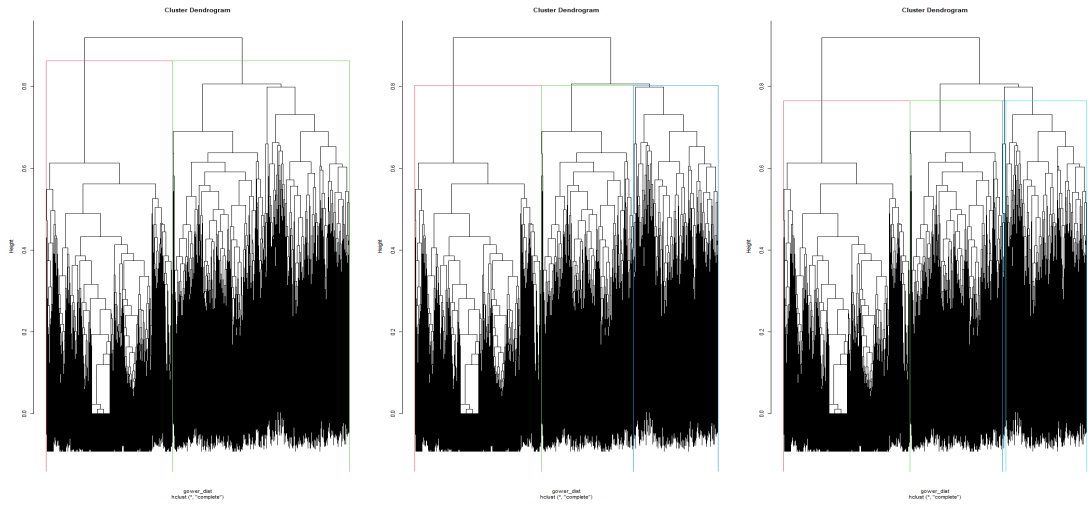

Figure 6.2: Dendrogram when split into 2, 3 and 4 clusters.

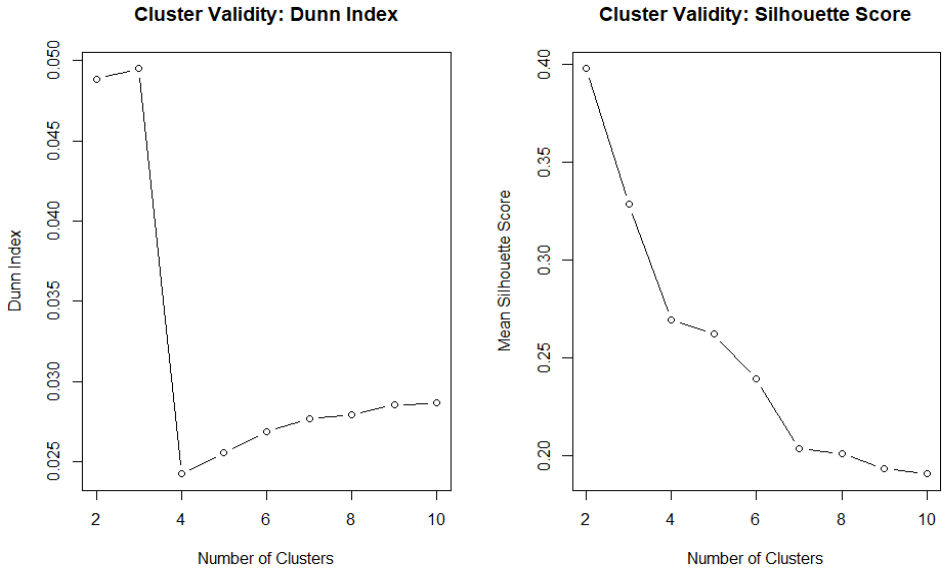

Figure 6.3: Internal validity of clusters assessed by the Dunn Index and mean Silhouette Score.

Clusters were externally validated by comparing them to the pre-defined PMD groups (probable single episode major depression, probable recurrent major depression, probable bipolar disorder, probable mania with subthreshold depression, and probable unipolar mania). This was done for 2, 3 and 4 clusters as the visual inspection of the dendogram and internal cluster validity scores above suggested that the optimal number of clusters is in this range. As shown in Figure 6.4, there appears to be little overlap between cluster groupings and PMD groupings when there are 2 clusters. In the 3-

cluster solution there is overlap with single episode/recurrent major depression and Cluster-2. The 4-cluster solution draws some clear parallels with the PMD groupings; Cluster-2 is more frequent in depression only mood disorders (single episode and recurrent major depression); Cluster-3 is more frequent in mood disorders where both mania and depression symptoms exist (BD and mania with subthreshold depression); and Cluster-4 is more frequent in mania only mood disorders (UM).

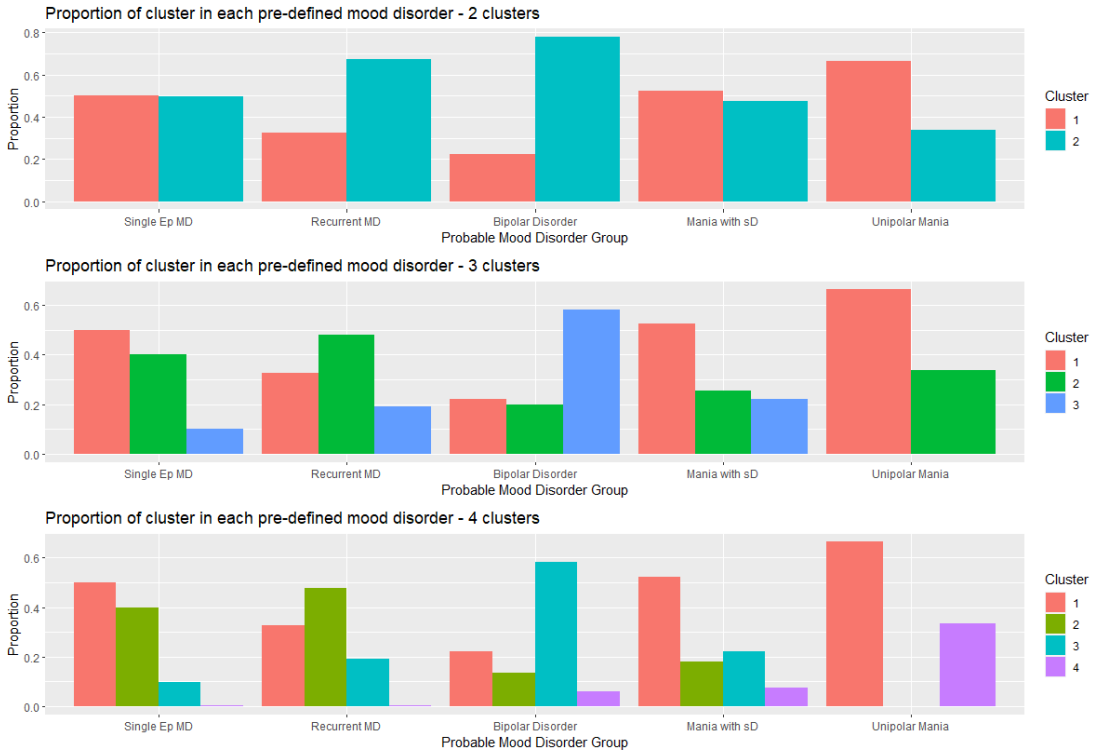

Figure 6.4: Cluster-PMD overlap (2, 3 and 4 cluster solution).

This shows the proportion of cluster belonging for each probable mood disorder group in a 2, 3 and 4 cluster scenario. The 4-cluster solution has clear parallels with the original PMD groups.

To further validate that these clusters are not spurious or unstable, the 4-cluster mood disorder comparison was assessed in both the training and test data set to ensure the same overall pattern persisted. As shown in Figure 6.5, the proportions remain similar across each PMD group suggesting that the clusters are stable and have similar meaning in both data sets.

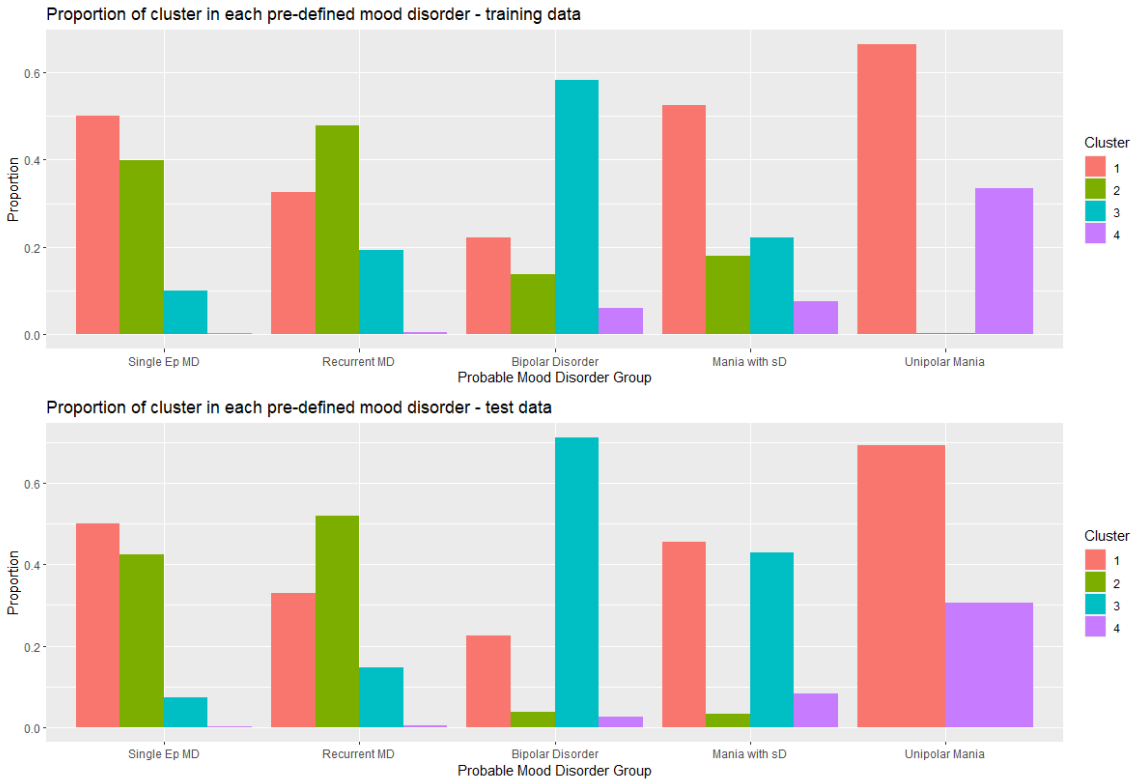

Figure 6.5: Cluster-PMD overlap (training vs test).

This shows the proportion of cluster belonging for each probable mood disorder group in the training and test data set. Similar results suggest good stability of clusters and their meaning.

Whilst the internal validity metrics suggest that 2 or 3 clusters is optimal, external validation suggests that 4 clusters are more applicable to clinical use. However, the lower Dunn index and Silhouette score suggest that these 4 clusters have higher levels of overlap than a 2 or 3 cluster solution.

6.3.2 Cluster meaning

Whilst meaning can be attributed to some of the clusters based on the above results, a full analysis of each cluster's relationship with each input variable (mental health question) allows for a more comprehensive description of cluster meaning. Statistical comparisons for each of these relationships were performed for the 4-cluster solution (Table 6.1), and additionally for the 3-cluster and 2-cluster solution (Supplementary Tables S6.2 and S6.3).

Table 6-1: Statistical analysis of symptoms in 4-cluster solution.

Mental Health Measure	Percentage (N)				Test Statistic	FDR Adjusted p-value	Effect Size
	Cluster-1	Cluster-2	Cluster-3	Cluster-4			
Anxiety: tense/sore muscles	0.0 (<5)	54.4 (4596)	37.8 (3646)	31.0 (126)	8779.977	<0.001	0.527
Anxiety: difficulty concentrating	0.0 (<5)	90.4 (7633)	78.5 (7562)	73.9 (300)	21888.13	<0.001	0.832
Anxiety: irritability	0.1 (<5)	85.4 (7212)	62.3 (6005)	75.4 (306)	17768.468	<0.001	0.749
Anxiety: feeling restless	0.0 (<5)	73.7 (6226)	57.4 (5528)	62.8 (255)	14282.679	<0.001	0.672
Anxiety: sleep problems	0.0 (6)	88.4 (7469)	84.6 (8146)	71.4 (290)	22814.446	<0.001	0.849
Anxiety: multiple worries	0.0 (<5)	88.5 (7475)	76.8 (7394)	76.1 (309)	21018.882	<0.001	0.815
Anxiety: increased worry	0.1 (13)	96.7 (8172)	94.1 (9060)	86.9 (353)	28159.189	<0.001	0.943
Anxiety: feeling tired	0.0 (<5)	82.8 (6994)	72.7 (7004)	47.8 (194)	18644.773	<0.001	0.767
Anxiety: impact on normal roles	-	-	-	-	30108.545	<0.001	0.563
None	99.9 (13154)	1.6 (138)	4.0 (385)	9.9 (40)	-	-	-
A little	0.1 (7)	13.6 (1148)	21.8 (2096)	37.2 (151)	-	-	-
Somewhat	0.0 (<5)	39.1 (3300)	39.8 (3838)	32.3 (131)	-	-	-
A lot	0.1 (8)	45.7 (3861)	34.4 (3314)	20.7 (84)	-	-	-
Anxiety: difficulty controlling worry	-	-	-	-	31232.578	<0.001	0.573
None	99.9 (13154)	0.7 (59)	1.5 (148)	1.5 (6)	-	-	-
Rarely	0.1 (10)	3.8 (325)	6.6 (637)	15.8 (64)	-	-	-
Sometimes	0.1 (8)	35.0 (2957)	41.0 (3946)	48.8 (198)	-	-	-
Often	0.0 (<5)	60.4 (5106)	50.9 (4902)	34.0 (138)	-	-	-
Anxiety: difficulty stopping worry	-	-	-	-	31414.135	<0.001	0.575
None	99.8 (13150)	0.5 (44)	1.3 (130)	2.7 (11)	-	-	-
Rarely	0.1 (17)	4.0 (335)	7.5 (719)	16.7 (68)	-	-	-
Sometimes	0.0 (5)	36.8 (3111)	42.8 (4124)	50.7 (206)	-	-	-

Often	0.0 (<5)	58.7 (4957)	48.4 (4660)	29.8 (121)	-	-	-
Anxiety: duration	-	-	-	-	14972.468	<0.001	0.397
None	88.6 (11671)	21.6 (1823)	22.9 (2208)	54.2 (220)	-	-	-
1 - 7 days	11.3 (1493)	17.5 (1482)	21.6 (2078)	15.0 (61)	-	-	-
8 - 31 days	0.1 (7)	22.3 (1881)	26.4 (2542)	12.8 (52)	-	-	-
> 31 days	0.0 (<5)	17.3 (1464)	14.9 (1440)	7.6 (31)	-	-	-
All rolled into each other	0.0 (<5)	21.3 (1797)	14.2 (1365)	10.3 (42)	-	-	-
Depression: difficulty concentrating	68.9 (9077)	93.2 (7875)	86.8 (8360)	16.0 (65)	3272.196	<0.001	0.322
Depression: feeling tired	68.0 (8954)	92.4 (7802)	85.4 (8229)	14.0 (57)	3158.174	<0.001	0.316
Depression: feeling worthless	48.2 (6343)	81.8 (6913)	72.3 (6963)	20.4 (83)	3228.808	<0.001	0.319
Depression: insomnia	50.3 (6625)	68.6 (5795)	63.5 (6121)	7.1 (29)	1263.794	<0.001	0.200
Depression: hypersomnia	15.7 (2073)	28.1 (2375)	19.7 (1894)	1.5 (6)	584.004	<0.001	0.136
Depression: waking early	50.1 (6600)	69.6 (5881)	67.1 (6463)	4.2 (17)	1590.831	<0.001	0.224
Depression: no weight change	46.0 (6062)	24.5 (2067)	36.5 (3518)	83.3 (338)	1379.366	<0.001	0.209
Depression: weight increase	16.0 (2111)	36.2 (3054)	9.9 (956)	5.7 (23)	2214.022	<0.001	0.264
Depression: weight decrease	32.3 (4249)	31.2 (2634)	45.0 (4338)	10.1 (41)	625.387	<0.001	0.141
Depression: weight fluctuations	5.7 (751)	8.2 (692)	8.5 (821)	1.0 (<5)	105.869	<0.001	0.058
Depression: fraction of day impacted	-	-	-	-	5091.207	<0.001	0.232
None	22.0 (2892)	1.5 (126)	2.4 (232)	72.7 (295)	-	-	-
Less than half	6.0 (784)	3.6 (307)	4.8 (464)	2.5 (10)	-	-	-
About half	9.6 (1262)	8.1 (683)	8.9 (857)	4.7 (19)	-	-	-
Most of the day	40.4 (5321)	46.6 (3936)	46.9 (4516)	11.1 (45)	-	-	-
All day	22.1 (2914)	40.2 (3395)	37.0 (3564)	9.1 (37)	-	-	-
Depression: duration	-	-	-	-	6321.393	<0.001	0.258
None	19.8 (2605)	0.8 (64)	0.9 (84)	71.4 (290)	-	-	-
< 1 month	8.6 (1133)	4.6 (389)	4.5 (429)	2.7 (11)	-	-	-

1 - 3 months	26.4 (3482)	19.4 (1641)	21.9 (2108)	5.9 (24)	-	-	-
3 - 6 months	16.2 (2130)	18.6 (1567)	20.0 (1928)	4.7 (19)	-	-	-
6 - 12 months	12.7 (1667)	19.5 (1643)	21.1 (2035)	4.4 (18)	-	-	-
1 - 2 years	8.7 (1145)	16.5 (1394)	15.7 (1511)	4.2 (17)	-	-	-
> 2 years	7.7 (1011)	20.7 (1749)	16.0 (1538)	6.7 (27)	-	-	-
Depression: impact on normal roles	-	-	-	-	5623.393	<0.001	0.243
None	21.4 (2821)	1.2 (103)	2.3 (222)	74.1 (301)	-	-	-
A little	16.6 (2187)	10.3 (867)	14.8 (1429)	5.7 (23)	-	-	-
Somewhat	31.7 (4179)	29.9 (2523)	36.3 (3492)	9.9 (40)	-	-	-
A lot	30.3 (3986)	58.6 (4954)	46.6 (4490)	10.3 (42)	-	-	-
Depression: N lifetime episodes	-	-	-	-	6369.078	<0.001	0.259
None	19.5 (2566)	1.1 (92)	0.1 (8)	71.4 (290)	-	-	-
One	34.6 (4557)	19.9 (1685)	29.6 (2852)	10.8 (44)	-	-	-
Multiple	27.6 (3634)	39.5 (3338)	39.0 (3755)	10.1 (41)	-	-	-
Too many to count	18.3 (2416)	39.4 (3332)	31.3 (3018)	7.6 (31)	-	-	-
Mania: severe (caused problems)	9.1 (1194)	39.4 (3331)	4.5 (430)	25.4 (103)	4909.174	<0.001	0.394
Mania: more talkative	9.7 (1277)	26.1 (2203)	2.8 (270)	41.9 (170)	2688.950	<0.001	0.291
Mania: more restless	17.9 (2364)	54.6 (4609)	4.6 (440)	71.9 (292)	7027.060	<0.001	0.471
Mania: had racing thoughts	15.3 (2018)	50.6 (4271)	4.3 (415)	67.2 (273)	6591.591	<0.001	0.456
Mania: needed less sleep	8.0 (1058)	19.1 (1617)	1.6 (156)	34.0 (138)	1947.535	<0.001	0.248
Mania: more creative	7.0 (924)	14.4 (1217)	1.6 (152)	24.4 (99)	1230.734	<0.001	0.197
Mania: more distracted	13.3 (1753)	43.9 (3707)	3.4 (328)	52.7 (214)	5507.662	<0.001	0.417
Mania: more confident	7.0 (926)	15.0 (1263)	2.0 (191)	23.6 (96)	1203.749	<0.001	0.195
Mania: more active	11.4 (1496)	26.2 (2217)	2.7 (264)	48.0 (195)	2647.220	<0.001	0.289
Mania: duration	-	-	-	-	8384.430	<0.001	0.297
None	66.4 (8748)	21.6 (1822)	80.9 (7797)	2.5 (10)	-	-	-

< 24 hours	7.6 (1000)	14.7 (1242)	7.6 (733)	4.9 (20)	-	-	-
1 day - 1 week	17.3 (2284)	33.2 (2808)	7.0 (670)	70.4 (286)	-	-	-
> 1 week	8.7 (1141)	30.5 (2575)	4.5 (433)	22.2 (90)	-	-	-
Psychosis: believed conspiracy	0.4 (59)	2.7 (229)	1.1 (104)	0.5 (<5)	219.831	<0.001	0.083
Psychosis: believed communications	0.6 (85)	1.6 (139)	0.7 (65)	1.5 (6)	66.539	<0.001	0.046
Psychosis: believed hearing voices	1.5 (198)	4.4 (368)	2.2 (216)	3.0 (12)	175.577	<0.001	0.074
Psychosis: believed seeing visions	3.0 (401)	6.4 (543)	3.9 (379)	5.7 (23)	149.872	<0.001	0.069
Self-harm: N times self-harmed	-	-	-	-	584.855	<0.001	0.078
None	93.6 (12324)	84.6 (7150)	91.4 (8802)	92.6 (376)	-	-	-
1	3.4 (442)	5.7 (481)	4.3 (416)	3.0 (12)	-	-	-
2	1.3 (165)	2.9 (249)	1.7 (163)	2.2 (9)	-	-	-
>= 3	1.8 (242)	6.7 (567)	2.6 (252)	2.2 (9)	-	-	-
Self-harm: N times contemplated	-	-	-	-	1484.130	<0.001	0.153
No	77.2 (10165)	54.6 (4610)	67.2 (6477)	80.3 (326)	-	-	-
Once	12.2 (1611)	16.4 (1384)	15.4 (1486)	8.4 (34)	-	-	-
More than once	10.6 (1397)	29.0 (2453)	17.3 (1670)	11.3 (46)	-	-	-

Based on the results in Table 6.1, Cluster-1 is primarily characterised by low levels of anxiety, but this group also exhibit decreased weight change, increased self-harm behaviours, and overall lower reporting of mental health symptoms. Cluster-2 exhibit a high level of depression symptoms, but not as high as Cluster-3. Weight loss is more likely to be reported during these episodes, and anxiety is more likely to manifest as tense muscles, sleep problems and tiredness. They are unlikely to report psychotic/unusual experiences, but do report some self-harm behaviours (less than Cluster-3 but more than Cluster-1 and Cluster-4). Cluster-3 exhibit the highest levels of depression symptoms/severity and are more likely to report weight gain during these episodes. They report higher levels of mania symptoms than Cluster-2, but less than Cluster-4, however they report the highest severity of mania, and this is most likely to manifest as distractedness, racing thoughts, and restlessness. They also report the highest level of anxiety, psychosis, and self-harm symptoms. Cluster-4 are characterised by low levels of depression symptoms and high levels of mania symptoms. Anxiety is more likely to manifest as irritability or restlessness. They are least likely to report self-harm behaviours and do report some psychosis (less than Cluster-3 but more than Cluster-2).

Whilst Cluster-2, Cluster-3 and Cluster-4 draw some clear parallels with the original PMD groupings, Cluster-1 is characterised by low anxiety, less severe symptoms, and is highly differentiated from the remaining clusters. Repeating the above external validation process for lower levels of the clustering hierarchy revealed 3 sub-clusters within Cluster-1 that have similar characteristics to Cluster-2, Cluster-3, and Cluster-4 (Figure 6.6). Broadly, Cluster-2 and Cluster-1.2 report mostly depression symptoms and can be compared to the PMD recurrent and single episode major depression groups. Cluster-3 and Cluster-1.3 report both mania and depression symptoms, like the PMD BD and probable mania with subthreshold depression groups. Cluster-4 and Cluster-1.4 report predominantly mania symptoms and are most similar to the PMD UM group. The existence of these sub-clusters suggests that co-morbid anxiety is linked to more diverse symptom profiles.

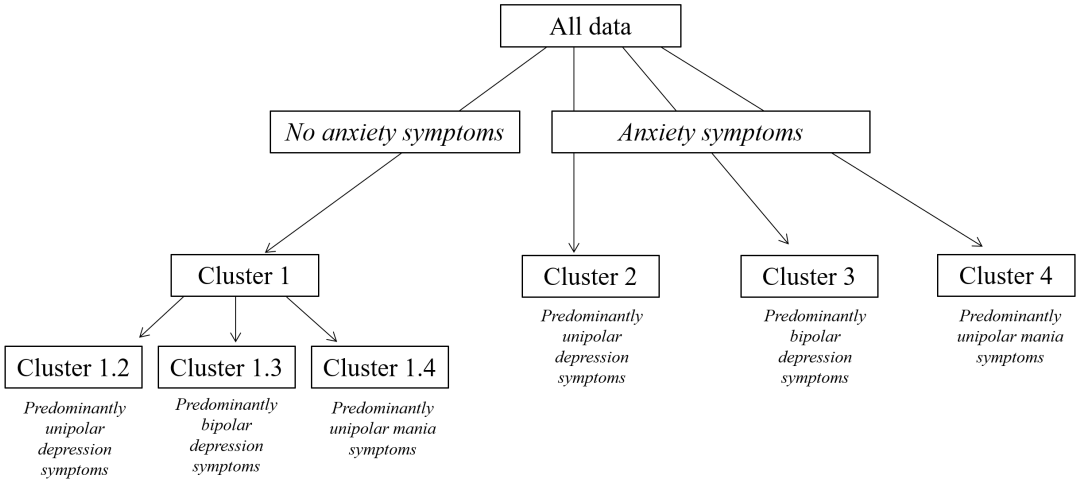

Figure 6.6: Diagram of clusters and sub-clusters for multidomain comparisons.

6.3.3 Multidomain comparisons

A range of potential biomarkers and behavioural phenotypes were compared across clusters. The 4-cluster solution was chosen for this analysis due to its clinical relevance, and Cluster-1 was split into sub-clusters to explore potential differences between anxiety and non-anxiety groups (Figure 6.6). Comparisons were also made across the PMD groups so that they could be compared to the cluster results.

6.3.3.1 Neuroimaging measures

Results are summarised in Figure 6.7, and a detailed results table is provided in Supplementary Table S6.4. Statistically significant differences in volume were found in three subcortical areas, but these differences were not significant after correcting for multiple comparisons. The right accumbens volume was higher in the mania sub-cluster (Cluster-1.4) when compared to the bipolar sub-cluster (Cluster-1.3), but this difference was not reflected in the co-morbid anxiety clusters or the PMD groups. The right amygdala and left putamen volumes were lower in the bipolar sub-cluster (Cluster-1.3) when compared to the depression sub-cluster (Cluster-1.2), but this difference was also exclusive to the sub-cluster groups.

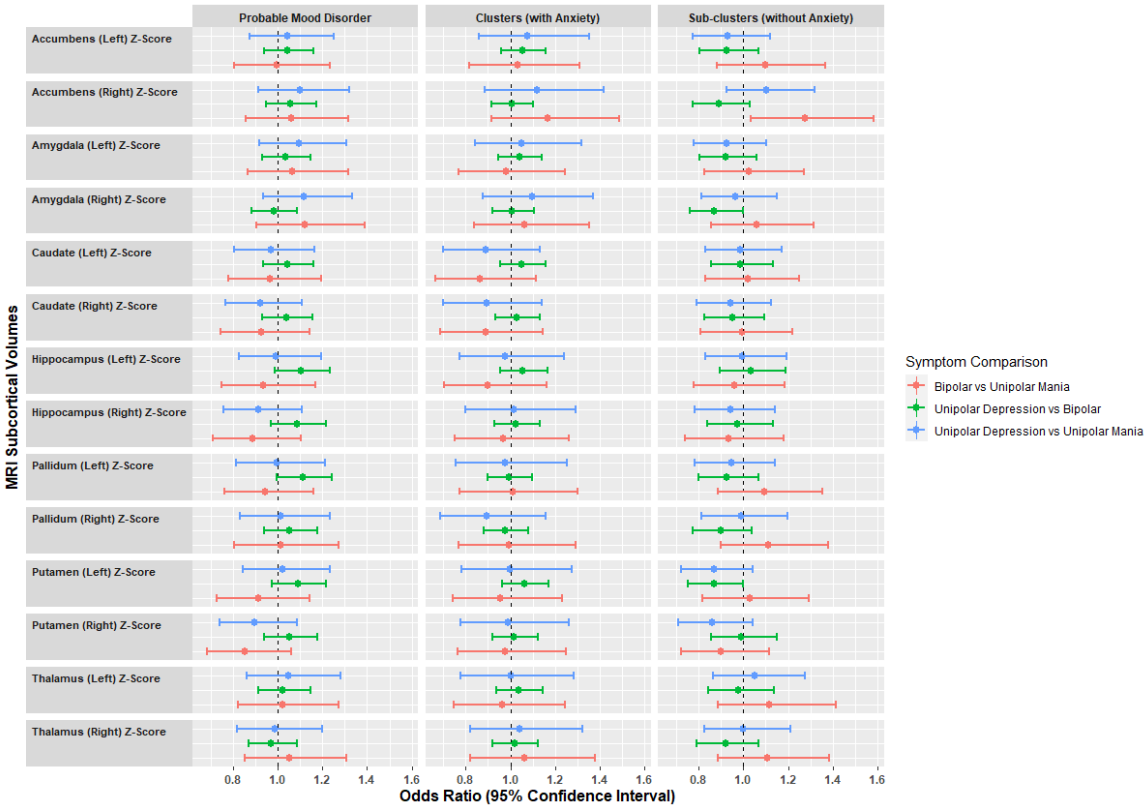

Figure 6.7: Odds ratios and their 95% confidence intervals for Magnetic Resonance Imaging (MRI) subcortical volumes.

These are shown for the original probable mood disorder groupings, the main clusters that include anxiety symptoms, and the sub-clusters that do not include anxiety symptoms. 'Bipolar' symptom groups include Cluster-2, Cluster-1.2, probable bipolar disorder and probable mania with sub-threshold depression. 'Unipolar Depression' symptom groups include Cluster-3, Cluster-1.3, probable recurrent and single episode major depression. 'Unipolar Mania' symptom groups include Cluster-4, Cluster-1.4 and probable unipolar mania.

6.3.3.2 Cognitive tests

Group differences were found in five cognitive tests, but these were also non-significant after multiple comparisons correction (Figure 6.8 and Supplementary Table S6.4). The mania cluster (Cluster-4) and bipolar cluster (Cluster-3) performed worse than the depression cluster (Cluster-2) in the matrix completion task. This was not mirrored in the sub-cluster comparisons, but the trend does appear to exist in the PMD groups. There were no differences in reaction time in the PMD groups, but there are differences in both clusters and sub-clusters. Within the co-morbid anxiety clusters the mania cluster (Cluster-4) exhibited slower reaction times than the bipolar cluster

(Cluster-3). In the sub-clusters the bipolar cluster (Cluster-1.3) were slower than the depression cluster (Cluster-1.2). For verbal-numerical reasoning the mania sub-cluster (Cluster-1.4) performed better than the bipolar sub-cluster (Cluster-1.3). In the symbol-digit substitution task the PMD bipolar group performed worse than the PMD depression group, but this was not reflected in the clusters or sub-clusters. Differences in the tower re-arranging task were only observed in the co-morbid anxiety clusters where the mania cluster (Cluster-4) performed worse than both the depression (Cluster-2) and bipolar clusters (Cluster-3).

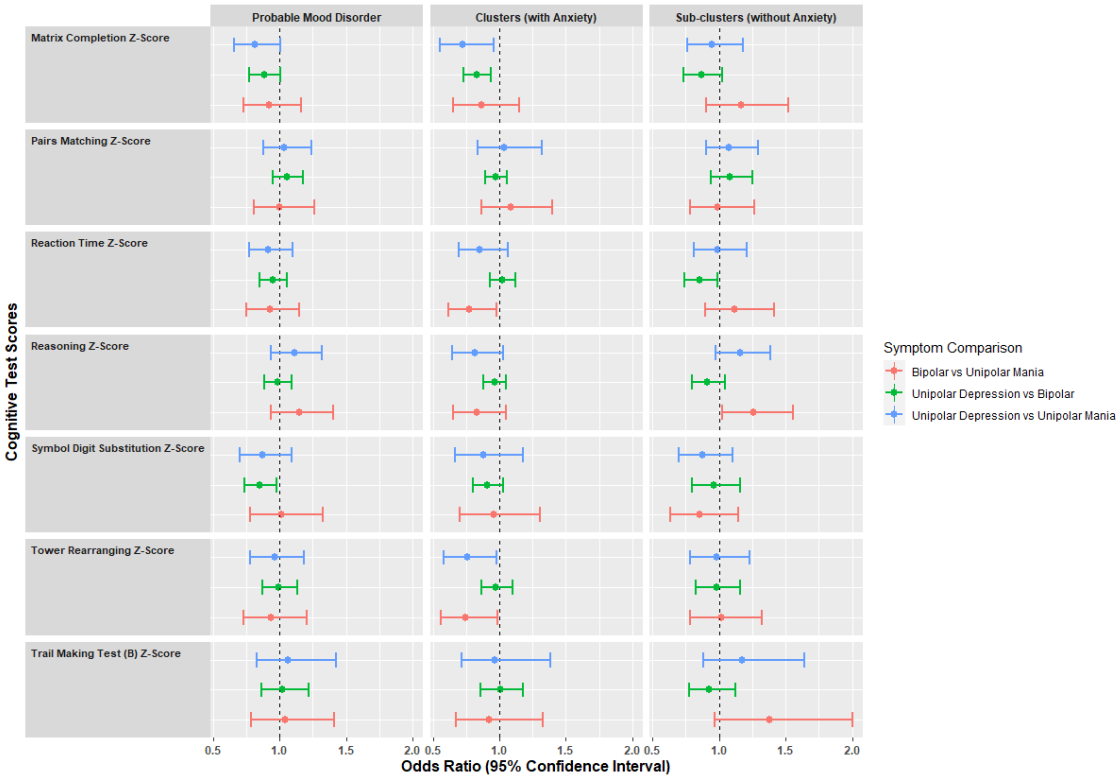

Figure 6.8: Odds ratios and their 95% confidence intervals for cognitive test scores.

These are shown for the original probable mood disorder groupings, the main clusters that include anxiety symptoms, and the sub-clusters that do not include anxiety symptoms. 'Bipolar' symptom groups include Cluster-2, Cluster-1.2, probable bipolar disorder and probable mania with sub-threshold depression. 'Unipolar Depression' symptom groups include Cluster-3, Cluster-1.3, probable recurrent and single episode major depression. 'Unipolar Mania' symptom groups include Cluster-4, Cluster-1.4 and probable unipolar mania.

6.3.3.3 Rest-activity measures

Both subjective and objective rest-activity rhythm results are summarised in Figure 6.9 and detailed results are included in Supplementary Table S6.4. Morning chronotype preference is more common in the mania cluster (Cluster-4) than both the bipolar (Cluster-3) and depression (Cluster-2) clusters. This is not observed in the sub-clusters and is only observed when comparing mania and depression in the PMD groups. Mania is also associated with less difficulty getting up when compared to depression and bipolar PMD groups. The depression sub-cluster (Cluster-1.2) also show more difficulty getting up than the bipolar sub-cluster (Cluster-1.3), but this is not statistically significant after multiple comparisons corrections. The bipolar groups are more likely to report a short sleep duration (< 7 hours) than both the mania and depression groups. This is observed in both the PMD groups and the co-morbid anxiety clusters. Whilst not statistically significant, this trend appears to exist in the sub-clusters too.

Intradaily variability is poorer in the depression cluster (Cluster-2) when compared to the bipolar cluster (Cluster-3). This is also seen in the PMD groups but is not statistically significant after correcting for multiple comparisons. Within the PMD groups mania is associated with higher mean acceleration than both the bipolar and depression groups. This is also seen in the co-morbid anxiety clusters, but only for mania (Cluster-4) when compared to depression (Cluster-2). Mania is also associated with lower objectively measured mean sleep duration when compared to depression in the PMD groups. Whilst also exhibited in the co-morbid anxiety clusters, this is no longer statistically significant after correcting for multiple comparisons. Poor sleep efficiency is more common in the mania cluster (Cluster-4) for the co-morbid anxiety clusters only.

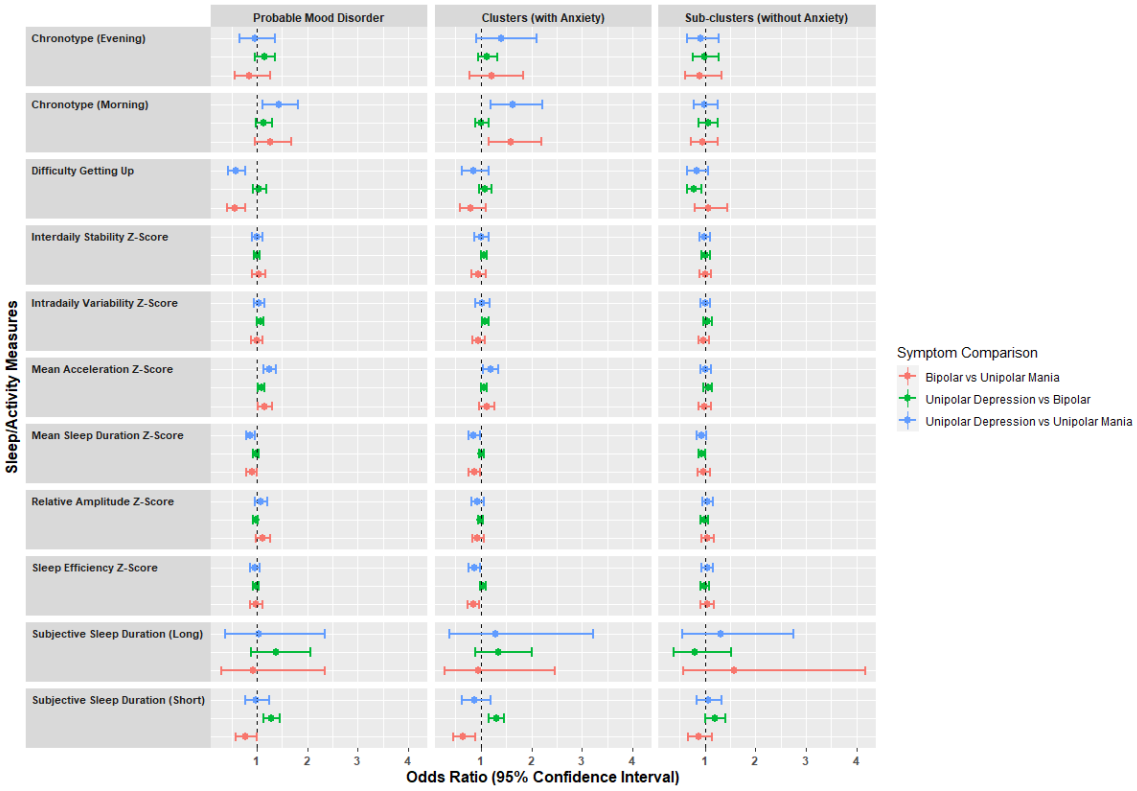

Figure 6.9: Odds ratios and their 95% confidence intervals for sleep and activity measures.

These are shown for the original probable mood disorder groupings, the main clusters that include anxiety symptoms, and the sub-clusters that do not include anxiety symptoms. 'Bipolar' symptom groups include Cluster-2, Cluster-1.2, probable bipolar disorder and probable mania with sub-threshold depression. 'Unipolar Depression' symptom groups include Cluster-3, Cluster-1.3, probable recurrent and single episode major depression. 'Unipolar Mania' symptom groups include Cluster-4, Cluster-1.4 and probable unipolar mania.

6.3.3.4 Polygenic risk scores

Bipolar groups are associated with a higher bipolar PRS when compared to depression groups in both the PMD groups and the co-morbid anxiety clusters (Figure 6.10, Supplementary Table S6.4). In the PMD groups mania is associated with a lower bipolar PRS compared to the bipolar group, whilst in the co-morbid anxiety clusters mania (Cluster-4) is associated with a higher bipolar PRS compared to the depression cluster (Cluster-2).

Major depression PRS is higher in the depression groups when compared to the bipolar groups for both PMD and co-morbid anxiety clusters (Cluster-2 vs Cluster-3). The

mania groups have a lower major depression PRS than the bipolar groups in both PMD and the sub-clusters (Cluster-1.4 vs Cluster-1.3). The PMD bipolar group have a higher schizophrenia PRS than the PMD depression group. This is also seen in the co-morbid anxiety clusters but is not significant after multiple comparisons corrections.

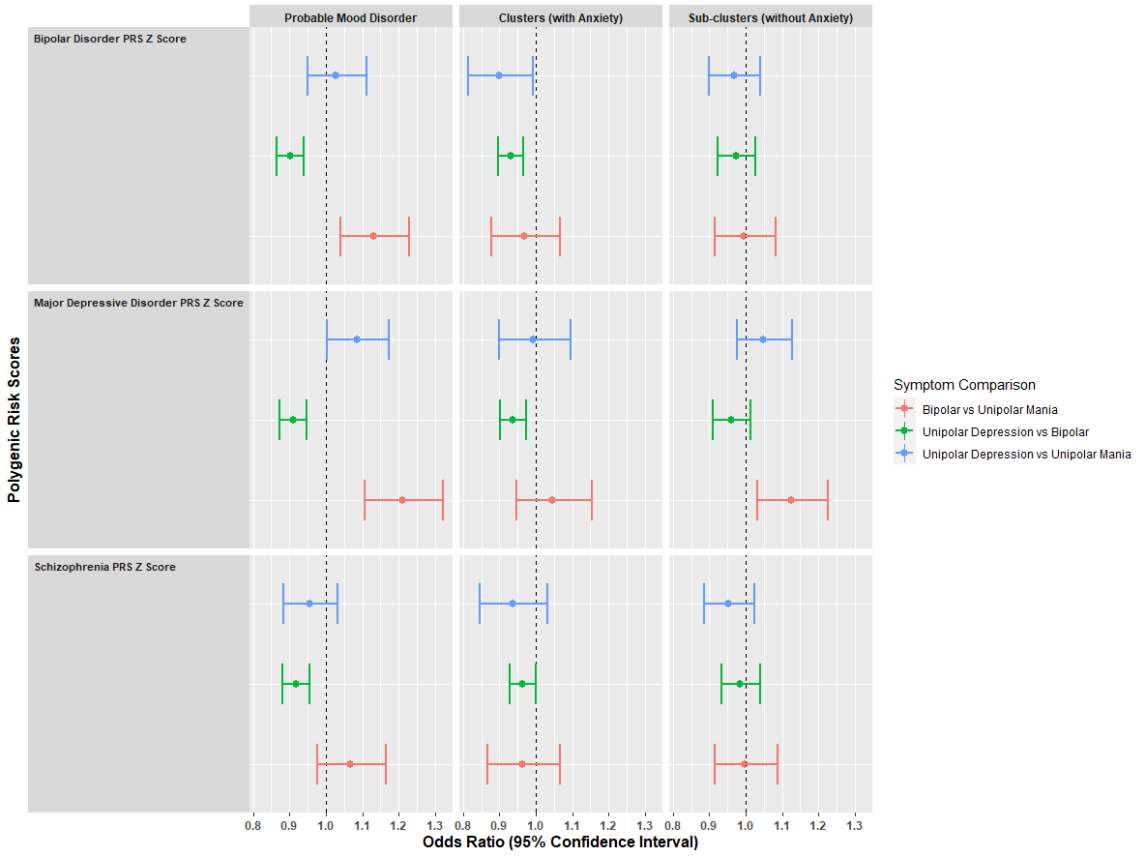

Figure 6.10: Odds ratios and their 95% confidence intervals for the polygenic risk scores.

These are shown for the original probable mood disorder groupings, the main clusters that include anxiety symptoms, and the sub-clusters that do not include anxiety symptoms. 'Bipolar' symptom groups include Cluster-2, Cluster-1.2, probable bipolar disorder and probable mania with sub-threshold depression. 'Unipolar Depression' symptom groups include Cluster-3, Cluster-1.3, probable recurrent and single episode major depression. 'Unipolar Mania' symptom groups include Cluster-4, Cluster-1.4 and probable unipolar mania.

6.4 Discussion

The results of the cluster analysis highlight the importance of co-morbid anxiety symptoms in MDD, BD, and UM. High levels of co-morbidity between anxiety and mood disorders have been reported in many studies and this is continually associated with a worse prognosis and longer illness duration (Goldberg & Fawcett, 2012). The results of this study support this finding by identifying a distinct group that report milder depression and mania symptoms, and particularly low levels of anxiety related symptoms. This milder-symptom group were split at the highest point of the cluster hierarchy indicating that anxiety is the largest differentiator in a symptom-based model.

For both those with co-morbid anxiety and those without, a further three groups were defined, and these broadly support the high-level categories within widely used diagnostic manuals (DSM-5 and ICD-11). These groups consisted of a predominantly unipolar depression group, a bipolar depression and mania group, and a predominantly unipolar mania/hypomania group. UM is currently considered a sub-type of BD under ICD-11 and DSM-5 criteria, but some research suggests that it should be considered a distinct disorder (Angst & Grobler, 2015; Perugi et al., 2007). This analysis supports categorising UM as a distinct disorder under this clustering hierarchy.

Clusters related to depression, bipolar and mania symptoms are less heterogeneous in groups with no co-morbid anxiety. However, few mood disorder studies consider anxiety symptoms during sampling or analysis, and this may be contributing to the mixed findings in this area of research.

6.4.1 Brain structure

There is some evidence that subcortical volumetric differences exist in the non-anxiety clusters, though larger samples would be required to validate statistical significance. The nucleus accumbens plays a significant role in reward processing and has been implicated in the reward hypersensitivity model of BD which theorises that (hypo)mania risk is linked to hypersensitivity to reward cues and, as a result, goal-orientated behaviours (Abler et al., 2008). Previous research has found that increased

activity in the nucleus accumbens is linked to increased risk of mania in BD (Damme et al., 2017) and here we find novel evidence to suggest that grey matter volume in the accumbens may also be larger in people with predominantly mania symptoms when compared to those with both mania and depression symptoms. This difference is not observed in the co-morbid anxiety groups, despite some research suggesting that anxiety and severity are linked to higher volume in the nucleus accumbens (Günther et al., 2018). However, improved treatment response in anxiety has also been linked to higher grey matter volume in the nucleus accumbens and so more research to understand the relationship between anxiety and nucleus accumbens volume is required (Burkhouse et al., 2020).

Amygdala and putamen volumes were lower in the bipolar group when compared to the depression group. Both the amygdala and putamen are implicated in emotional processing and are key targets in mood disorder research. Amygdala reductions have repeatedly been observed in adolescent BD groups but results have been mixed in adult samples (Usher et al., 2010). Anxiety may be linked to increased amygdala volume in both youth and adults (Suor et al., 2020) and here we find that smaller amygdala volumes are only present in the non-anxiety bipolar cluster. This suggests that co-morbid anxiety may be an important contributor to the lack of consistent findings so far. Putamen volume has been suggested as a possible biomarker for differentiating BD and MDD as higher volumes have been observed in BD whilst lower volumes have been observed in MDD (Luo et al., 2019). This trend is observed in the PMD groups and co-morbid anxiety clusters but is inverted in the non-anxiety clusters, highlighting the importance of considering anxiety symptoms when assessing this area.

Reduced volumes in the hippocampus have been frequently reported in MDD and BD when compared to control groups, however fewer studies have compared hippocampus volumes between MDD and BD. Of those that have, the evidence is mixed with some finding no volume differences between MDD and BD and others finding a greater volume decrease in MDD (Ham et al., 2019; Wise et al., 2017). The results of this analysis support the latter, finding a trend towards higher right and left hippocampus volumes in the PMD and co-morbid anxiety bipolar groups when compared to the unipolar depression groups. However, the bipolar depression group in this analysis mostly reported hypomania and some studies have suggested that hippocampus volume

reduction may be specific to BD subgroups that experience episodes of mania (Hibar et al., 2016). It is possible that hippocampus reductions would be more prominent in a more diverse bipolar sample.

6.4.2 Cognition

Cognitive test performance appears to differ across PMD groups, co-morbid anxiety clusters, and non-anxiety clusters, though larger samples would be required to validate statistical significance. The matrix completion test is adapted from the well-known matrix reasoning test and measures non-verbal reasoning ability. Here we find bipolar and unipolar mania perform worse than unipolar depression on this task which supports findings in the literature (Hellvin et al., 2012), though this is only found in the more severe co-morbid anxiety clusters. Whilst this trend is observed in the PMD groups, the lack of significance may be caused by the mix of symptom severity in the PMD samples. Reaction time may also be affected by this heterogeneity as differences are observed in the clusters but not the PMD groups. In this analysis we find a trend of clusters with reported mania symptoms (bipolar and unipolar mania) performing worse than depression only clusters. Within the literature mania has been associated with slower reaction times than controls and this appears to persist regardless of reward incentive, supporting the theory of impaired reward functioning in mania (Abler et al., 2008).

The tower re-arranging task is a modified version of the Tower of London task and can be used to assess executive function. Within the literature BD is associated with poorer performance on this task relative to controls, but number of manic episodes and mania severity have not been found to influence task scores (Sweeney et al., 2000; Tournikioti et al., 2017). Here we find that unipolar mania may be associated with worse performance than bipolar groups suggesting that a relationship between mania and poor executive function may exist. This would support findings from other tests of executive function where BD with mania was linked to worse performance than BD with hypomania (Cotrena et al., 2020).

Whilst mania has often been linked to poor cognitive test performance, in this analysis we find that unipolar mania groups have better performance in the verbal-numerical reasoning task when compared to bipolar groups. We have previously reported higher educational attainment in probable UM, and this is indirectly supported by this finding (chapter 3, Sangha et al., 2022).

6.4.3 Rest-activity rhythms

Here we find evidence of pervasive circadian disruption across all groups regardless of measurement type (subjective or objective) confirming the importance of this domain in mood disorder research. Our previous work suggested the morning chronotype, reduced difficulty getting up in the morning, shorter sleep duration and higher levels of average acceleration are all behavioural characteristics of UM (chapter 3, Sangha et al., 2022). In this analysis we find that this remains true in a smaller PMD sample, but not necessarily in the co-morbid anxiety and non-anxiety clusters. Morning chronotype preference and higher mean acceleration are found in the higher-severity (co-morbid anxiety) clusters, but not the low symptom severity clusters. Shorter objective sleep duration is also found in the higher-severity clusters, however larger sample sizes will be required to assess the validity of this finding as it is not statistically significant after multiple comparisons corrections. Differences in difficulty getting up in the morning are not reflected in any of the clusters. A trend towards poorer sleep efficiency in UM was also identified in previous work, but here we see that it is statistically significant in the co-morbid anxiety clusters only.

Sleep disturbances, including short sleep duration, are widely reported in BD (Dondé et al., 2021). In this analysis we find evidence to support this as bipolar symptom groups are more likely to report short sleep durations subjectively than both unipolar mania and depression groups. This was not found in the objective measure of sleep duration, however differences in samples and measurement period may contribute to this (the objective accelerometery covered a 7-day period and did not include napping, whilst the subjective questionnaire asked for a general estimate and did include daytime napping). As with the mania findings, this can be observed in the PMD and co-morbid anxiety cluster but not the non-anxiety cluster.

The unipolar depression PMD group and co-morbid anxiety cluster both show high levels of daily rhythm variability (IV) when compared to the bipolar groups. This suggests poor entrainment to external zeitgebers and could be driven by disturbed sleep or periods of inactivity during the daytime. IV has been identified as a strong feature in accelerometery-based machine learning models when classifying BD and controls, and these findings suggest that this measure could also be useful when distinguishing BD and MDD (Schneider, Bakštein, et al., 2022).

The lack of differences in the milder non-anxiety clusters suggest that the sleep and activity differences identified in PMD groups may be driven by those with higher symptom severity, as observed in the co-morbid anxiety clusters. A longitudinal study investigating psychiatric symptom severity and sleep found that shorter sleep duration, late chronotype and poor sleep efficiency were all associated with increasing symptom severity (Soehner et al., 2019).

6.4.4 Genetic risk

This study finds that genetic risk generally reflects the underlying symptom profile in both PMD groups and clusters; BD PRS is highest in the bipolar groups and MDD PRS is highest in the unipolar depression groups. Symptom bipolarity is also associated with the highest genetic risk for schizophrenia when compared to unipolar mania or depression groups. Higher polygenic risk for Schizophrenia has been linked to episodes of (hypo)mania in multiple longitudinal populations, however this is not observed in unipolar mania PMD or cluster groups (Richards et al., 2019). Instead, these results suggest a unipolar mania symptom profile is related to an intermediate BD PRS (lower than the bipolar groups, higher than the depression groups), and lower MDD polygenic risk than bipolar groups.

6.4.5 Limitations

We acknowledge some limitations to this work. The UK Biobank cohort may not represent the general population as they are older, healthier, and somewhat more affluent. PMD groups and symptom-driven clusters were based on self-report measures

rather than formal clinical assessments. There are varying levels of time between each of the measurements; subjective sleep and activity and genetic data were collected at the initial assessment visit; neuroimaging and cognitive tests were administered during a follow-up assessment sometime after the initial assessment centre visit; mental health questionnaires were collected remotely and at a separate time, as were the objective accelerometery measures. However, the strengths of this study include the relatively large samples and the comprehensive phenotyping information that was available from multiple domains.

6.5 Conclusions

The results of this analysis support grouping mood disorder participants by symptom polarity (unipolar depression, bipolar depression/mania, and unipolar mania). Under current commonly used diagnostic criteria (DSM-5 and ICD-11) unipolar mania is classified as a bipolar disorder, but here we find that this group have both a distinct symptom profile and show differences in brain structure, cognition, rest-activity rhythms, and polygenic risk when compared to bipolar and unipolar depression.

Furthermore, these results suggest that the presence of co-morbid anxiety should be considered in future mood disorder studies as this may be obscuring the identification of behavioural phenotypes and biomarkers. Here, brain structure differences across mood disorder groups are confined to clusters with less severe symptom profiles and no co-morbid anxiety, whilst differences in rest-activity rhythms are observed in clusters with higher symptom severity and co-morbid anxiety. Further investigation using dimensional and symptom-based approaches are recommended to better understand the mechanisms behind these observations.

Chapter 7 Conclusions.

7.1 An overview of key findings

Mood disorders, including depressive and bipolar disorders, are highly prevalent and a leading cause of disability worldwide. Increasing our understanding of these disorders may lead to more accurate and timely diagnosis and targeted treatment and therapies. Disturbances in sleep and activity are frequently reported in these disorders, giving rise to chronobiological theories of mood disorders. The overall objective of this thesis was to increase our understanding of sleep and circadian disruption in mood disorders whilst also addressing heterogeneity in the classification of mood disorder groups.

The first aim of this thesis was to investigate the nosological status of unipolar mania using behavioural and self-report phenotypes of circadian rhythms in a large population-based dataset (chapter 3). Self-report and behavioural rest-activity measures were compared between unipolar mania (UM), bipolar disorder (BD) and control groups in UK Biobank. UM and BD shared some rest-activity features when compared to controls, including increased difficulty getting up in the morning and increased reporting of a late chronotype preference. However, there was also evidence for rest-activity features that differentiate UM and BD groups: when compared to a control group, increased overall activity levels, increased reporting of an early chronotype preference and shorter sleep duration were specific to UM only.

Having confirmed that UM may be distinct from BD, the second aim was to characterise rest-activity rhythms in UM and other probable mood disorder groups (recurrent major depressive disorder (rMD), single episode depressive disorder (sMD), and BD), including any associated seasonal patterns (chapter 4). This was investigated using objective measures from the UK Biobank accelerometery study. In concordance with the results from chapter 3, the UM group exhibited better IV compared to a control group, suggesting they have a less fragmented daily rhythm (not statistically significant after multiple comparisons corrections). However, this was not specific to the UM group as it was also observed in the BD and rMD groups and may be indicative of low daytime activity levels. In all other measures, the UM group were indistinguishable from controls, whereas the remaining mood disorder groups frequently exhibited less favourable rest-activity profiles in comparison to controls. In season-specific group comparisons, sleep efficiency differences in spring and summer

appear to be distinct to UM, whilst increased rest-activity disruption was observed in the winter months for the other probable mood disorder groups.

Whilst the findings from chapter 4 indicate that rest-activity rhythm differences between probable mood disorder groups and a control group do exist, and these differences have seasonal variations, it was unclear whether the differences could be used to blindly identify someone with a probable mood disorder. Furthermore, a limitation of the analysis in chapter 4 was the lack of available information on the weather conditions during periods of accelerometer wear which would likely impact measured activity levels. This was addressed in Chapter 5 by assessing the ability of a machine learning model to differentiate between probable mood disorder groups and a control group using subjective and objective rest-activity rhythm measures, and meteorological measures from UKHad-Grid. Model performance was modest but improved upon a naïve model, and the inclusion of meteorological measures improved the model performance for UM and BD, but not rMD or sMD. In particular, the relationship between rainfall and activity levels was an important feature in these models, suggesting this may differ between control and mood disorder groups.

The modest model performance in chapter 5 could be the result of rest-activity rhythm differences not being of sufficient magnitude to differentiate between groups, and/or probable mood disorder groups still retaining high levels of overlap after separating the UM and BD groups. The latter was investigated using an unsupervised machine learning approach on reported symptoms from the UK Biobank online mental health questionnaire (chapter 6). Hierarchical clustering identified 3 clusters broadly corresponding to symptom polarity (UM, BD, and unipolar depression), all of which exhibited co-morbid anxiety symptoms. A fourth cluster appeared to capture all remaining participants with a less severe symptom profile and low/no anxiety. However, further investigation found that this fourth cluster contained 3 distinct sub-clusters further down the hierarchy which also broadly corresponded to UM, BD, and unipolar depression. These results suggest that co-morbid anxiety and higher symptom severity is associated with higher differentiation between mood disorder symptom profiles. Furthermore, comparison of a range of behavioural phenotypes and biomarkers found that rest-activity rhythm differences may exist in the co-morbid anxiety groups but not groups without anxiety symptoms.

When considered together, these results:

1. Provide further evidence of pervasive circadian disruption in mood disorders.
2. Provide some support for UM as a nosologically distinct mood disorder.
3. Suggest the need for further investigation into the relationship between seasonal measures and rest-activity rhythms as findings were mixed.
4. Suggest that the presence or absence of co-morbid anxiety symptoms may remove some heterogeneity in mood disorder groups and reveal new phenotypes and biomarkers.

7.2 Implications

7.2.1 Categorical vs dimensional approaches

A key implication of the results of this thesis is that traditional categorical diagnoses may indeed be obscuring biomarkers and behavioural phenotypes in mood disorder research. Evidence of circadian disruption in mood disorder groups was found in all analyses, some of which were specific to a single polarity. However, comparison to data-driven clusters highlighted that this may be driven primarily by participants with higher symptom severity and co-morbid anxiety (chapter 6). This suggests that phenotypic differences found in studies using categorical diagnoses would benefit from further investigation using a dimensional approach, particularly where mixed findings for that phenotype exist in the literature. This method has been used to link circadian disruption and mood disorder symptoms including sleep disturbances and somatic/vegetative symptoms in depression, and sleep maintenance problems with lower impulse control (Arns et al., 2015; Difrancesco et al., 2022). An alternative is use of the dimensional spectrum concept of mood disorders proposed by Angst et al. (2007). This proposes two dimensions for consideration in mood disorder research: (1) a mood spectrum from unipolar major depression, bipolar-II disorder, bipolar-I disorder, mania with sub-threshold depression, and finally unipolar mania; and (2) a severity spectrum from psychotic to major and then minor symptoms (Angst, 2007). Whilst not as detailed as the Research Domain Criteria (RDoC) or Hierarchical Taxonomy of Psychopathology (HiTOP) frameworks, this would reduce some of the heterogeneity caused by use of the traditional categorical mood disorder groupings defined in DSM-5 and ICD-11 (Conway et al., 2019; Cuthbert, 2015). A recommended

addition to this method would be the inclusion of co-morbid anxiety symptoms which have been linked to higher severity (Saha et al., 2021b), and may play a significant role in mood disorder symptom disparity (chapter 6).

7.2.2 Unipolar mania

The findings of the analyses in this thesis suggest that UM could be considered nosologically distinct from BD (Angst, 2015). A transition to dimensional approaches may ultimately remove the necessity to define mood disorder categories in research, as discussed above. However, clinical use of traditional categorical diagnoses remains, and it is therefore important to increase our understanding of any risk-factors and potential treatments that may benefit this group. In the limited available research, there is evidence that patients with UM may be less likely to respond to lithium, are at increased risk of cardiovascular mortality, and have higher risk of experiencing psychotic symptoms when compared to BD (Angst & Grobler, 2015).

In this thesis, a rest-activity rhythm profile that may distinguish potential UM from BD was identified: namely increased overall activity levels, shorter sleep duration, increased morningness and less difficulty getting up in the morning. Higher sleep efficiency in spring and lower sleep efficiency in summer may also be a distinctive pattern in UM (chapter 4), and this may contribute to the reported increases in mania admissions in spring (Parker & Walter, 1982). Further research is required to confirm these findings and assess their validity in other age-groups, as discussed in section 7.4.1. However, if replicated, these findings may be useful in the development of activity tracker and/or smartphone application based diagnostic tools (Fellendorf et al., 2021). These findings may also inform future sleep and circadian-based interventions.

7.2.3 Subjective vs objective rest-activity rhythm measures

A further implication regards the use of subjective vs objective measures of rest-activity rhythms in mood disorder research. Relative to subjective measures, objective measures have less potential for bias and recall error. Whilst objective measures have previously demonstrated poor validity when not accompanied by a sleep diary, recent

methods (including those used to derive the objective sleep measures in this thesis) have resolved this (van Hees et al., 2018). However, objective measures such as accelerometery are often less accessible to researchers and can require more participant involvement. The results of the analyses in this thesis demonstrate pervasive rest-activity rhythm differences in mood disorders from questionnaire data and accelerometer-derived measurements, suggesting both are useful methods for investigating rest-activity rhythms in these disorders. Furthermore, comparable subjective and objective measures exhibit consistent outcomes; UM and BD are frequently associated with disturbed sleep as measured by sleeplessness (subjective, chapter 3) and sleep efficiency (objective, chapters 3, 4 and 6); UM is associated with an earlier circadian clock whilst BD and unipolar depressions are associated with a later circadian clock, as measured by chronotype (subjective, chapters 3 and 6) and phase (objective, chapter 4). An exception to this is sleep duration for which UM had consistently short sleep duration, but BD were found to differ in subjective and objective sleep duration measurements. This identified underestimation of true sleep duration may be a behavioural phenotype for BD, as discussed in chapter 3. These results support findings that comparisons of subjective and objective phase preference and sleep latency are correlated in remitted BD participants (Boudebesse et al., 2014). Subjective and objective sleep duration was also shown to correlate, however subjective sleep duration was measured using the Pittsburgh Sleep Quality Index which is more detailed than the UK Biobank sleep duration question (Buysse et al., 1989). Comparisons of objective and subjectively measured chronotype have indicated that 3 weeks or longer of accelerometer data are needed for optimal estimation of subjective chronotype (Schneider, Fárková, et al., 2022). However, this was observed in healthy participants only, and so it may be that chronotype differences between control and mood disorder participants are of a sufficient magnitude that they are not obscured by shorter observation periods.

One benefit of opting for objective measurement of rest-activity rhythms is the ability to consider additional seasonal and meteorological measures and their interactions with observed rest-activity measures (chapter 5). This is of particular interest in mood disorder research where some evidence has suggested that episode onset in BD may be influenced by ambient air temperature and sunlight exposure (Geoffroy et al., 2014; Montes et al., 2021). The combination of variable meteorological conditions associated

with climate change and prevalence of mood disorders make this an important consideration in mood disorder research (Charlson et al., 2021).

7.3 Limitations

7.3.1 Participants

Whilst the number of participants and wide range of detailed health and biomedical data within UK Biobank make it an exceptional resource for health research, there are some limitations. Approximately 9.2 million individuals who lived within 25 miles of an assessment centre and were between the ages of 40 and 69 were invited to participate, with a 5.5% success rate. Those that volunteered were older, less ethnically diverse, more likely to be female and less likely to live in socioeconomically deprived areas than the general population. They were also healthier, reporting a lower number of health conditions, and less likely to be obese, to smoke, and to drink alcohol daily than the general population (Fry et al., 2017). As a result, it is unclear whether the associations between rest-activity rhythms and mood disorders identified in this thesis may be generalisable and replication in more representative samples is recommended as discussed in section 7.4.1.

7.3.2 Probable mood disorder definition

Despite using mental health questionnaires (MHQ) that closely approximate DSM-5 criteria, the probable mood disorder groups defined in this thesis are not identical to clinical classifications and were not based on formal diagnostic interviews with a trained professional. A benefit of this approach is the ability to capture potential mood disorder status for a wide range of participants, as a large proportion of people experiencing mood disorders do not present themselves for formal medical diagnosis (Goldberg & Huxley, 2012). However, this may also increase the heterogeneity of symptoms within these groups as self-report measures of mood disorders are prone to recall bias, and this has been shown to increase with increased time from an episode (Patten et al., 2012). More crucially, this methodology does not include adequate assessment of functional impairment or investigation into non-psychiatric disorders that

may present with similar symptoms, and therefore likely captures participants that do not have a true mood disorder. This was partially investigated in a study assessing overlap between mood disorder status in UK Biobank as assessed by the touchscreen MHQ, self-reported diagnosis, and hospital admission data; overlap between the MHQ and self-reported diagnosis was 62% for depression, and 47% for BD. The MHQ captured more potential mood disorder participants than the self-report measure, and the majority of those with relevant hospital admission data had been identified in the MHQ and self-reported diagnosis (Davis et al., 2019). However, this study did not include primary care records from general practitioners which are also available in UK Biobank and would capture mood disorder participants that did not require hospital admission. Regardless, replication of these findings in clinically assessed samples is needed to validate the results in this thesis, as discussed in section 7.4.1.

Whilst the use of the UK Biobank MHQs allowed for identification of perhaps the largest unipolar mania/hypomania group in the literature at the time of writing, this group were still considerably smaller than the other probable mood disorder groups. UM often demonstrated similar rest-activity rhythms to the control group and were more difficult to differentiate from controls in a supervised machine learning model (chapter 5), and it is currently unclear whether this is the result of a small sample size or true similarity between these groups.

Finally, the timing of probable mood disorder episodes and their proximity to objective rest-activity measures was unknown. Lifetime probable mood disorder status has been associated with rest-activity rhythm differences and the results within this thesis support this finding (Lyall et al., 2018). These chronic rest-activity rhythm differences may be useful for mood disorder diagnosis and identification of interventions and therapies, but they do not provide insight into circadian markers of mood disorder episodes.

7.3.3 Confounders

Covariate adjustments for statistical models are described in the relevant chapters, broadly including age, sex, Townsend deprivation score, education level, ethnicity,

smoking status, and alcohol status. Psychotropic medication was included in analyses where sample numbers allowed, however detailed consideration of medication was beyond the scope of this thesis. Medication may be important as, in BD, benzodiazepines have been associated with better sleep quality, aripiprazole with advanced phase and less rhythm stability, and lithium with phase delay (Benedetti et al., 2001; Hennion et al., 2024). However, accounting for medication use is difficult; for example, commonly used depression medications have been found to affect activity levels in a variety of ways leading to increased activity in some and decreased activity in others (Bernard & Carayol, 2015). Furthermore, medication adherence is poor in mood disorder groups and therefor true medication status is unknown in non-hospital settings (Semahegn et al., 2020).

Similarly, factors related to employment or caring duties may be important confounders but were beyond the scope of this thesis. Retirement has been associated with longer sleep duration, lower levels of sleep disturbance, and reduced risk of depression (Amerio et al., 2021; Bracke et al., 2020; Hagen et al., 2016). Informal caregiving responsibilities have also been linked to poorer mental health (Brown & Cohen, 2020). Whilst employment information is included within the UK Biobank touchscreen questionnaires, no specific category identifies those with caring responsibilities.

A key limitation of the findings within this thesis is that co-occurring illnesses were not fully considered. Participants reporting psychotic episodes were excluded to ensure that the BD criteria did not also capture participants with probable schizophrenia, and participants with severe brain injury or illness were excluded as this would impact both mental health and rest-activity rhythms. However, there are a myriad of other illnesses that could potentially impact mental health or rest-activity rhythms and were not accounted for in the analyses within this thesis. For example, short sleep duration has been linked to higher severity of depression symptoms in Parkinson's disease, and Alzheimer's disease may causally influence sleep patterns (Huang et al., 2020; Kay et al., 2018). The self-reported diagnoses, linked primary care data, and hospital admission data within UK Biobank may be used to investigate these relationships further.

7.3.4 Rest-activity rhythm measures

A limitation of both the objective and subjective rest-activity rhythm measures analysed in this thesis is that they do not account for weekday and weekend differences. A study of optimal wear time for reliable activity estimates in older adults found that 5 days is sufficient, but activity differences existed between days of the week (Hart et al., 2011). When weekday and weekend differences were assessed for differing chronotype preferences, evening-chronotypes exhibited poorer sleep quality and lower sleep duration on weekdays when compared to intermediate or morning chronotypes. However, this difference did not exist on weekends, demonstrating a 'social jetlag' effect that may be caused by social or work commitments (Vitale et al., 2015). Similarly, the accuracy of subjective sleep quality may be affected by weekday and weekend differences (Choilek et al., 2021). This was partially addressed in chapter 5 where weekday and weekend differences in average activity blocks were calculated and included within the machine learning models, but remains a limitation in the other analysis chapters.

7.4 Future directions

7.4.1 Replication in non-UK Biobank cohorts

UM is vastly understudied, and the rest-activity rhythm differences identified in this thesis are novel findings. Replication studies in additional UM groups are required to confirm these findings, most importantly in clinical mood disorder samples. UK Biobank have recently released linked primary care data for approximately 45% of the cohort, including clinically coded diagnoses. This additional information may address the key limitations of this thesis by allowing further investigation of rest-activity characteristics in participants with a clinically diagnosed mood disorder, whilst also providing additional insight into the timing of episodes, medication prescriptions, and co-morbid illnesses. Further information is available here: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf.

Whilst this thesis focuses on older adult groups, replication in groups of adolescents and young adults would allow us to identify whether these differences are pervasive across the lifetime. Circadian timing changes over time with adolescents frequently exhibiting later phase, and this progressively becomes earlier throughout their lifetime (Lee et al., 2011). Adolescence is also a risk period for mood disorder onset (Kessler et al., 2005). Findings in the literature are mixed but do indicate a relationship between mood disorder symptoms and disrupted rest-activity rhythms, including poor sleep efficiency during manic episodes (Lopes et al., 2020; O'Callaghan et al., 2021). However, further research in large cohorts that have been carefully assessed for bipolar features is required to better understand this relationship. A potential data source for investigating rest-activity rhythms and mood disorders in adolescents may be the Adolescent Brain Cognitive Development study, a large-scale US biobank studying child development and health. This includes objective measures of rest-activity rhythms and mood disorder questionnaires (Bagot et al., 2018). The longitudinal nature of this data set would also allow for the identification of sleep and circadian risk factors for future mood disorder onset; 11,500 participants aged 9-10 years old completed a baseline assessment between September 2016 and August 2018, and participate in yearly follow-up assessments (currently aged 15-18 years old) (Garavan et al., 2018). Approximately 5,000 of these participants also opted to wear an activity tracker during this time. Recent findings from this cohort have linked sedentary activity to greater risk of psychosis-like experiences, and lower cardiovascular fitness to greater risk of anxiety and depression symptoms (Damme et al., 2024).

As discussed in section 7.3.1, a limitation of the analyses in this thesis is that the UK Biobank cohort may exhibit a healthy volunteer bias and are therefore not representative of the general population. Potentially interesting groups for replication are non-white ethnicities in which UM is possibly more prevalent (Angst et al., 2019). Despite UK Biobank predominantly consisting of participants with white ethnicity, a higher proportion of 'Asian or Asian British' ethnicity was reported in the UM group compared to BD and control groups (chapter 3).

7.4.2 Longitudinal follow-up studies in UK Biobank

UK Biobank participants take part in follow-up assessment centre visits, during which they repeat the touchscreen mental health questionnaire and subjective rest-activity measures. A group of participants that did not report mood disorder symptoms at the initial baseline assessment centre, but met probable mood disorder criteria at least one year after the accelerometer study have been identified (N=321) (Lyall et al., 2023). It is expected that more participants will meet these criteria as further repeat assessment centre data is released by UK Biobank, and this may allow for the investigation of longitudinal relationships between rest-activity rhythms and mood disorder outcomes. For example, there is evidence to suggest that higher subjective sleep disturbance and lower objective sleep efficiency are associated with an increased risk of reporting more severe depression symptoms at a 5-year follow-up in a cohort of older adults (Maglione et al., 2014).

In 2018 UK Biobank began to collect repeat accelerometery data across each season for a small group of participants (approximately N=3,000). This is a relatively new release at the time of writing and there is therefore little information about the methodology used, however it is possible that this will allow for within-subject investigations into seasonal rest-activity rhythm differences in mood disorders, and these would be more robust than the between-group comparisons described in chapter 4.

7.4.3 Integrating multiple domains for improved mood disorder identification

Lifetime rest-activity rhythm differences, combined with demographic and lifestyle factors, can predict probable mood disorder status better than a naïve model (chapter 5), however the accuracy is modest and therefore of limited clinical use. Integrating measures from multiple domains that have been associated with both circadian disruption and mood disorders may lead to better discriminatory ability. For example, the relationship between circadian disruption and mood disorders may be mediated by structural and functional brain differences (Bedrosian & Nelson, 2013); and in BD, disrupted sleep may contribute to cognitive impairments in working memory and social cognition (Russo et al., 2015).

7.5 Conclusions

Symptoms related to sleep and circadian disruption are frequently reported in mood disorders and this can have a detrimental effect on quality of life for those affected. Identification of phenotypes for sleep and circadian disruption may improve diagnosis and treatment for mood disorders, however the heterogeneity of symptom profiles within and between mood disorder groups has led to inconsistent findings.

This thesis explored the relationship between behavioural phenotypes of sleep and circadian disruption and mood disorders in a large UK dataset using a range of statistical and data-driven methodologies. The findings identified a range of associations between subjective and objective rest-activity rhythm measures and mood disorder category, some of which appear to be distinct to individual mood disorder groups. There is also evidence of seasonal variation in these rest-activity rhythm differences.

Regarding heterogeneity in mood disorder groups, there is evidence to support a nosological distinction between unipolar mania and bipolar disorder, a differentiation that could reduce the heterogeneity found in bipolar disorder studies. Furthermore, accounting for co-morbid anxiety in mood disorder studies may further reduce heterogeneity in all mood disorder groups.

In conclusion, this thesis provides new evidence contributing to our understanding of sleep and circadian disruption in mood disorders, and the reduction of heterogeneity of symptoms within these groups. Further research is needed to better understand this relationship and its potential to inform future classification, diagnostic approaches and treatments.

Appendix: Supplementary Tables and Figures

Figure S3.1: Psychotropic medication list.

1- Lithium	1- unique code	*2- Other mood stabil*	2 - unique code	*3 - AD-SSRI*	3 - unique code	*4 - AD-Other*	4 - unique code	*5 - AP-Traditional*	5 - unique code	*6 - AP-second gen*	6 - unique code	*7 - Sedatives & hypnotics*	7 - unique code
lithium product	1140867490	sodium valproate	1140872198	paroxetine	1140867888	mirtazapine	1141152732	chlorpromazine	1140879658	quetiapine	1141152848	diazepam	1140863152
Priadel (lithium)	1140867504	Epilim (sodium valproate)	1140872200	Seroxat (paroxetine)	1140882236	Zispin (mirtazapine)	1141152736	cpz - chlorpromazine	1140910358	Seroquel (quetiapine)	1141152860	diazepam product	1141157496
Camcolit (lithium)	1140867494	Depakote (semisodium valproate)	1141172838	fluoxetine	1140879540	duloxetine	1141200564	Largactil (chlorpromazine)	1140863416	risperidone	1140867444	Valium tablet (diazepam)	1140863244
		valproic acid	1140872214	Prozac (fluoxetine)	1140867876	Cymbalta (duloxetine)	1141201834	haloperidol	1140867168	Risperdal (risperidone)	1141177762	Valium syrup (diazepam)	1140863250
		carbamazepine product	1140872064	citalopram	1140921600	Yentreve (duloxetine)	1141200570	Haldol (haloperidol)	1140867184	olanzapine	1140928916	Valium supp (diazepam)	1140855856
		carbamazepine	2038459704	Cipramil (citalopram)	1141151946	venlafaxine	1140916282	Serenace (haloperidol)	1140867092	Zyprexa (olanzapine)	1141167976	temazepam	1140863202
		Tegretol (carbamazepine)	1140872072	escitalopram	1141180212	Efexor (venlafaxine)	1140916288	fluphenazine decanoate	1140867398	aripiprazole	1141195974	Normison (temazepam)	1140863210
		Teril (carbamazepine)	1141167860	Cipralex (escitalopram)	1141190158	amitriptyline	1140879616	fluphenazine	1140882098	Abilify (aripiprazole)	1141202024	Euhypnos (temazepam)	1140863138
		Teril retard (carbamazepine)	1141185460	sertraline	1140867878	Elavil (amitriptyline)	1140867658	Modecate (fluphenazine)	1140867456	amisulpride	1141153490	zopiclone	1140863144
		Timonil retard (carbamazepine)	1141162898	Lustral (sertraline)	1140867884	Tryptizol (amitriptyline)	1140867668	Moditen tablet (fluphenazine)	1140867156	Solian (amisulpride)	1141184742	Zimovane (zopiclone)	1140928004
		Epimaz (carbamazepine)	1140864452	fluvoxamine	1140879544	Lentizol (amitriptyline)	1140867662	Moditen enanthate (fluphenazine)	1140856004	clozapine	1140867420	zaleplon	1141171404
		lamotrigine	1140872290			amitriptyline+perphenazine	1140867948	flupentixol	1140909800	Clozanil (clozapine)	1140882320	Sonata (zaleplon)	1141171410
		Lamictal (lamotrigine)	1140872302			Triptafen (amitriptyline+perphenazine)	1140867934	Flupenthixol (flupentixol)	1140867150			zolpidem	1140865016
						amitriptyline+chlordiazepoxide	1140867938	Depixol (flupentixol)	1140867152			Stilnoct (zolpidem)	1140864916
						Limbitrol 10 (amitriptyline+chlordiazepoxide)	1140856186	Fluanxol (flupentixol)	1140867952			nitrazepam	1140863182
						Limbitrol-5 (amitriptyline+chlordiazepoxide)	1140867928	zuclopenthixol	1140882100			Mogadon (nitrazepam)	1140863194
						phenelzine	1140867850	Clopixol (zuclopenthixol)	1140867342			Nitrados (nitrazepam)	1140855896
						maoi - phenelzine	1140910704	loxapine	1140867406			Remnos (nitrazepam)	1140863196
						Nardil (phenelzine)	1140867852	Loxapac (loxapine)	1140867414			Somnite (nitrazepam)	1140855900
						moclobemide	1140867920	droperidol	1140867084			Noctesed (nitrazepam)	1140855898
						Manerix (moclobemide)	1140867922	Droleptan (droperidol)	1140867086			Surem (nitrazepam)	1140855902
						imipramine	1140879630	trifluoperazine	1140868120			Unisomnia (nitrazepam)	1140855904
						Tofranil (imipramine)	1140867712	Stelazine (trifluoperazine)	1140867244			flunitrazepam	1140863104
						trimipramine	1140867756	thioridazine	1140879750			Rohypnol (flunitrazepam)	1140863106
						Surmontil (trimipramine)	1140867758	Melleril (thioridazine)	1140867312			triazolam	1140855914
						dothiepin	1140879628					Halcion (triazolam)	1140855920
						dosulepin	1140909806						
						Prothiaden (dosulepin)	1140867624						
						Thaden (dosulepin)	1141171824						
						clomipramine	1140879620						
						Anafranil (clomipramine)	1140867690						
						lofepramine	1140867726						
						Gamanil (lofepramine)	1140882310						
						Lomont (lofepramine)	1141146062						
						mianserin	1140879556						
						Bolvidon (mianserin)	1140867806						
						Norval (mianserin)	1140867812						

Table S3.1: Fishers exact test results for long sleep duration.

Objective/ Subjective	Group Comparison	Fishers Exact Test Odds Ratio	95% Confidence Interval	p value
Objective	BD vs UM	6.139	1.597, 52.354	0.002
Objective	UM vs Control	3.682	1.004, 30.654	0.053
Subjective	BD vs UM	2.530	1.349, 5.250	0.002
Subjective	UM vs Control	0.739	0.407, 1.497	0.288

Table S3.2: Group comparisons.

Variable	Group Comparison	Estimate	Std. Error	z value	Pr (>|z|)	Odds Ratio	2.50%	97.50%	p value (FDR Corrected)
Anxiety	BD vs Control	3.871	0.044	88.172	0.000	47.970	44.034	52.303	0.000
Anxiety	BD vs UM	2.739	0.093	29.606	0.000	15.466	12.934	18.591	0.000
Anxiety	UM vs Control	1.103	0.086	12.809	0.000	3.014	2.538	3.558	0.000
Chronotype (Early)	BD vs Control	0.015	0.039	0.393	0.694	1.016	0.940	1.096	0.744
Chronotype (Early)	BD vs UM	-0.212	0.080	-2.653	0.008	0.809	0.692	0.947	0.013
Chronotype (Early)	UM vs Control	0.260	0.069	3.777	0.000	1.297	1.132	1.482	0.000
Chronotype (Late)	BD vs Control	0.502	0.051	9.888	0.000	1.652	1.495	1.824	0.000
Chronotype (Late)	BD vs UM	0.170	0.114	1.492	0.136	1.185	0.951	1.485	0.167
Chronotype (Late)	UM vs Control	0.333	0.103	3.246	0.001	1.395	1.136	1.699	0.002
Difficulty Getting Up	BD vs Control	0.889	0.037	24.008	0.000	2.433	2.262	2.615	0.000
Difficulty Getting Up	BD vs UM	0.646	0.089	7.226	0.000	1.907	1.604	2.277	0.000
Difficulty Getting Up	UM vs Control	0.266	0.083	3.199	0.001	1.305	1.105	1.531	0.002
Happiness - General	BD vs Control	2.974	0.062	47.850	0.000	19.578	17.339	22.124	0.000
Happiness - General	BD vs UM	1.909	0.168	11.377	0.000	6.748	4.922	9.518	0.000
Happiness - General	UM vs Control	1.081	0.168	6.417	0.000	2.948	2.088	4.048	0.000
Happiness - Health	BD vs Control	1.714	0.041	42.100	0.000	5.553	5.126	6.014	0.000
Happiness - Health	BD vs UM	0.970	0.098	9.906	0.000	2.637	2.183	3.205	0.000
Happiness - Health	UM vs Control	0.748	0.092	8.136	0.000	2.113	1.758	2.522	0.000
Interdaily Stability	BD vs Control	-0.017	0.019	-0.921	0.357	0.983	0.947	1.020	0.407
Interdaily Stability	BD vs UM	-0.001	0.039	-0.027	0.978	0.999	0.925	1.078	0.978
Interdaily Stability	UM vs Control	-0.021	0.034	-0.602	0.547	0.980	0.916	1.048	0.598
Intradaily Variability	BD vs Control	-0.034	0.018	-1.890	0.059	0.967	0.934	1.001	0.079
Intradaily Variability	BD vs UM	0.061	0.038	1.622	0.105	1.063	0.987	1.145	0.132

Intradaily Variability	UM vs Control	-0.071	0.032	-2.209	0.027	0.931	0.874	0.992	0.039
Mean Acceleration	BD vs Control	0.062	0.019	3.237	0.001	1.064	1.025	1.104	0.002
Mean Acceleration	BD vs UM	0.112	0.040	2.793	0.005	1.119	1.034	1.211	0.009
Mean Acceleration	UM vs Control	-0.077	0.035	-2.204	0.028	0.926	0.864	0.991	0.039
Neuroticism	BD vs Control	0.437	0.006	69.552	0.000	1.549	1.530	1.568	0.000
Neuroticism	BD vs UM	0.228	0.012	18.953	0.000	1.256	1.227	1.286	0.000
Neuroticism	UM vs Control	0.220	0.010	21.984	0.000	1.247	1.222	1.271	0.000
Obj Sleep Duration (Long)	BD vs Control	0.656	0.180	3.638	0.000	1.927	1.334	2.709	0.001
Obj Sleep Duration (Short)	BD vs Control	0.062	0.053	1.166	0.244	1.064	0.958	1.181	0.293
Obj Sleep Duration (Short)	BD vs UM	-0.110	0.110	-1.001	0.317	0.896	0.723	1.112	0.374
Obj Sleep Duration (Short)	UM vs Control	0.227	0.094	2.409	0.016	1.255	1.042	1.509	0.024
Relative Amplitude	BD vs Control	0.133	0.019	7.072	0.000	1.142	1.101	1.185	0.000
Relative Amplitude	BD vs UM	0.164	0.040	4.136	0.000	1.178	1.090	1.274	0.000
Relative Amplitude	UM vs Control	-0.031	0.034	-0.918	0.358	0.969	0.906	1.036	0.407
Risk Taking	BD vs Control	0.665	0.034	19.388	0.000	1.944	1.817	2.078	0.000
Risk Taking	BD vs UM	-0.064	0.070	-0.904	0.366	0.938	0.818	1.077	0.407
Risk Taking	UM vs Control	0.735	0.062	11.893	0.000	2.086	1.848	2.354	0.000
Self-Harm	BD vs Control	2.924	0.068	43.104	0.000	18.613	16.306	21.274	0.000
Self-Harm	BD vs UM	1.533	0.161	9.513	0.000	4.630	3.417	6.435	0.000
Self-Harm	UM vs Control	1.414	0.164	8.601	0.000	4.114	2.942	5.615	0.000
Sleep Duration Difference (Overestimate)	BD vs Control	0.011	0.086	0.125	0.900	1.011	0.853	1.196	0.932
Sleep Duration Difference (Overestimate)	BD vs UM	-0.300	0.178	-1.684	0.092	0.741	0.522	1.051	0.118
Sleep Duration Difference (Overestimate)	UM vs Control	0.339	0.149	2.272	0.023	1.403	1.047	1.880	0.034
Sleep Duration Difference (Underestimate)	BD vs Control	0.354	0.075	4.746	0.000	1.425	1.232	1.650	0.000
Sleep Duration Difference (Underestimate)	BD vs UM	0.005	0.163	0.028	0.977	1.005	0.729	1.381	0.978
Sleep Duration Difference (Underestimate)	UM vs Control	0.369	0.139	2.647	0.008	1.446	1.102	1.904	0.013

Sleep Efficiency	BD vs Control	0.041	0.019	2.165	0.030	1.042	1.004	1.081	0.042
Sleep Efficiency	BD vs UM	-0.014	0.039	-0.350	0.726	0.986	0.913	1.065	0.765
Sleep Efficiency	UM vs Control	0.059	0.034	1.701	0.089	1.060	0.991	1.134	0.117
Sleeplessness	BD vs Control	0.665	0.023	29.038	0.000	1.944	1.859	2.033	0.000
Sleeplessness	BD vs UM	0.312	0.048	6.442	0.000	1.366	1.243	1.502	0.000
Sleeplessness	UM vs Control	0.365	0.041	8.852	0.000	1.440	1.329	1.562	0.000
Sub Sleep Duration (Long)	BD vs Control	1.279	0.123	10.365	0.000	3.594	2.809	4.559	0.000
Sub Sleep Duration (Short)	BD vs Control	0.557	0.036	15.635	0.000	1.746	1.628	1.872	0.000
Sub Sleep Duration (Short)	BD vs UM	0.246	0.078	3.175	0.001	1.279	1.100	1.490	0.003
Sub Sleep Duration (Short)	UM vs Control	0.302	0.069	4.383	0.000	1.352	1.180	1.546	0.000

Table S4.1: Full multivariable logistic regression model results.

Probable Mood Disorder	Season	Term	Estimate	Std Error	Statistic	p.value	95% CI (lower)	95% CI (upper)	p.value (FDR corrected)
sMD	Spring	(Intercept)	0.284	0.571	-2.202	0.028	0.092	0.862	0.065
sMD	Spring	Phase	1.105	0.04	2.465	0.014	1.021	1.196	0.036
sMD	Spring	RA	1.093	0.041	2.149	0.032	1.006	1.183	0.073
sMD	Spring	IV	0.966	0.042	-0.829	0.407	0.889	1.049	0.541
sMD	Spring	IS	0.916	0.045	-1.979	0.048	0.839	0.999	0.096
sMD	Spring	Sleep Duration	1.08	0.047	1.655	0.098	0.987	1.184	0.178
sMD	Spring	Sleep Efficiency	1.077	0.049	1.509	0.131	0.978	1.187	0.226
sMD	Spring	Easting	1	0	-0.271	0.786	1	1	0.845
sMD	Spring	Age	0.968	0.005	-6.216	0	0.958	0.978	0
sMD	Spring	Sex	0.315	0.087	-13.342	0	0.265	0.373	0
sMD	Spring	Townsend	1.067	0.034	1.898	0.058	0.997	1.141	0.113
sMD	Spring	Alcoholcurrent	1.285	0.25	1.004	0.316	0.805	2.158	0.45
sMD	Spring	Alcoholprevious	1.89	0.327	1.945	0.052	1.001	3.631	0.102
sMD	Spring	BMI	1.031	0.008	3.641	0	1.014	1.049	0.001
sMD	Spring	Smoking	1.385	0.063	5.196	0	1.224	1.566	0
sMD	Spring	Educationcollege	1.144	0.122	1.097	0.272	0.901	1.456	0.404
sMD	Spring	Educationcontinued	1.008	0.174	0.043	0.966	0.712	1.412	0.97
sMD	Spring	Educationincomplete	0.87	0.18	-0.775	0.438	0.608	1.231	0.571
sMD	Spring	Educationuniversity	1.297	0.113	2.293	0.022	1.041	1.624	0.054
sMD	Spring	Ethnicity_Bin	1.682	0.246	2.112	0.035	1.061	2.796	0.078
rMD	Spring	(Intercept)	2.949	0.408	2.653	0.008	1.324	6.545	0.022
rMD	Spring	Phase	1.131	0.03	4.147	0	1.068	1.2	0
rMD	Spring	RA	1.104	0.031	3.212	0.001	1.039	1.173	0.004
rMD	Spring	IV	0.963	0.031	-1.232	0.218	0.906	1.023	0.342
rMD	Spring	IS	0.961	0.032	-1.245	0.213	0.901	1.023	0.337

rMD	Spring	Sleep Duration	1.125	0.035	3.369	0.001	1.051	1.205	0.003
rMD	Spring	Sleep Efficiency	1.043	0.037	1.143	0.253	0.97	1.121	0.387
rMD	Spring	Easting	1	0	-1.629	0.103	1	1	0.184
rMD	Spring	Age	0.953	0.004	-12.581	0	0.946	0.96	0
rMD	Spring	Sex	0.356	0.062	-16.695	0	0.315	0.402	0
rMD	Spring	Townsend	1.188	0.025	6.903	0	1.131	1.247	0
rMD	Spring	Alcoholcurrent	0.974	0.169	-0.157	0.875	0.703	1.365	0.921
rMD	Spring	Alcoholprevious	2.036	0.225	3.161	0.002	1.313	3.175	0.005
rMD	Spring	BMI	1.024	0.006	3.724	0	1.011	1.037	0.001
rMD	Spring	Smoking	1.407	0.047	7.306	0	1.284	1.542	0
rMD	Spring	Educationcollege	1.201	0.091	2.009	0.044	1.005	1.436	0.093
rMD	Spring	Educationcontinued	1.117	0.127	0.874	0.382	0.87	1.43	0.52
rMD	Spring	Educationincomplete	0.924	0.135	-0.586	0.558	0.707	1.201	0.672
rMD	Spring	Educationuniversity	1.24	0.085	2.538	0.011	1.051	1.466	0.031
rMD	Spring	Ethnicity_Bin	1.444	0.163	2.253	0.024	1.054	1.999	0.06
BD	Spring	(Intercept)	2.594	0.723	1.319	0.187	0.621	10.593	0.306
BD	Spring	Phase	1.172	0.053	3.029	0.002	1.058	1.3	0.008
BD	Spring	RA	1.137	0.052	2.481	0.013	1.025	1.255	0.035
BD	Spring	IV	0.888	0.058	-2.06	0.039	0.793	0.994	0.086
BD	Spring	IS	0.905	0.06	-1.67	0.095	0.804	1.017	0.173
BD	Spring	Sleep Duration	1.231	0.066	3.167	0.002	1.083	1.401	0.005
BD	Spring	Sleep Efficiency	1.219	0.069	2.875	0.004	1.066	1.396	0.012
BD	Spring	Easting	1	0	-2.433	0.015	1	1	0.039
BD	Spring	Age	0.928	0.007	-10.678	0	0.915	0.94	0
BD	Spring	Sex	0.597	0.111	-4.654	0	0.48	0.741	0
BD	Spring	Townsend	1.202	0.044	4.172	0	1.102	1.31	0
BD	Spring	Alcoholcurrent	0.878	0.311	-0.419	0.675	0.495	1.689	0.772

BD	Spring	Alcoholprevious	2.709	0.382	2.611	0.009	1.303	5.873	0.025
BD	Spring	BMI	1.055	0.011	4.912	0	1.032	1.077	0
BD	Spring	Smoking	1.454	0.082	4.586	0	1.238	1.705	0
BD	Spring	Educationcollege	1.307	0.178	1.505	0.132	0.927	1.866	0.227
BD	Spring	Educationcontinued	1.264	0.234	1	0.317	0.793	1.992	0.45
BD	Spring	Educationincomplete	1.392	0.242	1.366	0.172	0.859	2.227	0.286
BD	Spring	Educationuniversity	1.37	0.167	1.882	0.06	0.994	1.918	0.115
BD	Spring	Ethnicity_Bin	0.975	0.255	-0.098	0.922	0.603	1.646	0.946
UM	Spring	(Intercept)	0.123	1.468	-1.43	0.153	0.006	2.056	0.258
UM	Spring	Phase	0.929	0.099	-0.74	0.459	0.769	1.132	0.585
UM	Spring	RA	1.099	0.096	0.982	0.326	0.897	1.308	0.461
UM	Spring	IV	0.879	0.109	-1.185	0.236	0.709	1.086	0.368
UM	Spring	IS	1.046	0.113	0.395	0.693	0.838	1.303	0.787
UM	Spring	Sleep Duration	0.939	0.117	-0.536	0.592	0.752	1.191	0.707
UM	Spring	Sleep Efficiency	0.777	0.125	-2.018	0.044	0.609	0.996	0.092
UM	Spring	Easting	1	0	-0.215	0.83	1	1	0.88
UM	Spring	Age	0.949	0.014	-3.843	0	0.924	0.975	0
UM	Spring	Sex	1.486	0.221	1.794	0.073	0.968	2.304	0.137
UM	Spring	Townsend	1.109	0.092	1.129	0.259	0.922	1.322	0.392
UM	Spring	Alcoholcurrent	0.669	0.617	-0.652	0.515	0.233	2.843	0.634
UM	Spring	Alcoholprevious	1.383	0.796	0.408	0.684	0.288	7.411	0.779
UM	Spring	BMI	1.038	0.024	1.538	0.124	0.989	1.086	0.216
UM	Spring	Smoking	1.396	0.163	2.044	0.041	1.006	1.912	0.088
UM	Spring	Educationcollege	1.146	0.367	0.371	0.711	0.572	2.447	0.797
UM	Spring	Educationcontinued	1.17	0.492	0.319	0.75	0.424	3.018	0.823
UM	Spring	Educationincomplete	0.356	0.776	-1.33	0.183	0.055	1.351	0.302
UM	Spring	Educationuniversity	1.537	0.341	1.26	0.208	0.818	3.153	0.329

UM	Spring	Ethnicity_Bin	1.052	0.546	0.092	0.927	0.405	3.629	0.948
sMD	Summer	(Intercept)	0.49	0.493	-1.445	0.149	0.185	1.281	0.252
sMD	Summer	Phase	0.987	0.034	-0.373	0.709	0.924	1.055	0.797
sMD	Summer	RA	0.994	0.039	-0.144	0.885	0.92	1.072	0.925
sMD	Summer	IV	0.979	0.035	-0.597	0.55	0.914	1.049	0.667
sMD	Summer	IS	1.024	0.038	0.611	0.541	0.95	1.103	0.658
sMD	Summer	Sleep Duration	1.085	0.04	2.051	0.04	1.004	1.174	0.087
sMD	Summer	Sleep Efficiency	1.092	0.041	2.127	0.033	1.007	1.185	0.075
sMD	Summer	Easting	1	0	-0.819	0.413	1	1	0.542
sMD	Summer	Age	0.965	0.005	-7.807	0	0.956	0.974	0
sMD	Summer	Sex	0.333	0.073	-15.077	0	0.288	0.384	0
sMD	Summer	Townsend	0.989	0.03	-0.367	0.713	0.932	1.049	0.797
sMD	Summer	Alcoholcurrent	1.294	0.201	1.285	0.199	0.887	1.951	0.321
sMD	Summer	Alcoholprevious	1.669	0.271	1.888	0.059	0.982	2.855	0.114
sMD	Summer	BMI	1.038	0.007	5.06	0	1.023	1.054	0
sMD	Summer	Smoking	1.389	0.053	6.157	0	1.251	1.542	0
sMD	Summer	Educationcollege	1.125	0.103	1.147	0.251	0.921	1.378	0.385
sMD	Summer	Educationcontinued	1.109	0.148	0.697	0.486	0.826	1.479	0.609
sMD	Summer	Educationincomplete	0.734	0.15	-2.052	0.04	0.544	0.983	0.087
sMD	Summer	Educationuniversity	1.097	0.096	0.961	0.337	0.91	1.328	0.473
sMD	Summer	Ethnicity_Bin	1.524	0.214	1.973	0.049	1.019	2.361	0.097
rMD	Summer	(Intercept)	3.429	0.362	3.408	0.001	1.686	6.961	0.002
rMD	Summer	Phase	1.075	0.026	2.837	0.005	1.023	1.131	0.013
rMD	Summer	RA	1.18	0.028	5.941	0	1.117	1.246	0
rMD	Summer	IV	0.934	0.027	-2.517	0.012	0.886	0.985	0.032
rMD	Summer	IS	0.956	0.029	-1.531	0.126	0.903	1.012	0.218
rMD	Summer	Sleep Duration	1.135	0.03	4.221	0	1.07	1.204	0

rMD	Summer	Sleep Efficiency	1.104	0.032	3.127	0.002	1.038	1.174	0.006
rMD	Summer	Easting	1	0	-1.753	0.08	1	1	0.147
rMD	Summer	Age	0.951	0.003	-14.432	0	0.944	0.957	0
rMD	Summer	Sex	0.35	0.055	-19.173	0	0.314	0.389	0
rMD	Summer	Townsend	1.104	0.022	4.475	0	1.057	1.153	0
rMD	Summer	Alcoholcurrent	1.068	0.14	0.468	0.64	0.814	1.413	0.744
rMD	Summer	Alcoholprevious	2.098	0.186	3.99	0	1.461	3.027	0
rMD	Summer	BMI	1.031	0.006	5.459	0	1.02	1.043	0
rMD	Summer	Smoking	1.512	0.041	10.14	0	1.396	1.637	0
rMD	Summer	Educationcollege	1.085	0.081	1.002	0.316	0.925	1.273	0.45
rMD	Summer	Educationcontinued	1.125	0.116	1.008	0.313	0.894	1.411	0.449
rMD	Summer	Educationincomplete	0.837	0.113	-1.578	0.115	0.67	1.043	0.2
rMD	Summer	Educationuniversity	1.248	0.075	2.953	0.003	1.078	1.447	0.01
rMD	Summer	Ethnicity_Bin	1.263	0.142	1.645	0.1	0.959	1.676	0.18
BD	Summer	(Intercept)	2.154	0.713	1.076	0.282	0.524	8.588	0.411
BD	Summer	Phase	1.162	0.049	3.063	0.002	1.056	1.28	0.007
BD	Summer	RA	1.105	0.05	1.988	0.047	0.999	1.217	0.095
BD	Summer	IV	0.954	0.052	-0.914	0.361	0.862	1.055	0.498
BD	Summer	IS	0.997	0.058	-0.06	0.952	0.89	1.115	0.967
BD	Summer	Sleep Duration	1.228	0.061	3.342	0.001	1.09	1.386	0.003
BD	Summer	Sleep Efficiency	1.156	0.063	2.31	0.021	1.023	1.309	0.052
BD	Summer	Easting	1	0	-3.218	0.001	1	1	0.004
BD	Summer	Age	0.918	0.007	-12.59	0	0.905	0.93	0
BD	Summer	Sex	0.544	0.105	-5.787	0	0.442	0.668	0
BD	Summer	Townsend	1.179	0.041	3.977	0	1.086	1.278	0
BD	Summer	Alcoholcurrent	1.03	0.295	0.102	0.919	0.599	1.915	0.946
BD	Summer	Alcoholprevious	2.127	0.366	2.062	0.039	1.052	4.46	0.086

BD	Summer	BMI	1.066	0.011	5.869	0	1.043	1.089	0
BD	Summer	Smoking	1.838	0.073	8.359	0	1.593	2.119	0
BD	Summer	Educationcollege	0.952	0.156	-0.314	0.753	0.703	1.296	0.823
BD	Summer	Educationcontinued	0.839	0.23	-0.763	0.446	0.529	1.304	0.577
BD	Summer	Educationincomplete	0.933	0.218	-0.318	0.751	0.603	1.421	0.823
BD	Summer	Educationuniversity	1.006	0.145	0.045	0.964	0.76	1.344	0.97
BD	Summer	Ethnicity_Bin	2.018	0.319	2.202	0.028	1.124	3.961	0.065
UM	Summer	(Intercept)	0.048	1.488	-2.045	0.041	0.002	0.801	0.088
UM	Summer	Phase	0.935	0.095	-0.707	0.48	0.778	1.127	0.605
UM	Summer	RA	0.881	0.116	-1.09	0.276	0.692	1.089	0.407
UM	Summer	IV	0.922	0.096	-0.851	0.395	0.762	1.109	0.531
UM	Summer	IS	1.027	0.107	0.252	0.801	0.832	1.265	0.859
UM	Summer	Sleep Duration	0.967	0.115	-0.288	0.774	0.778	1.22	0.838
UM	Summer	Sleep Efficiency	1.257	0.113	2.022	0.043	1.011	1.573	0.092
UM	Summer	Easting	1	0	-0.958	0.338	1	1	0.473
UM	Summer	Age	0.952	0.013	-3.818	0	0.928	0.976	0.001
UM	Summer	Sex	0.915	0.201	-0.441	0.659	0.618	1.36	0.758
UM	Summer	Townsend	0.923	0.094	-0.853	0.394	0.763	1.103	0.531
UM	Summer	Alcoholcurrent	1.84	0.727	0.839	0.401	0.564	11.335	0.537
UM	Summer	Alcoholprevious	1.902	0.926	0.695	0.487	0.308	14.713	0.609
UM	Summer	BMI	1.056	0.023	2.417	0.016	1.009	1.102	0.041
UM	Summer	Smoking	1.05	0.163	0.3	0.764	0.755	1.433	0.83
UM	Summer	Educationcollege	1.574	0.355	1.278	0.201	0.809	3.3	0.322
UM	Summer	Educationcontinued	1.268	0.514	0.463	0.644	0.432	3.376	0.744
UM	Summer	Educationincomplete	1.028	0.518	0.053	0.957	0.348	2.763	0.969
UM	Summer	Educationuniversity	1.815	0.336	1.774	0.076	0.977	3.696	0.142
UM	Summer	Ethnicity_Bin	1.326	0.605	0.466	0.641	0.475	5.537	0.744

sMD	Autumn	(Intercept)	0.587	0.477	-1.118	0.263	0.229	1.484	0.396
sMD	Autumn	Phase	1.046	0.034	1.328	0.184	0.979	1.118	0.302
sMD	Autumn	RA	1.113	0.037	2.924	0.003	1.035	1.195	0.01
sMD	Autumn	IV	0.967	0.035	-0.941	0.347	0.902	1.037	0.483
sMD	Autumn	IS	0.897	0.038	-2.866	0.004	0.833	0.966	0.012
sMD	Autumn	Sleep Duration	1.073	0.039	1.813	0.07	0.995	1.159	0.132
sMD	Autumn	Sleep Efficiency	1.093	0.041	2.153	0.031	1.008	1.185	0.072
sMD	Autumn	Easting	1	0	-0.514	0.607	1	1	0.718
sMD	Autumn	Age	0.961	0.004	-9.017	0	0.953	0.97	0
sMD	Autumn	Sex	0.351	0.072	-14.561	0	0.305	0.404	0
sMD	Autumn	Townsend	1.05	0.029	1.65	0.099	0.991	1.112	0.179
sMD	Autumn	Alcoholcurrent	1.277	0.193	1.27	0.204	0.887	1.893	0.325
sMD	Autumn	Alcoholprevious	2.216	0.26	3.064	0.002	1.336	3.706	0.007
sMD	Autumn	BMI	1.028	0.007	3.848	0	1.013	1.042	0
sMD	Autumn	Smoking	1.4	0.052	6.449	0	1.263	1.55	0
sMD	Autumn	Educationcollege	1.28	0.101	2.436	0.015	1.051	1.564	0.039
sMD	Autumn	Educationcontinued	1.125	0.151	0.778	0.437	0.833	1.508	0.571
sMD	Autumn	Educationincomplete	0.817	0.157	-1.291	0.197	0.598	1.105	0.318
sMD	Autumn	Educationuniversity	1.2	0.096	1.902	0.057	0.996	1.451	0.112
sMD	Autumn	Ethnicity_Bin	1.619	0.214	2.252	0.024	1.082	2.51	0.06
rMD	Autumn	(Intercept)	1.206	0.365	0.513	0.608	0.589	2.459	0.718
rMD	Autumn	Phase	1.16	0.026	5.729	0	1.103	1.221	0
rMD	Autumn	RA	1.183	0.028	6.011	0	1.12	1.25	0
rMD	Autumn	IV	0.941	0.027	-2.21	0.027	0.892	0.993	0.065
rMD	Autumn	IS	0.947	0.029	-1.873	0.061	0.894	1.002	0.117
rMD	Autumn	Sleep Duration	1.213	0.031	6.31	0	1.142	1.288	0
rMD	Autumn	Sleep Efficiency	1.144	0.033	4.129	0	1.073	1.219	0

rMD	Autumn	Easting	1	0	0.1	0.92	1	1	0.946
rMD	Autumn	Age	0.956	0.003	-13.189	0	0.95	0.962	0
rMD	Autumn	Sex	0.375	0.054	-18.104	0	0.337	0.416	0
rMD	Autumn	Townsend	1.159	0.022	6.733	0	1.11	1.21	0
rMD	Autumn	Alcoholcurrent	1.287	0.148	1.703	0.089	0.968	1.732	0.163
rMD	Autumn	Alcoholprevious	2.814	0.198	5.226	0	1.914	4.161	0
rMD	Autumn	BMI	1.029	0.006	5.119	0	1.018	1.041	0
rMD	Autumn	Smoking	1.389	0.041	8.062	0	1.282	1.505	0
rMD	Autumn	Educationcollege	0.988	0.079	-0.147	0.883	0.847	1.155	0.925
rMD	Autumn	Educationcontinued	1.174	0.113	1.418	0.156	0.94	1.463	0.263
rMD	Autumn	Educationincomplete	0.985	0.111	-0.134	0.894	0.791	1.224	0.929
rMD	Autumn	Educationuniversity	1.107	0.073	1.388	0.165	0.96	1.278	0.275
rMD	Autumn	Ethnicity_Bin	1.635	0.154	3.181	0.001	1.213	2.224	0.005
BD	Autumn	(Intercept)	1.874	0.701	0.896	0.37	0.465	7.286	0.507
BD	Autumn	Phase	1.001	0.045	0.026	0.979	0.917	1.095	0.979
BD	Autumn	RA	1.278	0.046	5.331	0	1.167	1.398	0
BD	Autumn	IV	0.948	0.051	-1.053	0.292	0.857	1.047	0.423
BD	Autumn	IS	0.976	0.055	-0.448	0.654	0.876	1.086	0.754
BD	Autumn	Sleep Duration	1.132	0.058	2.132	0.033	1.011	1.271	0.075
BD	Autumn	Sleep Efficiency	1.116	0.061	1.8	0.072	0.991	1.259	0.136
BD	Autumn	Easting	1	0	-2.007	0.045	1	1	0.093
BD	Autumn	Age	0.923	0.007	-12.242	0	0.911	0.935	0
BD	Autumn	Sex	0.46	0.104	-7.423	0	0.375	0.564	0
BD	Autumn	Townsend	1.213	0.04	4.77	0	1.12	1.312	0
BD	Autumn	Alcoholcurrent	1.605	0.336	1.405	0.16	0.873	3.308	0.268
BD	Autumn	Alcoholprevious	4.562	0.388	3.916	0	2.206	10.222	0
BD	Autumn	BMI	1.038	0.01	3.743	0	1.018	1.059	0.001

BD	Autumn	Smoking	1.663	0.073	6.983	0	1.441	1.917	0
BD	Autumn	Educationcollege	1.413	0.154	2.248	0.025	1.05	1.921	0.06
BD	Autumn	Educationcontinued	0.935	0.243	-0.278	0.781	0.572	1.488	0.842
BD	Autumn	Educationincomplete	1.16	0.227	0.656	0.512	0.737	1.798	0.634
BD	Autumn	Educationuniversity	1.13	0.148	0.825	0.409	0.849	1.521	0.541
BD	Autumn	Ethnicity_Bin	1.358	0.272	1.127	0.26	0.818	2.384	0.392
UM	Autumn	(Intercept)	0.1	1.172	-1.968	0.049	0.01	0.959	0.098
UM	Autumn	Phase	0.97	0.079	-0.382	0.703	0.834	1.136	0.792
UM	Autumn	RA	1.021	0.086	0.239	0.811	0.854	1.198	0.866
UM	Autumn	IV	0.937	0.086	-0.751	0.453	0.79	1.109	0.581
UM	Autumn	IS	0.933	0.093	-0.746	0.455	0.777	1.117	0.582
UM	Autumn	Sleep Duration	0.942	0.096	-0.624	0.533	0.785	1.144	0.65
UM	Autumn	Sleep Efficiency	1.096	0.099	0.923	0.356	0.905	1.336	0.493
UM	Autumn	Easting	1	0	1.054	0.292	1	1	0.423
UM	Autumn	Age	0.947	0.011	-4.866	0	0.927	0.968	0
UM	Autumn	Sex	1.483	0.18	2.194	0.028	1.046	2.118	0.066
UM	Autumn	Townsend	0.992	0.078	-0.105	0.916	0.848	1.151	0.946
UM	Autumn	Alcoholcurrent	0.893	0.474	-0.238	0.812	0.389	2.593	0.866
UM	Autumn	Alcoholprevious	0.775	0.746	-0.342	0.732	0.155	3.256	0.812
UM	Autumn	BMI	1.05	0.019	2.601	0.009	1.011	1.088	0.026
UM	Autumn	Smoking	1.041	0.14	0.285	0.775	0.785	1.362	0.838
UM	Autumn	Educationcollege	1.27	0.292	0.818	0.413	0.73	2.308	0.542
UM	Autumn	Educationcontinued	0.789	0.483	-0.492	0.623	0.281	1.93	0.731
UM	Autumn	Educationincomplete	0.692	0.485	-0.759	0.448	0.246	1.703	0.578
UM	Autumn	Educationuniversity	1.404	0.274	1.239	0.215	0.841	2.481	0.339
UM	Autumn	Ethnicity_Bin	0.71	0.39	-0.876	0.381	0.351	1.648	0.52
sMD	Winter	(Intercept)	0.293	0.56	-2.191	0.028	0.097	0.87	0.067

sMD	Winter	Phase	1.101	0.041	2.367	0.018	1.017	1.193	0.046
sMD	Winter	RA	1.127	0.04	2.977	0.003	1.04	1.218	0.009
sMD	Winter	IV	0.933	0.042	-1.64	0.101	0.858	1.013	0.181
sMD	Winter	IS	1.016	0.045	0.35	0.727	0.929	1.11	0.807
sMD	Winter	Sleep Duration	1.098	0.047	1.981	0.048	1.002	1.204	0.096
sMD	Winter	Sleep Efficiency	1.034	0.049	0.681	0.496	0.939	1.14	0.616
sMD	Winter	Easting	1	0	0.649	0.516	1	1	0.634
sMD	Winter	Age	0.961	0.005	-7.754	0	0.951	0.971	0
sMD	Winter	Sex	0.299	0.086	-14.046	0	0.252	0.353	0
sMD	Winter	Townsend	1.026	0.035	0.73	0.465	0.957	1.098	0.591
sMD	Winter	Alcoholcurrent	1.692	0.252	2.086	0.037	1.059	2.859	0.083
sMD	Winter	Alcoholprevious	2.036	0.331	2.147	0.032	1.07	3.942	0.073
sMD	Winter	BMI	1.045	0.008	5.229	0	1.028	1.063	0
sMD	Winter	Smoking	1.327	0.063	4.51	0	1.173	1.5	0
sMD	Winter	Educationcollege	1.405	0.12	2.832	0.005	1.112	1.781	0.014
sMD	Winter	Educationcontinued	1.159	0.175	0.847	0.397	0.819	1.626	0.533
sMD	Winter	Educationincomplete	0.905	0.179	-0.557	0.578	0.633	1.279	0.692
sMD	Winter	Educationuniversity	1.254	0.114	1.995	0.046	1.007	1.572	0.094
sMD	Winter	Ethnicity_Bin	1.158	0.227	0.649	0.517	0.755	1.84	0.634
rMD	Winter	(Intercept)	1.14	0.419	0.313	0.755	0.5	2.584	0.823
rMD	Winter	Phase	1.187	0.03	5.715	0	1.12	1.259	0
rMD	Winter	RA	1.183	0.031	5.47	0	1.114	1.256	0
rMD	Winter	IV	0.905	0.032	-3.109	0.002	0.849	0.964	0.006
rMD	Winter	IS	0.968	0.034	-0.969	0.332	0.905	1.034	0.468
rMD	Winter	Sleep Duration	1.134	0.035	3.581	0	1.059	1.215	0.001
rMD	Winter	Sleep Efficiency	1.034	0.037	0.909	0.363	0.962	1.112	0.499
rMD	Winter	Easting	1	0	-0.339	0.735	1	1	0.812

rMD	Winter	Age	0.955	0.004	-11.876	0	0.947	0.962	0
rMD	Winter	Sex	0.361	0.062	-16.399	0	0.32	0.408	0
rMD	Winter	Townsend	1.176	0.025	6.453	0	1.119	1.235	0
rMD	Winter	Alcoholcurrent	1.013	0.165	0.077	0.939	0.738	1.408	0.958
rMD	Winter	Alcoholprevious	1.435	0.228	1.585	0.113	0.919	2.246	0.198
rMD	Winter	BMI	1.04	0.006	6.153	0	1.027	1.053	0
rMD	Winter	Smoking	1.462	0.047	8.097	0	1.334	1.603	0
rMD	Winter	Educationcollege	1.128	0.092	1.313	0.189	0.943	1.351	0.308
rMD	Winter	Educationcontinued	1.232	0.129	1.617	0.106	0.955	1.585	0.188
rMD	Winter	Educationincomplete	1.043	0.127	0.334	0.739	0.812	1.335	0.814
rMD	Winter	Educationuniversity	1.263	0.084	2.781	0.005	1.072	1.49	0.016
rMD	Winter	Ethnicity_Bin	1.548	0.181	2.416	0.016	1.094	2.226	0.041
BD	Winter	(Intercept)	2.436	0.769	1.158	0.247	0.531	10.848	0.381
BD	Winter	Phase	1.217	0.055	3.571	0	1.094	1.356	0.001
BD	Winter	RA	1.207	0.051	3.662	0	1.088	1.332	0.001
BD	Winter	IV	0.842	0.062	-2.764	0.006	0.745	0.951	0.016
BD	Winter	IS	0.919	0.066	-1.281	0.2	0.808	1.045	0.322
BD	Winter	Sleep Duration	1.048	0.066	0.718	0.473	0.923	1.195	0.598
BD	Winter	Sleep Efficiency	1.04	0.07	0.567	0.571	0.908	1.193	0.685
BD	Winter	Easting	1	0	-1.152	0.249	1	1	0.383
BD	Winter	Age	0.914	0.007	-12.232	0	0.901	0.927	0
BD	Winter	Sex	0.54	0.118	-5.229	0	0.428	0.679	0
BD	Winter	Townsend	1.113	0.048	2.206	0.027	1.011	1.223	0.065
BD	Winter	Alcoholcurrent	0.95	0.33	-0.155	0.877	0.519	1.917	0.921
BD	Winter	Alcoholprevious	2.131	0.407	1.858	0.063	0.977	4.885	0.12
BD	Winter	BMI	1.066	0.011	5.605	0	1.043	1.09	0
BD	Winter	Smoking	1.93	0.083	7.893	0	1.638	2.272	0

BD	Winter	Educationcollege	1.292	0.173	1.485	0.138	0.925	1.821	0.235
BD	Winter	Educationcontinued	0.987	0.262	-0.052	0.959	0.58	1.63	0.969
BD	Winter	Educationincomplete	0.744	0.287	-1.034	0.301	0.413	1.279	0.435
BD	Winter	Educationuniversity	1.146	0.163	0.835	0.403	0.837	1.589	0.538
BD	Winter	Ethnicity_Bin	1.265	0.312	0.754	0.451	0.709	2.425	0.58
UM	Winter	(Intercept)	0.025	1.707	-2.159	0.031	0.001	0.593	0.072
UM	Winter	Phase	1.13	0.113	1.078	0.281	0.906	1.41	0.411
UM	Winter	RA	0.907	0.128	-0.764	0.445	0.693	1.142	0.577
UM	Winter	IV	0.881	0.115	-1.104	0.27	0.701	1.101	0.403
UM	Winter	IS	0.985	0.123	-0.123	0.902	0.772	1.25	0.935
UM	Winter	Sleep Duration	0.867	0.123	-1.165	0.244	0.69	1.113	0.379
UM	Winter	Sleep Efficiency	0.979	0.127	-0.17	0.865	0.766	1.261	0.913
UM	Winter	Easting	1	0	-0.825	0.41	1	1	0.541
UM	Winter	Age	0.963	0.014	-2.72	0.007	0.937	0.99	0.019
UM	Winter	Sex	1.315	0.225	1.218	0.223	0.849	2.056	0.349
UM	Winter	Townsend	1.106	0.098	1.032	0.302	0.908	1.332	0.435
UM	Winter	Alcoholcurrent	2.57	1.016	0.929	0.353	0.553	45.783	0.49
UM	Winter	Alcoholprevious	1.059	1.426	0.04	0.968	0.041	27.203	0.97
UM	Winter	BMI	1.064	0.024	2.583	0.01	1.013	1.113	0.027
UM	Winter	Smoking	1.12	0.18	0.63	0.529	0.778	1.58	0.647
UM	Winter	Educationcollege	0.838	0.341	-0.517	0.605	0.433	1.667	0.718
UM	Winter	Educationcontinued	1.727	0.406	1.345	0.179	0.76	3.805	0.295
UM	Winter	Educationincomplete	0.14	1.038	-1.893	0.058	0.008	0.703	0.113
UM	Winter	Educationuniversity	0.982	0.308	-0.06	0.952	0.549	1.853	0.967
UM	Winter	Ethnicity_Bin	0.692	0.533	-0.69	0.49	0.274	2.337	0.611
sMD	All	(Intercept)	0.412	0.259	-3.426	0.001	0.247	0.683	0.002
sMD	All	Phase	1.056	0.018	2.97	0.003	1.019	1.095	0.009

sMD	All	RA	1.078	0.019	3.855	0	1.037	1.119	0
sMD	All	IV	0.961	0.019	-2.068	0.039	0.926	0.998	0.086
sMD	All	IS	0.96	0.02	-2.002	0.045	0.922	0.999	0.093
sMD	All	Sleep Duration	1.077	0.021	3.501	0	1.033	1.123	0.002
sMD	All	Sleep Efficiency	1.074	0.022	3.208	0.001	1.028	1.122	0.004
sMD	All	Easting	1	0	-0.505	0.614	1	1	0.722
sMD	All	Age	0.964	0.002	-15.47	0	0.959	0.968	0
sMD	All	Sex	0.328	0.039	-28.521	0	0.304	0.354	0
sMD	All	Townsend	1.031	0.016	1.93	0.054	0.999	1.064	0.106
sMD	All	Alcoholcurrent	1.358	0.109	2.806	0.005	1.102	1.691	0.015
sMD	All	Alcoholprevious	1.924	0.145	4.497	0	1.448	2.563	0
sMD	All	BMI	1.035	0.004	8.91	0	1.027	1.043	0
sMD	All	Smoking	1.375	0.028	11.179	0	1.3	1.453	0
sMD	All	Educationcollege	1.228	0.055	3.738	0	1.103	1.369	0.001
sMD	All	Educationcontinued	1.093	0.08	1.104	0.27	0.933	1.277	0.403
sMD	All	Educationincomplete	0.816	0.082	-2.476	0.013	0.693	0.957	0.035
sMD	All	Educationuniversity	1.197	0.052	3.47	0.001	1.082	1.325	0.002
sMD	All	Ethnicity_Bin	1.491	0.111	3.584	0	1.204	1.863	0.001
rMD	All	(Intercept)	1.914	0.192	3.383	0.001	1.313	2.787	0.003
rMD	All	Phase	1.137	0.014	9.371	0	1.107	1.169	0
rMD	All	RA	1.162	0.015	10.308	0	1.129	1.195	0
rMD	All	IV	0.934	0.014	-4.678	0	0.908	0.961	0
rMD	All	IS	0.959	0.015	-2.726	0.006	0.93	0.988	0.018
rMD	All	Sleep Duration	1.15	0.016	8.668	0	1.114	1.187	0
rMD	All	Sleep Efficiency	1.085	0.017	4.766	0	1.049	1.121	0
rMD	All	Easting	1	0	-1.769	0.077	1	1	0.143
rMD	All	Age	0.954	0.002	-25.981	0	0.95	0.957	0

rMD	All	Sex	0.361	0.029	-35.286	0	0.341	0.382	0
rMD	All	Townsend	1.154	0.012	12.24	0	1.127	1.18	0
rMD	All	Alcoholcurrent	1.091	0.077	1.138	0.255	0.94	1.271	0.388
rMD	All	Alcoholprevious	2.093	0.103	7.178	0	1.712	2.563	0
rMD	All	BMI	1.031	0.003	10.304	0	1.025	1.037	0
rMD	All	Smoking	1.443	0.022	16.901	0	1.383	1.505	0
rMD	All	Educationcollege	1.089	0.043	2.014	0.044	1.002	1.184	0.093
rMD	All	Educationcontinued	1.155	0.06	2.389	0.017	1.026	1.299	0.043
rMD	All	Educationincomplete	0.937	0.06	-1.085	0.278	0.833	1.054	0.408
rMD	All	Educationuniversity	1.206	0.039	4.766	0	1.117	1.303	0
rMD	All	Ethnicity_Bin	1.443	0.079	4.65	0	1.238	1.686	0
BD	All	(Intercept)	2.329	0.358	2.363	0.018	1.151	4.68	0.046
BD	All	Phase	1.127	0.025	4.803	0	1.073	1.183	0
BD	All	RA	1.175	0.024	6.587	0	1.119	1.232	0
BD	All	IV	0.912	0.027	-3.361	0.001	0.864	0.962	0.003
BD	All	IS	0.954	0.029	-1.599	0.11	0.901	1.011	0.194
BD	All	Sleep Duration	1.158	0.031	4.715	0	1.09	1.231	0
BD	All	Sleep Efficiency	1.135	0.032	3.896	0	1.065	1.21	0
BD	All	Easting	1	0	-4.421	0	1	1	0
BD	All	Age	0.921	0.003	-24.006	0	0.915	0.927	0
BD	All	Sex	0.529	0.054	-11.712	0	0.476	0.589	0
BD	All	Townsend	1.177	0.022	7.583	0	1.129	1.228	0
BD	All	Alcoholcurrent	1.097	0.157	0.591	0.554	0.815	1.511	0.67
BD	All	Alcoholprevious	2.737	0.19	5.301	0	1.897	3.999	0
BD	All	BMI	1.056	0.005	10.157	0	1.045	1.067	0
BD	All	Smoking	1.703	0.038	13.858	0	1.579	1.836	0
BD	All	Educationcollege	1.223	0.081	2.476	0.013	1.044	1.437	0.035

BD	All	Educationcontinued	0.984	0.12	-0.139	0.89	0.776	1.241	0.927
BD	All	Educationincomplete	1.028	0.119	0.234	0.815	0.812	1.295	0.867
BD	All	Educationuniversity	1.143	0.077	1.734	0.083	0.984	1.331	0.153
BD	All	Ethnicity_Bin	1.328	0.141	2.006	0.045	1.014	1.765	0.093
UM	All	(Intercept)	0.073	0.692	-3.782	0	0.018	0.279	0.001
UM	All	Phase	0.982	0.047	-0.391	0.696	0.897	1.077	0.789
UM	All	RA	0.981	0.051	-0.383	0.702	0.883	1.08	0.792
UM	All	IV	0.906	0.049	-1.997	0.046	0.822	0.998	0.094
UM	All	IS	0.99	0.053	-0.18	0.857	0.892	1.099	0.907
UM	All	Sleep Duration	0.923	0.056	-1.444	0.149	0.83	1.031	0.252
UM	All	Sleep Efficiency	1.041	0.057	0.696	0.486	0.931	1.165	0.609
UM	All	Easting	1	0	-0.351	0.725	1	1	0.807
UM	All	Age	0.952	0.006	-7.718	0	0.94	0.964	0
UM	All	Sex	1.271	0.102	2.362	0.018	1.043	1.553	0.046
UM	All	Townsend	1.021	0.044	0.462	0.644	0.934	1.112	0.744
UM	All	Alcohol current	1.176	0.314	0.516	0.606	0.668	2.309	0.718
UM	All	Alcoholprevious	1.224	0.434	0.466	0.642	0.517	2.896	0.744
UM	All	BMI	1.05	0.011	4.485	0	1.028	1.073	0
UM	All	Smoking	1.138	0.08	1.623	0.105	0.971	1.327	0.186
UM	All	Educationcollege	1.2	0.166	1.099	0.272	0.872	1.673	0.404
UM	All	Educationcontinued	1.222	0.231	0.867	0.386	0.768	1.907	0.523
UM	All	Educationincomplete	0.542	0.296	-2.067	0.039	0.293	0.944	0.086
UM	All	Educationuniversity	1.408	0.155	2.212	0.027	1.048	1.925	0.065
UM	All	Ethnicity_Bin	0.9	0.246	-0.427	0.669	0.571	1.506	0.767

Table S5.1: Model variables.

Feature Name	Category	Description	Source	Type
acc_sleep_dur_AD_mn	Accelerometery	Mean sleep duration	UK Biobank	Numerical
acc_sleep_dur_AD_sd	Accelerometery	Std dev sleep duration	UK Biobank	Numerical
acc_sleep_eff_AD_mn_2	Accelerometery	Mean sleep efficiency	UK Biobank	Numerical
acc_sleep_midp_AD_mn	Accelerometery	Mean sleep midpoint	UK Biobank	Numerical
acc_timeinbed_AD_mn	Accelerometery	Mean time in bed	UK Biobank	Numerical
cosinor_amp	Accelerometery	Cosinor amplitude	UK Biobank	Numerical
diff_mean_PA_100_150	Accelerometery	Weekday/weekend difference mean percentage acceleration (101-150mg)	UK Biobank	Numerical
diff_mean_PA_150_200	Accelerometery	Weekday/weekend difference mean percentage acceleration (151-200mg)	UK Biobank	Numerical
diff_mean_PA_200	Accelerometery	Weekday/weekend difference mean percentage acceleration (200+mg)	UK Biobank	Numerical
diff_mean_PA_50	Accelerometery	Weekday/weekend difference mean percentage acceleration (50mg and less)	UK Biobank	Numerical
diff_mean_PA_50_100	Accelerometery	Weekday/weekend difference mean percentage acceleration (51-100mg)	UK Biobank	Numerical
diff_sd_PA_100_150	Accelerometery	Weekday/weekend difference std dev (101-150mg)	UK Biobank	Numerical
diff_sd_PA_150_200	Accelerometery	Weekday/weekend difference std dev (151-200mg)	UK Biobank	Numerical
diff_sd_PA_200	Accelerometery	Weekday/weekend difference std dev (200+mg)	UK Biobank	Numerical
diff_sd_PA_50	Accelerometery	Weekday/weekend difference std dev (50mg and less)	UK Biobank	Numerical
diff_sd_PA_50_100	Accelerometery	Weekday/weekend difference std dev (51-100mg)	UK Biobank	Numerical
is	Accelerometery	Interdaily stability	UK Biobank	Numerical

iv	Accelerometery	Intradaily variability	UK Biobank	Numerical
mean_PA_100_150_0	Accelerometery	Mean percentage acceleration between 101 and 150mg (weekdays only)	UK Biobank	Numerical
mean_PA_100_150_1	Accelerometery	Mean percentage acceleration between 101 and 150mg (weekends only)	UK Biobank	Numerical
mean_PA_150_200_0	Accelerometery	Mean percentage acceleration between 151 and 200mg (weekdays only)	UK Biobank	Numerical
mean_PA_150_200_1	Accelerometery	Mean percentage acceleration between 151 and 200mg (weekends only)	UK Biobank	Numerical
mean_PA_200_0	Accelerometery	Mean percentage acceleration 200mg and over (weekdays only)	UK Biobank	Numerical
mean_PA_200_1	Accelerometery	Mean percentage acceleration 200mg and over (weekends only)	UK Biobank	Numerical
mean_PA_50_0	Accelerometery	Mean percentage acceleration 50mg and lower (weekdays only)	UK Biobank	Numerical
mean_PA_50_1	Accelerometery	Mean percentage acceleration 50mg and lower (weekends only)	UK Biobank	Numerical
mean_PA_50_100_0	Accelerometery	Mean percentage acceleration between 51 and 100mg (weekdays only)	UK Biobank	Numerical
mean_PA_50_100_1	Accelerometery	Mean percentage acceleration between 51 and 100mg (weekends only)	UK Biobank	Numerical
mesor	Accelerometery	Mesor	UK Biobank	Numerical
MVPA_100	Accelerometery	N moderate to vigorous physical activity sessions (10mins with 80% at 100mg or above)	UK Biobank	Numerical
phase	Accelerometery	Phase	UK Biobank	Numerical
ra	Accelerometery	Relative amplitude	UK Biobank	Numerical
sd_PA_100_150_0	Accelerometery	Std dev acceleration between 101 and 150mg (weekdays only)	UK Biobank	Numerical
sd_PA_100_150_1	Accelerometery	Std dev acceleration between 101 and 150mg (weekends only)	UK Biobank	Numerical
sd_PA_150_200_0	Accelerometery	Std dev acceleration between 151 and 200mg (weekdays only)	UK Biobank	Numerical
sd_PA_150_200_1	Accelerometery	Std dev acceleration between 151 and 200mg (weekends only)	UK Biobank	Numerical

sd_PA_200_0	Accelerometery	Std dev acceleration 200mg and over (weekdays only)	UK Biobank	Numerical
sd_PA_200_1	Accelerometery	Std dev acceleration 200mg and over (weekends only)	UK Biobank	Numerical
sd_PA_50_0	Accelerometery	Std dev acceleration 50mg and lower (weekdays only)	UK Biobank	Numerical
sd_PA_50_1	Accelerometery	Std dev acceleration 50mg and lower (weekends only)	UK Biobank	Numerical
sd_PA_50_100_0	Accelerometery	Std dev acceleration between 51 and 100mg (weekdays only)	UK Biobank	Numerical
sd_PA_50_100_1	Accelerometery	Std dev acceleration between 51 and 100mg (weekends only)	UK Biobank	Numerical
av_acc	Accelerometery	Average acceleration	UK Biobank	Numerical
age_actig_years	Demographic	Age in years (at time of accelerometer study)	UK Biobank	Numerical
alcohol._never	Demographic	Alcohol drinking status = non-alcohol drinker	UK Biobank	Binary
alcohol.current	Demographic	Alcohol drinking status = previous alcohol drinker	UK Biobank	Binary
alcohol.previous	Demographic	Alcohol drinking status = current alcohol drinker	UK Biobank	Binary
BMI.1	Demographic	BMI <18.5	UK Biobank	Binary
BMI.2	Demographic	BMI >=18.5 & <25	UK Biobank	Binary
BMI.3	Demographic	BMI >=25 & <30	UK Biobank	Binary
BMI.4	Demographic	BMI >=30 & <40	UK Biobank	Binary
BMI.5	Demographic	BMI >=40	UK Biobank	Binary
ethnicity_bin	Demographic	Binary ethnicity status (0=white, 1=other)	UK Biobank	Binary
education.college	Demographic	Highest level of education - college	UK Biobank	Binary
education.compulsory	Demographic	Highest level of education - compulsory	UK Biobank	Binary

education.continued	Demographic	Highest level of education - continued	UK Biobank	Binary
education.incomplete	Demographic	Highest level of education - incomplete	UK Biobank	Binary
education.university	Demographic	Highest level of education - university	UK Biobank	Binary
townsend	Demographic	Townsend deprivation score buckets (see methods)	UK Biobank	Ordinal
lat	Demographic	Approximate home latitude	UK Biobank	Numerical
long	Demographic	Approximate home longitude	UK Biobank	Numerical
sex.0	Demographic	Sex = male	UK Biobank	Binary
sex.1	Demographic	Sex = female	UK Biobank	Binary
smoking.0	Demographic	Smoking status = non-smoker	UK Biobank	Binary
smoking.1	Demographic	Smoking status = previous smoker	UK Biobank	Binary
smoking.2	Demographic	Smoking status = current smoker	UK Biobank	Binary
acc_season.Spring	Seasonal	Season of accelerometer wear based on first day of wear (spring)	UK Biobank	Binary
acc_season.Summer	Seasonal	Season of accelerometer wear based on first day of wear (summer)	UK Biobank	Binary
acc_season.Autumn	Seasonal	Season of accelerometer wear based on first day of wear (autumn)	UK Biobank	Binary
acc_season.Winter	Seasonal	Season of accelerometer wear based on first day of wear (winter)	UK Biobank	Binary
avAcc_frost_ratio	Seasonal	Ratio of mean acceleration and average ground frost across period of accelerometer wear	UK Biobank/HadUK-Grid	Numerical
avAcc_rain_ratio	Seasonal	Ratio of mean acceleration and average rainfall across period of accelerometer wear	UK Biobank/HadUK-Grid	Numerical

avAcc_sun_ratio	Seasonal	Ratio of mean acceleration and average sunshine across period of accelerometer wear	UK Biobank/HadUK-Grid	Numerical
day_len_hrs	Seasonal	Day length (hrs between surise and sunset) during period of accelerometer wear, based on first day of wear.	UK Biobank	Numerical
frost_avg_curr	Seasonal	N days with ground frost in month of accelerometer wear	HadUK-Grid	Numerical
frost_avg_prev_month	Seasonal	N days with ground frost month prior to accelerometer wear	HadUK-Grid	Numerical
LAN_home_binary.0	Seasonal	Light at night not present in home area	NASA	Binary
LAN_home_binary.1	Seasonal	Light at night present in home area	NASA	Binary
MVPA_frost_ratio	Seasonal	Ratio of n MVPA sessions and N ground frost days in month of accelerometer wear	UK Biobank/HadUK-Grid	Numerical
MVPA_rain_ratio	Seasonal	Ratio of n MVPA sessions and average rainfall across week(s) of accelerometer wear	UK Biobank/HadUK-Grid	Numerical
MVPA_sun_ratio	Seasonal	Ratio of n MVPA sessions and average sunshine in month of accelerometer wear	UK Biobank/HadUK-Grid	Numerical
rain_avg_curr	Seasonal	Average rainfall (mm) across period of accelerometer wear	HadUK-Grid	Numerical
rain_avg_prev_week	Seasonal	Average rainfall (mm) week prior to accelerometer wear	HadUK-Grid	Numerical
sun_avg_curr	Seasonal	Average sunshine (hrs) in month of accelerometer wear	HadUK-Grid	Numerical
sun_avg_prev_month	Seasonal	Average sunshine (hrs) in month prior to accelerometer wear	HadUK-Grid	Numerical
f_1160_0_0	Sleep_Questionnaire	Reported sleep duration	UK Biobank	Numerical
f_1170_0_0	Sleep_Questionnaire	Difficulty getting up in the morning	UK Biobank	Ordinal
f_1180_0_0	Sleep_Questionnaire	Reported chronotype	UK Biobank	Ordinal

Table S5.2: Mood disorder group differences (high importance variables).

	Mean (SD) / Percentage (N)					Test Statistic	p value	Effect Size
	Control	**UM**	**BD**	**rMD**	**sMD**			
Age	63.72 (7.60)	60.65 (7.93)	58.75 (7.53)	60.73 (7.67)	61.39 (7.51)	416.932	<0.001	0.040
Sex	-	-	-	-	-	1971.808	<0.001	0.223
Female	48.01 (11,582)	41.14 (188)	61.88 (1,138)	70.92 (6,409)	72.31 (3,090)	-	-	-
Male	51.99 (12,544)	58.86 (269)	38.12 (701)	29.08 (2,628)	27.69 (1,183)	-	-	-
Latitude (standardised)	0.00 (1.01)	-0.08 (1.00)	0.01 (0.99)	-0.01 (0.99)	0.01 (0.99)	1.131	0.340	0.000
Difficulty getting up in the morning	3.28 (0.68)	3.15 (0.77)	2.84 (0.87)	2.86 (0.84)	3.04 (0.77)	627.106	<0.001	0.060
Average acceleration/rainfall ratio (standardised)	0.00 (1.11)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.29)	0.02 (1.45)	0.388	0.817	0.000
N MVPA Periods	9.61 (10.15)	10.29 (10.41)	9.05 (10.46)	8.76 (10.01)	8.54 (9.59)	19.775	<0.001	0.002
MVPA/rainfall ratio (standardised)	0.00 (1.24)	-0.01 (0.01)	-0.01 (0.00)	0.00 (0.35)	0.01 (0.66)	0.100	0.982	0.000
Average rainfall	2.20 (2.08)	2.06 (2.06)	2.12 (1.94)	2.20 (2.08)	2.14 (2.01)	2.064	0.083	0.000

Table S6.1: Clustering analysis variables.

Symptom Category	Measure	UKB Field Number
Depression	Duration	20438
Depression	Number of lifetime episodes	20442
Depression	Fraction of day impacted	20436
Depression	Level of impact on normal roles	20440
Depression	Hypersomnia	20533
Depression	Insomnia	20534
Depression	Early waking	20535
Depression	Difficulty concentrating	20435
Depression	Increased tiredness	20449
Depression	Feelings of worthlessness	20450
Depression	Weight change - no change	20536
Depression	Weight change - increase	20536
Depression	Weight change - decrease	20536
Depression	Weight change - increase and decrease	20536
Mania	Duration	20492
Mania	Severity	20493
Mania	Increased talkativeness	20548
Mania	Restlessness	20548
Mania	Racing thoughts	20548
Mania	Reduced sleep	20548
Mania	Increased creativity	20548
Mania	Increased distraction	20548
Mania	Increased confidence	20548
Mania	More active	20548
Anxiety	Duration	20420
Anxiety	Multiple worries	20540
Anxiety	Difficulty controlling worry	20537
Anxiety	Difficulty stopping worry	20539
Anxiety	Level of impact on normal roles	20418

Anxiety	Increased worry	20541
Anxiety	Reduced concentration	20419
Anxiety	Increased tiredness	20429
Anxiety	Difficulty sleeping	20427
Anxiety	Feeling restless	20426
Anxiety	Feeling irritable	20422
Anxiety	Tense/sore muscles	20417
Self-harm	Contemplated self-harm	20485
Self-harm	N times self-harmed	20482
Unsual/psychotic experience	N times believed an un-real conspiracy	20470
Unsual/psychotic experience	N times believed in un-real communications	20476
Unsual/psychotic experience	N times heard an un-real voice	20465
Unsual/psychotic experience	N times seen an un-real vision	20473

Table S6.2: Chi-squared Tests for 3 clusters.

	Percentage (N)			Test Statistic	p-value	FDR Adjusted p-value	Effect Size
Mental Health Measure	**Cluster 1**	**Cluster 2**	**Cluster 3**				
anx_TenseMuscles	0.0 (1)	53.3 (4722)	37.8 (3646)	8671.133394	<0.001	<0.001	0.5233
anx_Concentration	0.0 (2)	89.6 (7933)	78.5 (7562)	21846.07396	<0.001	<0.001	0.8307
anx_Irritability	0.1 (8)	84.9 (7518)	62.3 (6005)	17752.60729	<0.001	<0.001	0.7488
anx_Restless	0.0 (4)	73.2 (6481)	57.4 (5528)	14263.13729	<0.001	<0.001	0.6712
anx_SleepProblem	0.0 (6)	87.6 (7759)	84.6 (8146)	22769.69904	<0.001	<0.001	0.8481
anx_NWorries	0.0 (3)	87.9 (7784)	76.8 (7394)	20995.0767	<0.001	<0.001	0.8143
anx_Worry	0.1 (13)	96.3 (8525)	94.1 (9060)	28144.12364	<0.001	<0.001	0.9429
anx_Tiredness	0.0 (3)	81.2 (7188)	72.7 (7004)	18452.74195	<0.001	<0.001	0.7635
anx_Impact	-	-	-	29788.26212	<0.001	<0.001	0.6859
None	99.9 (13154)	2.0 (178)	4.0 (385)	-	-	-	-
A little	0.1 (7)	14.7 (1299)	21.8 (2096)	-	-	-	-
Somewhat	0.0 (4)	38.8 (3431)	39.8 (3838)	-	-	-	-
A lot	0.1 (8)	44.6 (3945)	34.4 (3314)	-	-	-	-
anx_ControlWorry	-	-	-	30947.15651	<0.001	<0.001	0.6991
None	99.9 (13154)	0.7 (65)	1.5 (148)	-	-	-	-
Rarely	0.1 (10)	4.4 (389)	6.6 (637)	-	-	-	-
Sometimes	0.1 (8)	35.6 (3155)	41.0 (3946)	-	-	-	-
Often	0.0 (1)	59.2 (5244)	50.9 (4902)	-	-	-	-
anx_StopWorry	-	-	-	31100.85298	<0.001	<0.001	0.7008
None	99.8 (13150)	0.6 (55)	1.3 (130)	-	-	-	-
Rarely	0.1 (17)	4.6 (403)	7.5 (719)	-	-	-	-
Sometimes	0.0 (5)	37.5 (3317)	42.8 (4124)	-	-	-	-
Often	0.0 (1)	57.4 (5078)	48.4 (4660)	-	-	-	-

anx_Duration	-	-	-	14779.59019	<0.001	<0.001	0.4831
None	88.6 (11671)	23.1 (2043)	22.9 (2208)	-	-	-	-
1 - 7 days	11.3 (1493)	17.4 (1543)	21.6 (2078)	-	-	-	-
8 - 31 days	0.1 (7)	21.8 (1933)	26.4 (2542)	-	-	-	-
> 31 days	0.0 (1)	16.9 (1495)	14.9 (1440)	-	-	-	-
All rolled into each other	0.0 (1)	20.8 (1839)	14.2 (1365)	-	-	-	-
dep_Concentration	68.9 (9077)	89.7 (7940)	86.8 (8360)	1819.960437	<0.001	<0.001	0.2398
dep_Tiredness	68.0 (8954)	88.8 (7859)	85.4 (8229)	1720.699413	<0.001	<0.001	0.2331
dep_Worthlessness	48.2 (6343)	79.0 (6996)	72.3 (6963)	2594.039619	<0.001	<0.001	0.2862
dep_Insomnia	50.3 (6625)	65.8 (5824)	63.5 (6121)	660.3756664	<0.001	<0.001	0.1444
dep_Hypersomnia	15.7 (2073)	26.9 (2381)	19.7 (1894)	412.5255015	<0.001	<0.001	0.1142
dep_WakingEarly	50.1 (6600)	66.6 (5898)	67.1 (6463)	900.3396114	<0.001	<0.001	0.1686
dep_WeightChange_0	46.0 (6062)	27.2 (2405)	36.5 (3518)	810.4135754	<0.001	<0.001	0.16
dep_WeightChange_1	16.0 (2111)	34.8 (3077)	9.9 (956)	1983.774463	<0.001	<0.001	0.2503
dep_WeightChange_2	32.3 (4249)	30.2 (2675)	45.0 (4338)	550.2487902	<0.001	<0.001	0.1318
dep_WeightChange_3	5.7 (751)	7.9 (696)	8.5 (821)	75.61443073	<0.001	<0.001	0.04887
dep_FractionDay	-	-	-	3101.382849	<0.001	<0.001	0.2213
None	22.0 (2892)	4.8 (421)	2.4 (232)	-	-	-	-
Less than half	6.0 (784)	3.6 (317)	4.8 (464)	-	-	-	-
About half	9.6 (1262)	7.9 (702)	8.9 (857)	-	-	-	-
Most of the day	40.4 (5321)	45.0 (3981)	46.9 (4516)	-	-	-	-
All day	22.1 (2914)	38.8 (3432)	37.0 (3564)	-	-	-	-
dep_Duration	-	-	-	4080.264549	<0.001	<0.001	0.2539
None	19.8 (2605)	4.0 (354)	0.9 (84)	-	-	-	-
< 1 month	8.6 (1133)	4.5 (400)	4.5 (429)	-	-	-	-
1 - 3 months	26.4 (3482)	18.8 (1665)	21.9 (2108)	-	-	-	-
3 - 6 months	16.2 (2130)	17.9 (1586)	20.0 (1928)	-	-	-	-

6 - 12 months	12.7 (1667)	18.8 (1661)	21.1 (2035)	-	-	-	-
1 - 2 years	8.7 (1145)	15.9 (1411)	15.7 (1511)	-	-	-	-
> 2 years	7.7 (1011)	20.1 (1776)	16.0 (1538)	-	-	-	-
dep_Impact	-	-	-	3465.445513	<0.001	<0.001	0.2339
None	21.4 (2821)	4.6 (404)	2.3 (222)	-	-	-	-
A little	16.6 (2187)	10.1 (890)	14.8 (1429)	-	-	-	-
Somewhat	31.7 (4179)	29.0 (2563)	36.3 (3492)	-	-	-	-
A lot	30.3 (3986)	56.4 (4996)	46.6 (4490)	-	-	-	-
dep_NEpisodes	-	-	-	4065.583536	<0.001	<0.001	0.2534
None	19.5 (2566)	4.3 (382)	0.1 (8)	-	-	-	-
One	34.6 (4557)	19.5 (1729)	29.6 (2852)	-	-	-	-
Multiple	27.6 (3634)	38.2 (3379)	39.0 (3755)	-	-	-	-
Too many to count	18.3 (2416)	38.0 (3363)	31.3 (3018)	-	-	-	-
man_Severity	9.1 (1194)	38.8 (3434)	4.5 (430)	4852.090038	<0.001	<0.001	0.3915
man_Talkative	9.7 (1277)	26.8 (2373)	2.8 (270)	2599.904294	<0.001	<0.001	0.2866
man_Restless	17.9 (2364)	55.4 (4901)	4.6 (440)	6963.680231	<0.001	<0.001	0.469
man_RacingThoughts	15.3 (2018)	51.3 (4544)	4.3 (415)	6528.867791	<0.001	<0.001	0.4541
man_LessSleep	8.0 (1058)	19.8 (1755)	1.6 (156)	1847.053519	<0.001	<0.001	0.2415
man_Creative	7.0 (924)	14.9 (1316)	1.6 (152)	1175.530288	<0.001	<0.001	0.1927
man_Distracted	13.3 (1753)	44.3 (3921)	3.4 (328)	5488.030822	<0.001	<0.001	0.4164
man_Confident	7.0 (926)	15.4 (1359)	2.0 (191)	1163.139983	<0.001	<0.001	0.1917
man_MoreActive	11.4 (1496)	27.2 (2412)	2.7 (264)	2486.556489	<0.001	<0.001	0.2803
man_Duration	-	-	-	8020.28475	<0.001	<0.001	0.3559
None	66.4 (8748)	20.7 (1832)	80.9 (7797)	-	-	-	-
< 24 hours	7.6 (1000)	14.3 (1262)	7.6 (733)	-	-	-	-
1 day - 1 week	17.3 (2284)	34.9 (3094)	7.0 (670)	-	-	-	-
> 1 week	8.7 (1141)	30.1 (2665)	4.5 (433)	-	-	-	-

psy_FreqConspiracy	0.4 (59)	2.6 (231)	1.1 (104)	204.319193	<0.001	<0.001	0.08034
psy_FreqCommunications	0.6 (85)	1.6 (145)	0.7 (65)	66.42075997	<0.001	<0.001	0.0458
psy_FreqVoices	1.5 (198)	4.3 (380)	2.2 (216)	172.4677181	<0.001	<0.001	0.07381
psy_FreqVisions	3.0 (401)	6.4 (566)	3.9 (379)	149.3176776	<0.001	<0.001	0.06868
sel_NTimes	-	-	-	551.0465284	<0.001	<0.001	0.09329
None	93.6 (12324)	85.0 (7526)	91.4 (8802)	-	-	-	-
1	3.4 (442)	5.6 (493)	4.3 (416)	-	-	-	-
2	1.3 (165)	2.9 (258)	1.7 (163)	-	-	-	-
>= 3	1.8 (242)	6.5 (576)	2.6 (252)	-	-	-	-
sel_Contemplated	-	-	-	1359.996282	<0.001	<0.001	0.1466
No	77.2 (10165)	55.8 (4936)	67.2 (6477)	-	-	-	-
Once	12.2 (1611)	16.0 (1418)	15.4 (1486)	-	-	-	-
More than once	10.6 (1397)	28.2 (2499)	17.3 (1670)	-	-	-	-

Table S6.3: Chi-squared Tests for 2 clusters.

	Percentage (N)		Test Statistic	p-value	FDR Adjusted p-value	Effect Size
Mental Health Measure	**Cluster 1**	**Cluster 2**				
anx_TenseMuscles	0.0 (1)	45.3 (8368)	8099.697243	<0.001	<0.001	0.5059
anx_Concentration	0.0 (2)	83.8 (15495)	21614.97026	<0.001	<0.001	0.8263
anx_Irritability	0.1 (8)	73.2 (13523)	16788.29551	<0.001	<0.001	0.7283
anx_Restless	0.0 (4)	65.0 (12009)	13770.00047	<0.001	<0.001	0.6596
anx_SleepProblem	0.0 (6)	86.0 (15905)	22748.76349	<0.001	<0.001	0.8477
anx_NWorries	0.0 (3)	82.1 (15178)	20761.24569	<0.001	<0.001	0.8099
anx_Worry	0.1 (13)	95.1 (17585)	28130.87057	<0.001	<0.001	0.9427
anx_Tiredness	0.0 (3)	76.8 (14192)	18315.37231	<0.001	<0.001	0.7607
anx_Impact	-	-	29358.74975	<0.001	<0.001	0.963
None	99.9 (13154)	3.0 (563)	-	-	-	-
A little	0.1 (7)	18.4 (3395)	-	-	-	-
Somewhat	0.0 (4)	39.3 (7269)	-	-	-	-
A lot	0.1 (8)	39.3 (7259)	-	-	-	-
anx_ControlWorry	-	-	30718.51156	<0.001	<0.001	0.985
None	99.9 (13154)	1.2 (213)	-	-	-	-
Rarely	0.1 (10)	5.6 (1026)	-	-	-	-
Sometimes	0.1 (8)	38.4 (7101)	-	-	-	-
Often	0.0 (1)	54.9 (10146)	-	-	-	-
anx_StopWorry	-	-	30814.5113	<0.001	<0.001	0.9866
None	99.8 (13150)	1.0 (185)	-	-	-	-
Rarely	0.1 (17)	6.1 (1122)	-	-	-	-
Sometimes	0.0 (5)	40.3 (7441)	-	-	-	-
Often	0.0 (1)	52.7 (9738)	-	-	-	-

anx_Duration	-	-	14445.62896	<0.001	<0.001	0.6755
None	88.6 (11671)	23.0 (4251)	-	-	-	-
1 - 7 days	11.3 (1493)	19.6 (3621)	-	-	-	-
8 - 31 days	0.1 (7)	24.2 (4475)	-	-	-	-
> 31 days	0.0 (1)	15.9 (2935)	-	-	-	-
All rolled into each other	0.0 (1)	17.3 (3204)	-	-	-	-
dep_Concentration	68.9 (9077)	88.2 (16300)	1794.321032	<0.001	<0.001	0.2381
dep_Tiredness	68.0 (8954)	87.0 (16088)	1688.286049	<0.001	<0.001	0.231
dep_Worthlessness	48.2 (6343)	75.5 (13959)	2501.715268	<0.001	<0.001	0.2812
dep_Insomnia	50.3 (6625)	64.6 (11945)	650.2091523	<0.001	<0.001	0.1434
dep_Hypersomnia	15.7 (2073)	23.1 (4275)	261.4993971	<0.001	<0.001	0.09096
dep_WakingEarly	50.1 (6600)	66.9 (12361)	899.2161797	<0.001	<0.001	0.1686
dep_WeightChange_0	46.0 (6062)	32.0 (5923)	638.2259307	<0.001	<0.001	0.142
dep_WeightChange_1	16.0 (2111)	21.8 (4033)	164.571907	<0.001	<0.001	0.07218
dep_WeightChange_2	32.3 (4249)	37.9 (7013)	108.0852557	<0.001	<0.001	0.0585
dep_WeightChange_3	5.7 (751)	8.2 (1517)	72.20709046	<0.001	<0.001	0.04788
dep_FractionDay	-	-	3051.110392	<0.001	<0.001	0.3104
None	22.0 (2892)	3.5 (653)	-	-	-	-
Less than half	6.0 (784)	4.2 (781)	-	-	-	-
About half	9.6 (1262)	8.4 (1559)	-	-	-	-
Most of the day	40.4 (5321)	46.0 (8497)	-	-	-	-
All day	22.1 (2914)	37.8 (6996)	-	-	-	-
dep_Duration	-	-	3930.789713	<0.001	<0.001	0.3524
None	19.8 (2605)	2.4 (438)	-	-	-	-
< 1 month	8.6 (1133)	4.5 (829)	-	-	-	-
1 - 3 months	26.4 (3482)	20.4 (3773)	-	-	-	-
3 - 6 months	16.2 (2130)	19.0 (3514)	-	-	-	-

6 - 12 months	12.7 (1667)	20.0 (3696)	-	-	-	-
1 - 2 years	8.7 (1145)	15.8 (2922)	-	-	-	-
> 2 years	7.7 (1011)	17.9 (3314)	-	-	-	-
dep_Impact	-	-	3189.089917	<0.001	<0.001	0.3174
None	21.4 (2821)	3.4 (626)	-	-	-	-
A little	16.6 (2187)	12.5 (2319)	-	-	-	-
Somewhat	31.7 (4179)	32.8 (6055)	-	-	-	-
A lot	30.3 (3986)	51.3 (9486)	-	-	-	-
dep_NEpisodes	-	-	3740.339097	<0.001	<0.001	0.3437
None	19.5 (2566)	2.1 (390)	-	-	-	-
One	34.6 (4557)	24.8 (4581)	-	-	-	-
Multiple	27.6 (3634)	38.6 (7134)	-	-	-	-
Too many to count	18.3 (2416)	34.5 (6381)	-	-	-	-
man_Severity	9.1 (1194)	20.9 (3864)	802.1403883	<0.001	<0.001	0.1593
man_Talkative	9.7 (1277)	14.3 (2643)	149.8120687	<0.001	<0.001	0.06889
man_Restless	17.9 (2364)	28.9 (5341)	499.9145372	<0.001	<0.001	0.1257
man_RacingThoughts	15.3 (2018)	26.8 (4959)	592.0669778	<0.001	<0.001	0.1368
man_LessSleep	8.0 (1058)	10.3 (1911)	47.85645965	<0.001	<0.001	0.03899
man_Creative	7.0 (924)	7.9 (1468)	9.326983472	0.002	0.003	0.01729
man_Distracted	13.3 (1753)	23.0 (4249)	468.2310259	<0.001	<0.001	0.1217
man_Confident	7.0 (926)	8.4 (1550)	19.40754126	<0.001	<0.001	0.02488
man_MoreActive	11.4 (1496)	14.5 (2676)	65.13935939	<0.001	<0.001	0.04545
man_Duration	-	-	768.4604458	<0.001	<0.001	0.1558
None	66.4 (8748)	52.1 (9629)	-	-	-	-
< 24 hours	7.6 (1000)	10.8 (1995)	-	-	-	-
1 day - 1 week	17.3 (2284)	20.4 (3764)	-	-	-	-
> 1 week	8.7 (1141)	16.8 (3098)	-	-	-	-

psy_FreqConspiracy	0.4 (59)	1.8 (335)	115.3823051	<0.001	<0.001	0.06066
psy_FreqCommunications	0.6 (85)	1.1 (210)	19.53817677	<0.001	<0.001	0.02518
psy_FreqVoices	1.5 (198)	3.2 (596)	92.47114484	<0.001	<0.001	0.05425
psy_FreqVisions	3.0 (401)	5.1 (945)	80.290308	<0.001	<0.001	0.05052
sel_NTimes	-	-	269.7079816	<0.001	<0.001	0.0923
None	93.6 (12324)	88.3 (16328)	-	-	-	-
1	3.4 (442)	4.9 (909)	-	-	-	-
2	1.3 (165)	2.3 (421)	-	-	-	-
>= 3	1.8 (242)	4.5 (828)	-	-	-	-
sel_Contemplated	-	-	958.3547541	<0.001	<0.001	0.174
No	77.2 (10165)	61.7 (11413)	-	-	-	-
Once	12.2 (1611)	15.7 (2904)	-	-	-	-
More than once	10.6 (1397)	22.6 (4169)	-	-	-	-

Table S6.4: Full cluster, sub-cluster and PMD group comparison results.

Variable	Comparison	Comparison symptom categories	Estimate	Std. Error	z value	Pr(>|z|)	Odds Ratio	2.50%	97.50%	p_FDR
Relative Amplitude Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	- 0.008	0.027	- 0.298	0.766	0.992	0.94	1.047	0.956
Relative Amplitude Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.074	0.066	- 1.120	0.263	0.929	0.821	1.064	0.591
Relative Amplitude Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.071	0.064	- 1.104	0.269	0.932	0.826	1.063	0.593
Relative Amplitude Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.011	0.040	- 0.279	0.780	0.989	0.916	1.071	0.956
Relative Amplitude Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.041	0.052	0.786	0.432	1.042	0.943	1.158	0.764
Relative Amplitude Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.045	0.060	0.751	0.453	1.046	0.932	1.179	0.786
Relative Amplitude Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.030	0.028	- 1.080	0.280	0.97	0.919	1.026	0.603
Relative Amplitude Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.075	0.059	1.275	0.202	1.078	0.965	1.215	0.466
Relative Amplitude Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.107	0.064	1.675	0.094	1.113	0.987	1.268	0.344

Intradaily Variability Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.083	0.028	3.009	0.003	1.087	1.03	1.148	0.037
Intradaily Variability Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.015	0.070	0.220	0.826	1.015	0.887	1.165	0.956
Intradaily Variability Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.056	0.070	- 0.806	0.420	0.945	0.825	1.085	0.764
Intradaily Variability Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	0.050	0.038	1.306	0.192	1.051	0.976	1.132	0.452
Intradaily Variability Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.010	0.047	0.210	0.834	1.01	0.921	1.109	0.956
Intradaily Variability Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	- 0.032	0.056	- 0.575	0.565	0.968	0.867	1.082	0.835
Intradaily Variability Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.063	0.030	2.142	0.032	1.065	1.006	1.129	0.160
Intradaily Variability Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.033	0.053	0.634	0.526	1.034	0.933	1.147	0.818
Intradaily Variability Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.011	0.059	- 0.179	0.858	0.989	0.881	1.112	0.956
Interdaily Stability Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.051	0.028	1.803	0.071	1.053	0.996	1.113	0.283
Interdaily Stability Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.006	0.072	- 0.079	0.937	0.994	0.863	1.146	0.956

Interdaily Stability Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.048	0.076	-0.629	0.529	0.953	0.822	1.107	0.818
Interdaily Stability Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	0.015	0.039	0.372	0.710	1.015	0.94	1.096	0.937
Interdaily Stability Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.005	0.051	-0.092	0.927	0.995	0.901	1.1	0.956
Interdaily Stability Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.002	0.059	0.034	0.973	1.002	0.892	1.126	0.973
Interdaily Stability Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-0.003	0.031	-0.112	0.911	0.997	0.939	1.058	0.956
Interdaily Stability Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.004	0.056	0.066	0.948	1.004	0.9	1.119	0.957
Interdaily Stability Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.033	0.065	0.504	0.614	1.033	0.91	1.173	0.866
Mean Acceleration Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.055	0.029	1.920	0.055	1.056	0.999	1.117	0.236
Mean Acceleration Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.173	0.067	2.594	0.009	1.189	1.04	1.351	0.068
Mean Acceleration Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.106	0.071	1.483	0.138	1.112	0.965	1.276	0.420
Mean Acceleration Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	0.056	0.042	1.346	0.178	1.058	0.975	1.147	0.449

Mean Acceleration Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.009	0.053	0.163	0.871	1.009	0.908	1.118	0.956
Mean Acceleration Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.010	0.064	-0.148	0.883	0.991	0.873	1.124	0.956
Mean Acceleration Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.086	0.031	2.812	0.005	1.09	1.026	1.157	0.044
Mean Acceleration Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.223	0.052	4.261	0.000	1.249	1.126	1.383	0.001
Mean Acceleration Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.139	0.061	2.276	0.023	1.15	1.019	1.296	0.133
Sleep Efficiency Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.038	0.027	1.409	0.159	1.039	0.985	1.096	0.436
Sleep Efficiency Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.148	0.066	-2.249	0.025	0.862	0.76	0.983	0.135
Sleep Efficiency Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.168	0.065	-2.592	0.010	0.846	0.746	0.962	0.068
Sleep Efficiency Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.004	0.042	-0.098	0.922	0.996	0.918	1.081	0.956
Sleep Efficiency Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.039	0.054	0.731	0.465	1.04	0.937	1.156	0.794
Sleep Efficiency Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.042	0.065	0.641	0.521	1.043	0.918	1.186	0.818

Sleep Efficiency Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.026	0.030	- 0.885	0.376	0.974	0.919	1.033	0.716
Sleep Efficiency Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.044	0.053	- 0.826	0.409	0.957	0.863	1.064	0.764
Sleep Efficiency Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.020	0.062	- 0.324	0.746	0.98	0.869	1.107	0.956
Mean Sleep Duration Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.007	0.026	0.254	0.800	1.007	0.956	1.06	0.956
Mean Sleep Duration Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.155	0.066	- 2.342	0.019	0.857	0.754	0.977	0.119
Mean Sleep Duration Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.141	0.066	- 2.140	0.032	0.868	0.763	0.989	0.160
Mean Sleep Duration Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.062	0.040	- 1.568	0.117	0.94	0.869	1.016	0.386
Mean Sleep Duration Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.072	0.052	- 1.396	0.163	0.931	0.841	1.03	0.436
Mean Sleep Duration Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	- 0.027	0.060	- 0.442	0.659	0.974	0.865	1.097	0.881
Mean Sleep Duration Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.017	0.029	- 0.578	0.563	0.983	0.929	1.041	0.835
Mean Sleep Duration Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.148	0.051	- 2.879	0.004	0.863	0.781	0.955	0.044

Mean Sleep Duration Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-	0.111	0.060	-	1.862	0.063	0.895	0.796	1.006	0.258
Subjective Sleep Duration (Long)	Clusters (with Anxiety)	Unipolar Depression vs Bipolar		0.299	0.207		1.444	0.149	1.349	0.893	2.017	0.420
Subjective Sleep Duration (Short)	Clusters (with Anxiety)	Unipolar Depression vs Bipolar		0.266	0.059		4.489	0.000	1.305	1.162	1.466	0.001
Subjective Sleep Duration (Long)	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania		0.256	0.527		0.486	0.627	1.292	0.386	3.216	0.866
Subjective Sleep Duration (Short)	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-	0.148	0.166	-	0.889	0.374	0.863	0.617	1.186	0.716
Subjective Sleep Duration (Long)	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-	0.051	0.542	-	0.095	0.924	0.95	0.278	2.457	0.956
Subjective Sleep Duration (Short)	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-	0.432	0.169	-	2.552	0.011	0.649	0.462	0.898	0.071
Subjective Sleep Duration (Long)	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-	0.230	0.349	-	0.657	0.511	0.795	0.382	1.523	0.818
Subjective Sleep Duration (Short)	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar		0.173	0.087		1.986	0.047	1.189	1.001	1.409	0.220
Subjective Sleep Duration (Long)	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania		0.266	0.406		0.654	0.513	1.305	0.549	2.753	0.818
Subjective Sleep Duration (Short)	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania		0.063	0.116		0.543	0.587	1.065	0.847	1.333	0.855

Subjective Sleep Duration (Long)	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.455	0.502	0.906	0.365	1.576	0.569	4.185	0.716
Subjective Sleep Duration (Short)	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.128	0.134	-0.955	0.339	0.88	0.676	1.142	0.700
Subjective Sleep Duration (Long)	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.317	0.215	1.474	0.141	1.373	0.884	2.06	0.420
Subjective Sleep Duration (Short)	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.244	0.065	3.789	0.000	1.277	1.124	1.448	0.005
Subjective Sleep Duration (Long)	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.039	0.466	0.083	0.934	1.039	0.362	2.343	0.956
Subjective Sleep Duration (Short)	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	-0.026	0.124	-0.206	0.837	0.975	0.761	1.238	0.956
Subjective Sleep Duration (Long)	Probable Mood Disorder	Bipolar vs Unipolar Mania	-0.079	0.515	-0.153	0.878	0.924	0.3	2.351	0.956
Subjective Sleep Duration (Short)	Probable Mood Disorder	Bipolar vs Unipolar Mania	-0.272	0.138	-1.970	0.049	0.762	0.579	0.996	0.220
Difficulty Getting Up	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.077	0.058	1.323	0.186	1.08	0.964	1.209	0.449
Difficulty Getting Up	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.165	0.160	-1.029	0.303	0.848	0.615	1.153	0.639
Difficulty Getting Up	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.220	0.163	-1.352	0.176	0.802	0.579	1.097	0.449

Difficulty Getting Up	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.249	0.093	- 2.676	0.007	0.78	0.649	0.934	0.061
Difficulty Getting Up	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.186	0.127	- 1.463	0.143	0.83	0.644	1.061	0.420
Difficulty Getting Up	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.071	0.150	0.470	0.638	1.073	0.798	1.437	0.866
Difficulty Getting Up	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.043	0.065	0.666	0.506	1.044	0.918	1.186	0.818
Difficulty Getting Up	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.545	0.147	- 3.714	0.000	0.58	0.431	0.767	0.005
Difficulty Getting Up	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.572	0.159	- 3.590	0.000	0.565	0.41	0.767	0.007
Chronotype (Evening)	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.113	0.085	1.333	0.182	1.119	0.948	1.32	0.449
Chronotype (Morning)	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.010	0.066	0.153	0.878	1.01	0.887	1.15	0.956
Chronotype (Evening)	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.337	0.213	1.580	0.114	1.4	0.907	2.098	0.386
Chronotype (Morning)	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.489	0.158	3.103	0.002	1.631	1.193	2.215	0.032
Chronotype (Evening)	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.196	0.219	0.897	0.370	1.217	0.781	1.845	0.716

Chronotype (Morning)	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.470	0.162	2.893	0.004	1.6	1.159	2.194	0.044
Chronotype (Evening)	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.013	0.128	-0.105	0.916	0.987	0.765	1.265	0.956
Chronotype (Morning)	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	0.056	0.091	0.617	0.537	1.058	0.884	1.264	0.818
Chronotype (Evening)	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.084	0.174	-0.482	0.630	0.92	0.648	1.283	0.866
Chronotype (Morning)	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.011	0.123	-0.091	0.927	0.989	0.775	1.255	0.956
Chronotype (Evening)	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.106	0.201	-0.529	0.597	0.899	0.603	1.328	0.856
Chronotype (Morning)	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.049	0.142	-0.346	0.730	0.952	0.72	1.256	0.950
Chronotype (Evening)	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.133	0.091	1.461	0.144	1.142	0.953	1.362	0.420
Chronotype (Morning)	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.119	0.072	1.655	0.098	1.126	0.977	1.295	0.346
Chronotype (Evening)	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	-0.048	0.189	-0.253	0.800	0.953	0.648	1.363	0.956
Chronotype (Morning)	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.355	0.125	2.848	0.004	1.426	1.114	1.816	0.044

Chronotype (Evening)	Probable Mood Disorder	Bipolar vs Unipolar Mania	-	0.163	0.207	-	0.786	0.432	0.85	0.559	1.263	0.764
Chronotype (Morning)	Probable Mood Disorder	Bipolar vs Unipolar Mania		0.241	0.142		1.692	0.091	1.272	0.961	1.679	0.344
Reasoning Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	-	0.039	0.046	-	0.837	0.403	0.962	0.879	1.053	0.764
Reasoning Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-	0.202	0.117	-	1.723	0.085	0.817	0.648	1.027	0.429
Reasoning Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-	0.185	0.121	-	1.525	0.127	0.831	0.654	1.053	0.535
Reasoning Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-	0.094	0.070	-	1.340	0.180	0.911	0.794	1.044	0.616
Reasoning Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania		0.149	0.089		1.668	0.095	1.16	0.974	1.383	0.429
Reasoning Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania		0.230	0.107		2.151	0.031	1.259	1.022	1.556	0.316
Reasoning Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-	0.018	0.052	-	0.343	0.732	0.982	0.887	1.088	0.941
Reasoning Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania		0.104	0.088		1.184	0.236	1.109	0.934	1.317	0.680
Reasoning Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania		0.136	0.103		1.323	0.186	1.146	0.937	1.402	0.616

Reaction Time Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.020	0.048	0.424	0.671	1.021	0.929	1.123	0.914
Reaction Time Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.159	0.109	-1.454	0.146	0.853	0.694	1.066	0.541
Reaction Time Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.259	0.119	-2.181	0.029	0.772	0.614	0.98	0.316
Reaction Time Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.157	0.074	-2.127	0.033	0.855	0.74	0.989	0.316
Reaction Time Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.014	0.102	-0.137	0.891	0.986	0.81	1.208	0.966
Reaction Time Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.112	0.116	0.968	0.333	1.119	0.895	1.411	0.699
Reaction Time Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-0.056	0.055	-1.019	0.308	0.946	0.851	1.054	0.699
Reaction Time Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	-0.091	0.089	-1.015	0.310	0.913	0.771	1.094	0.699
Reaction Time Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-0.079	0.107	-0.734	0.463	0.924	0.751	1.144	0.810
Pairs Matching Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	-0.030	0.044	-0.675	0.499	0.971	0.891	1.059	0.828
Pairs Matching Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.033	0.115	0.289	0.773	1.034	0.838	1.317	0.944

Pairs Matching Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.080	0.124	0.648	0.517	1.084	0.862	1.401	0.835
Pairs Matching Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	0.076	0.074	1.036	0.300	1.079	0.937	1.251	0.699
Pairs Matching Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.071	0.092	0.770	0.442	1.074	0.901	1.295	0.795
Pairs Matching Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.010	0.122	-0.081	0.935	0.99	0.78	1.262	0.966
Pairs Matching Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.051	0.054	0.944	0.345	1.052	0.949	1.173	0.701
Pairs Matching Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.036	0.088	0.407	0.684	1.036	0.88	1.241	0.914
Pairs Matching Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.001	0.114	0.006	0.995	1.001	0.803	1.259	0.995
Trail Making Test (B) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.004	0.081	0.047	0.962	1.004	0.858	1.18	0.978
Trail Making Test (B) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.036	0.166	-0.219	0.827	0.964	0.718	1.383	0.947
Trail Making Test (B) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.078	0.166	-0.471	0.638	0.925	0.676	1.326	0.914
Trail Making Test (B) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.077	0.094	-0.819	0.413	0.926	0.774	1.123	0.764

Trail Making Test (B) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.157	0.159	0.988	0.323	1.17	0.882	1.641	0.699
Trail Making Test (B) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.319	0.185	1.726	0.084	1.376	0.967	2.006	0.429
Trail Making Test (B) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.019	0.088	0.220	0.826	1.02	0.864	1.221	0.947
Trail Making Test (B) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.060	0.138	0.436	0.663	1.062	0.83	1.423	0.914
Trail Making Test (B) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.038	0.145	0.261	0.794	1.038	0.788	1.41	0.944
Matrix Completion Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	- 0.188	0.063	- 2.987	0.003	0.829	0.732	0.937	0.178
Matrix Completion Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.321	0.140	- 2.291	0.022	0.726	0.551	0.955	0.316
Matrix Completion Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.143	0.144	- 0.994	0.320	0.867	0.654	1.152	0.699
Matrix Completion Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.145	0.085	- 1.701	0.089	0.865	0.732	1.023	0.429
Matrix Completion Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.054	0.112	- 0.482	0.630	0.948	0.762	1.181	0.914
Matrix Completion Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.154	0.133	1.165	0.244	1.167	0.902	1.519	0.680

Matrix Completion Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.125	0.067	- 1.884	0.060	0.882	0.774	1.005	0.375
Matrix Completion Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.210	0.109	- 1.932	0.053	0.811	0.656	1.004	0.374
Matrix Completion Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.083	0.119	- 0.698	0.485	0.92	0.728	1.164	0.827
Tower Rearranging Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	- 0.027	0.061	- 0.434	0.664	0.974	0.864	1.098	0.914
Tower Rearranging Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.279	0.132	- 2.106	0.035	0.757	0.584	0.981	0.316
Tower Rearranging Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.292	0.143	- 2.044	0.041	0.747	0.563	0.987	0.322
Tower Rearranging Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.023	0.087	- 0.262	0.794	0.978	0.825	1.159	0.944
Tower Rearranging Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.019	0.115	- 0.165	0.869	0.981	0.783	1.231	0.966
Tower Rearranging Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.016	0.134	0.121	0.904	1.016	0.781	1.322	0.966
Tower Rearranging Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.006	0.067	- 0.084	0.933	0.994	0.872	1.134	0.966
Tower Rearranging Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.041	0.105	- 0.390	0.697	0.96	0.781	1.181	0.914

Tower Rearranging Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-	0.068	0.128	-	0.532	0.595	0.934	0.727	1.201	0.914
Symbol Digit Substitution Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	-	0.095	0.065	-	1.474	0.141	0.909	0.8	1.032	0.541
Symbol Digit Substitution Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-	0.126	0.145	-	0.867	0.386	0.882	0.665	1.175	0.759
Symbol Digit Substitution Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-	0.044	0.158	-	0.281	0.779	0.957	0.702	1.308	0.944
Symbol Digit Substitution Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-	0.043	0.096	-	0.446	0.656	0.958	0.794	1.158	0.914
Symbol Digit Substitution Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-	0.134	0.116	-	1.155	0.248	0.874	0.697	1.101	0.680
Symbol Digit Substitution Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-	0.163	0.151	-	1.078	0.281	0.85	0.631	1.143	0.699
Symbol Digit Substitution Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-	0.166	0.072	-	2.327	0.020	0.847	0.736	0.975	0.316

Symbol Digit Substitution Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	-0.137	0.113	-1.214	0.225	0.872	0.7	1.091	0.680
Symbol Digit Substitution Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.014	0.135	0.106	0.916	1.014	0.779	1.324	0.966
Bipolar Disorder PRS Z Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	-0.072	0.019	-3.868	0.000	0.93	0.897	0.965	0.001
Bipolar Disorder PRS Z Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.106	0.050	-2.106	0.035	0.9	0.815	0.993	0.106
Bipolar Disorder PRS Z Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.033	0.050	-0.665	0.506	0.967	0.877	1.067	0.594
Bipolar Disorder PRS Z Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.026	0.027	-0.959	0.338	0.974	0.924	1.027	0.507
Bipolar Disorder PRS Z Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.033	0.037	-0.901	0.368	0.967	0.9	1.04	0.522
Bipolar Disorder PRS Z Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.005	0.043	-0.114	0.909	0.995	0.915	1.083	0.942
Bipolar Disorder PRS Z Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-0.104	0.021	-4.945	0.000	0.902	0.865	0.939	0.000
Bipolar Disorder PRS Z Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.027	0.040	0.691	0.489	1.028	0.951	1.111	0.594

Bipolar Disorder PRS Z Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.123	0.043	2.888	0.004	1.131	1.041	1.23	0.015
Major Depressive Disorder PRS Z Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	-0.065	0.019	-3.427	0.001	0.937	0.903	0.973	0.003
Major Depressive Disorder PRS Z Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.007	0.051	-0.141	0.888	0.993	0.899	1.097	0.942
Major Depressive Disorder PRS Z Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.044	0.051	0.866	0.387	1.045	0.946	1.155	0.522
Major Depressive Disorder PRS Z Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.042	0.027	-1.539	0.124	0.959	0.909	1.012	0.279
Major Depressive Disorder PRS Z Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.047	0.037	1.281	0.200	1.049	0.975	1.127	0.338
Major Depressive Disorder PRS Z Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.118	0.044	2.667	0.008	1.125	1.032	1.227	0.026
Major Depressive Disorder PRS Z Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-0.096	0.021	-4.536	0.000	0.909	0.872	0.947	0.000

Major Depressive Disorder PRS Z Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.081	0.040	2.042	0.041	1.085	1.003	1.173	0.111
Major Depressive Disorder PRS Z Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.190	0.045	4.177	0.000	1.209	1.106	1.322	0.000
Schizophrenia PRS Z Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	- 0.038	0.019	- 1.993	0.046	0.963	0.928	0.999	0.114
Schizophrenia PRS Z Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.067	0.051	- 1.318	0.187	0.935	0.847	1.033	0.338
Schizophrenia PRS Z Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.038	0.052	- 0.735	0.462	0.962	0.868	1.066	0.594
Schizophrenia PRS Z Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.015	0.028	- 0.555	0.579	0.985	0.933	1.04	0.651
Schizophrenia PRS Z Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.048	0.037	- 1.295	0.195	0.953	0.885	1.025	0.338
Schizophrenia PRS Z Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	- 0.003	0.044	- 0.072	0.942	0.997	0.914	1.087	0.942
Schizophrenia PRS Z Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.086	0.021	- 4.063	0.000	0.917	0.88	0.956	0.000
Schizophrenia PRS Z Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.047	0.040	- 1.186	0.236	0.954	0.882	1.031	0.374

Schizophrenia PRS Z Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.065	0.045	1.446	0.148	1.067	0.977	1.166	0.308
Accumbens (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.051	0.047	1.084	0.279	1.052	0.96	1.155	0.996
Accumbens (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.071	0.116	0.615	0.539	1.074	0.857	1.352	0.996
Accumbens (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.030	0.120	0.251	0.802	1.031	0.816	1.31	0.996
Accumbens (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.076	0.072	-1.042	0.297	0.927	0.805	1.069	0.996
Accumbens (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.072	0.094	-0.764	0.445	0.931	0.775	1.12	0.996
Accumbens (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.093	0.112	0.831	0.406	1.097	0.882	1.368	0.996
Accumbens (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.042	0.054	0.774	0.439	1.043	0.938	1.16	0.996
Accumbens (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.044	0.092	0.477	0.633	1.045	0.873	1.253	0.996
Accumbens (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-0.005	0.109	-0.042	0.966	0.995	0.804	1.235	0.996
Accumbens (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.004	0.048	0.082	0.935	1.004	0.914	1.103	0.996

Accumbens (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.111	0.120	0.923	0.356	1.117	0.883	1.415	0.996
Accumbens (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.153	0.123	1.237	0.216	1.165	0.916	1.487	0.996
Accumbens (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.114	0.072	-1.578	0.115	0.892	0.774	1.028	0.996
Accumbens (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.098	0.090	1.087	0.277	1.103	0.925	1.319	0.996
Accumbens (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.243	0.109	2.231	0.026	1.275	1.032	1.582	0.996
Accumbens (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.054	0.054	0.988	0.323	1.055	0.949	1.174	0.996
Accumbens (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.094	0.093	1.010	0.312	1.098	0.916	1.319	0.996
Accumbens (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.060	0.109	0.548	0.584	1.062	0.857	1.316	0.996
Amygdala (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.038	0.047	0.804	0.422	1.039	0.947	1.139	0.996
Amygdala (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.050	0.114	0.434	0.665	1.051	0.841	1.317	0.996
Amygdala (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.022	0.122	-0.180	0.857	0.978	0.77	1.242	0.996

Amygdala (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.082	0.070	-1.165	0.244	0.921	0.802	1.057	0.996
Amygdala (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.077	0.089	-0.862	0.389	0.926	0.777	1.103	0.996
Amygdala (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.023	0.110	0.209	0.834	1.023	0.825	1.27	0.996
Amygdala (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.034	0.053	0.630	0.528	1.034	0.932	1.148	0.996
Amygdala (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.091	0.090	1.014	0.311	1.096	0.919	1.308	0.996
Amygdala (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.064	0.107	0.600	0.549	1.066	0.865	1.316	0.996
Amygdala (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.008	0.047	0.162	0.871	1.008	0.92	1.104	0.996
Amygdala (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.091	0.113	0.801	0.423	1.095	0.878	1.369	0.996
Amygdala (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.058	0.122	0.478	0.633	1.06	0.836	1.35	0.996
Amygdala (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.139	0.069	-2.002	0.045	0.87	0.759	0.997	0.996
Amygdala (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.035	0.088	-0.402	0.688	0.965	0.812	1.148	0.996

Amygdala (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.057	0.109	0.521	0.603	1.058	0.855	1.312	0.996
Amygdala (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	-0.019	0.052	-0.365	0.715	0.981	0.885	1.088	0.996
Amygdala (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.109	0.090	1.210	0.226	1.116	0.935	1.333	0.996
Amygdala (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.114	0.109	1.046	0.296	1.12	0.907	1.39	0.996
Caudate (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.048	0.050	0.975	0.330	1.05	0.952	1.157	0.996
Caudate (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.117	0.122	-0.954	0.340	0.89	0.7	1.131	0.996
Caudate (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.148	0.131	-1.125	0.260	0.863	0.665	1.113	0.996
Caudate (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.013	0.071	-0.189	0.850	0.987	0.858	1.133	0.996
Caudate (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.014	0.088	-0.164	0.870	0.986	0.828	1.171	0.996
Caudate (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.018	0.104	0.171	0.864	1.018	0.831	1.248	0.996
Caudate (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.042	0.055	0.757	0.449	1.043	0.936	1.161	0.996

Caudate (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.032	0.094	- 0.343	0.732	0.968	0.805	1.163	0.996
Caudate (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.035	0.108	- 0.323	0.746	0.966	0.781	1.193	0.996
Caudate (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.028	0.049	0.568	0.570	1.028	0.933	1.133	0.996
Caudate (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.112	0.123	- 0.910	0.363	0.894	0.701	1.138	0.996
Caudate (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.119	0.130	- 0.914	0.361	0.888	0.686	1.145	0.996
Caudate (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.052	0.071	- 0.723	0.469	0.95	0.825	1.092	0.996
Caudate (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.058	0.089	- 0.657	0.511	0.943	0.792	1.122	0.996
Caudate (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	- 0.008	0.105	- 0.072	0.943	0.993	0.808	1.22	0.996
Caudate (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.037	0.055	0.670	0.503	1.038	0.931	1.157	0.996
Caudate (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.081	0.094	- 0.859	0.390	0.922	0.766	1.109	0.996
Caudate (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.078	0.109	- 0.713	0.476	0.925	0.746	1.145	0.996

Hippocampus (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.054	0.051	1.051	0.293	1.055	0.955	1.166	0.996
Hippocampus (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.023	0.120	-0.194	0.846	0.977	0.774	1.241	0.996
Hippocampus (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.105	0.127	-0.826	0.409	0.9	0.703	1.16	0.996
Hippocampus (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	0.031	0.072	0.423	0.672	1.031	0.895	1.19	0.996
Hippocampus (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.007	0.091	-0.073	0.942	0.993	0.831	1.191	0.996
Hippocampus (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-0.043	0.107	-0.397	0.692	0.958	0.777	1.184	0.996
Hippocampus (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.098	0.057	1.727	0.084	1.103	0.988	1.234	0.996
Hippocampus (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	-0.008	0.094	-0.081	0.936	0.992	0.827	1.196	0.996
Hippocampus (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-0.069	0.114	-0.605	0.545	0.934	0.748	1.169	0.996
Hippocampus (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.024	0.051	0.470	0.638	1.024	0.927	1.132	0.996
Hippocampus (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.013	0.123	0.108	0.914	1.013	0.799	1.293	0.996

Hippocampus (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.032	0.133	- 0.242	0.809	0.968	0.749	1.261	0.996
Hippocampus (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.028	0.077	- 0.367	0.714	0.972	0.837	1.131	0.996
Hippocampus (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.059	0.097	- 0.608	0.543	0.943	0.781	1.141	0.996
Hippocampus (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	- 0.068	0.119	- 0.567	0.571	0.935	0.739	1.181	0.996
Hippocampus (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.082	0.059	1.397	0.162	1.085	0.968	1.218	0.996
Hippocampus (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.087	0.097	- 0.904	0.366	0.916	0.76	1.11	0.996
Hippocampus (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.120	0.112	- 1.074	0.283	0.887	0.712	1.105	0.996
Pallidum (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	- 0.006	0.050	- 0.119	0.906	0.994	0.9	1.097	0.996
Pallidum (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.024	0.129	- 0.190	0.849	0.976	0.756	1.252	0.996
Pallidum (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.009	0.133	0.065	0.948	1.009	0.774	1.301	0.996
Pallidum (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.080	0.074	- 1.081	0.280	0.924	0.799	1.066	0.996

Pallidum (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.056	0.097	- 0.576	0.565	0.946	0.781	1.142	0.996
Pallidum (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.090	0.109	0.832	0.405	1.095	0.884	1.354	0.996
Pallidum (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.107	0.056	1.898	0.058	1.113	0.996	1.242	0.996
Pallidum (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.004	0.101	- 0.043	0.965	0.996	0.815	1.211	0.996
Pallidum (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	- 0.059	0.108	- 0.543	0.587	0.943	0.761	1.162	0.996
Pallidum (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	- 0.025	0.052	- 0.476	0.634	0.976	0.881	1.08	0.996
Pallidum (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.114	0.134	- 0.857	0.391	0.892	0.685	1.155	0.996
Pallidum (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.005	0.133	- 0.035	0.972	0.995	0.767	1.291	0.996
Pallidum (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.108	0.075	- 1.439	0.150	0.898	0.775	1.039	0.996
Pallidum (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.012	0.099	- 0.126	0.900	0.988	0.812	1.198	0.996
Pallidum (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.106	0.109	0.968	0.333	1.111	0.897	1.378	0.996

Pallidum (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.052	0.058	0.899	0.369	1.053	0.94	1.179	0.996
Pallidum (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.015	0.100	0.147	0.883	1.015	0.832	1.233	0.996
Pallidum (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.014	0.116	0.124	0.902	1.014	0.807	1.273	0.996
Putamen (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.060	0.051	1.182	0.237	1.061	0.962	1.172	0.996
Putamen (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-0.003	0.124	-0.023	0.982	0.997	0.781	1.273	0.998
Putamen (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-0.046	0.129	-0.360	0.719	0.955	0.742	1.23	0.996
Putamen (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-0.141	0.072	-1.966	0.049	0.869	0.754	1	0.996
Putamen (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-0.143	0.093	-1.538	0.124	0.867	0.721	1.04	0.996
Putamen (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.027	0.116	0.236	0.814	1.028	0.819	1.292	0.996
Putamen (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.085	0.057	1.506	0.132	1.089	0.975	1.217	0.996
Putamen (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.020	0.097	0.203	0.839	1.02	0.844	1.234	0.996

Putamen (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-	0.092	0.114	-	0.804	0.421	0.912	0.728	1.141	0.996
Putamen (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar		0.016	0.050		0.315	0.753	1.016	0.92	1.122	0.996
Putamen (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	-	0.010	0.124	-	0.082	0.935	0.99	0.777	1.263	0.996
Putamen (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	-	0.025	0.126	-	0.196	0.844	0.976	0.762	1.25	0.996
Putamen (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	-	0.008	0.074	-	0.107	0.915	0.992	0.858	1.148	0.996
Putamen (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	-	0.152	0.098	-	1.554	0.120	0.859	0.709	1.04	0.996
Putamen (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	-	0.108	0.111	-	0.974	0.330	0.897	0.721	1.116	0.996
Putamen (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar		0.050	0.057		0.884	0.377	1.052	0.94	1.176	0.996
Putamen (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	-	0.108	0.097	-	1.119	0.263	0.897	0.742	1.085	0.996
Putamen (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	-	0.159	0.112	-	1.424	0.154	0.853	0.684	1.061	0.996
Thalamus (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar		0.034	0.052		0.652	0.515	1.034	0.935	1.145	0.996

Thalamus (Left) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.000	0.127	- 0.002	0.998	1	0.779	1.284	0.998
Thalamus (Left) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	- 0.038	0.130	- 0.292	0.770	0.963	0.747	1.243	0.996
Thalamus (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.022	0.076	- 0.294	0.769	0.978	0.842	1.136	0.996
Thalamus (Left) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	0.047	0.100	0.475	0.635	1.049	0.863	1.277	0.996
Thalamus (Left) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.111	0.119	0.933	0.351	1.117	0.885	1.412	0.996
Thalamus (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	0.022	0.058	0.380	0.704	1.022	0.912	1.147	0.996
Thalamus (Left) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	0.049	0.101	0.484	0.628	1.05	0.863	1.28	0.996
Thalamus (Left) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.021	0.112	0.191	0.849	1.022	0.821	1.272	0.996
Thalamus (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Bipolar	0.017	0.051	0.336	0.737	1.017	0.921	1.124	0.996
Thalamus (Right) Z-Score	Clusters (with Anxiety)	Unipolar Depression vs Unipolar Mania	0.041	0.122	0.333	0.739	1.041	0.821	1.323	0.996
Thalamus (Right) Z-Score	Clusters (with Anxiety)	Bipolar vs Unipolar Mania	0.061	0.131	0.466	0.641	1.063	0.822	1.376	0.996

Thalamus (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Bipolar	- 0.083	0.076	- 1.098	0.272	0.92	0.793	1.068	0.996
Thalamus (Right) Z-Score	Sub-clusters (without Anxiety)	Unipolar Depression vs Unipolar Mania	- 0.001	0.098	- 0.012	0.990	0.999	0.824	1.212	0.998
Thalamus (Right) Z-Score	Sub-clusters (without Anxiety)	Bipolar vs Unipolar Mania	0.103	0.113	0.908	0.364	1.108	0.888	1.384	0.996
Thalamus (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Bipolar	- 0.028	0.057	- 0.487	0.626	0.972	0.869	1.088	0.996
Thalamus (Right) Z-Score	Probable Mood Disorder	Unipolar Depression vs Unipolar Mania	- 0.011	0.098	- 0.109	0.913	0.989	0.817	1.199	0.996
Thalamus (Right) Z-Score	Probable Mood Disorder	Bipolar vs Unipolar Mania	0.052	0.109	0.482	0.630	1.054	0.852	1.305	0.996

List of References

Abler, B., Greenhouse, I., Ongur, D., Walter, H., & Heckers, S. (2008). Abnormal Reward System Activation in Mania. *Neuropsychopharmacology*, *33*(9), 2217–2227. https://doi.org/10.1038/sj.npp.1301620

Akhter, A., Fiedorowicz, J. G., Zhang, T., Potash, J. B., Cavanaugh, J., Solomon, D. A., & Coryell, W. H. (2013). Seasonal variation of manic and depressive symptoms in bipolar disorder. *Bipolar Disorders*, *15*(4), 377–384. https://doi.org/https://doi.org/10.1111/bdi.12072

Albrecht, B. M., Stalling, I., Recke, C., & Bammann, K. (2020). Accelerometer-assessed outdoor physical activity is associated with meteorological conditions among older adults: Cross-sectional results from the OUTDOOR ACTIVE study. *PLOS ONE*, *15*(1), e0228053. https://doi.org/10.1371/journal.pone.0228053

Alloy, L. B., Ng, T. H., Titone, M. K., & Boland, E. M. (2017). Circadian Rhythm Dysregulation in Bipolar Spectrum Disorders. *Current Psychiatry Reports*, *19*(4). https://doi.org/10.1007/s11920-017-0772-z

Allsopp, K., Read, J., Corcoran, R., & Kinderman, P. (2019). Heterogeneity in psychiatric diagnostic classification. *Psychiatry Research*, *279*, 15–22. https://doi.org/https://doi.org/10.1016/j.psychres.2019.07.005

Almeida, H. S., Mitjans, M., Arias, B., Vieta, E., Ríos, J., & Benabarre, A. (2020). Genetic differences between bipolar disorder subtypes: A systematic review focused in bipolar disorder type II. *Neuroscience & Biobehavioral Reviews*, *118*, 623–630. https://doi.org/https://doi.org/10.1016/j.neubiorev.2020.07.033

Amerio, A., Ardito, C., Costa, G., Gianfredi, V., Odone, A., Stuckler, D., Vigezzi, G. P., & d'Errico, A. (2021). Does retirement trigger depressive symptoms? A systematic review and meta-analysis. *Epidemiology and Psychiatric Sciences*, *30*, e77. https://doi.org/DOI: 10.1017/S2045796021000627

Andrade-Nascimento, M., Miranda-Scippa, Â., Nery-Fernandes, F., Kapczinski, F., & Quarantini, L. C. (2011). The identification of unipolar mania subtype based on anxiety comorbidity. *Journal of Affective Disorders*, *132*(3), 356–359. https://doi.org/https://doi.org/10.1016/j.jad.2011.03.005

Angst, J. (2007). The bipolar spectrum. *The British Journal of Psychiatry*, *190*(3), 189–191.

Angst, J. (2015). Will mania survive DSM-5 and ICD-11? *International Journal of Bipolar Disorders*, *3*(1), 24. https://doi.org/10.1186/s40345-015-0041-1

Angst, J., Ajdacic-Gross, V., & Rössler, W. (2020). Bipolar disorders in ICD-11: current status and strengths. *International Journal of Bipolar Disorders*, *8*(1), 3. https://doi.org/10.1186/s40345-019-0165-9

References

Angst, J., Gerber-Werder, R., Zuberbühler, H.-U., & Gamma, A. (2004). Is bipolar I disorder heterogeneous? *European Archives of Psychiatry and Clinical Neuroscience*, *254*(2), 82–91. https://doi.org/10.1007/s00406-004-0501-6

Angst, J., & Grobler, C. (2015). Unipolar mania: a necessary diagnostic concept. *European Archives of Psychiatry and Clinical Neuroscience*, *265*(4), 273–280. https://doi.org/10.1007/s00406-015-0577-1

Angst, J., Rössler, W., Ajdacic-Gross, V., Angst, F., Wittchen, H. U., Lieb, R., Beesdo-Baum, K., Asselmann, E., Merikangas, K. R., Cui, L., Andrade, L. H., Viana, M. C., Lamers, F., Penninx, B. W. J. H., de Azevedo Cardoso, T., Jansen, K., Dias de Mattos Souza, L., Azevedo da Silva, R., Kapczinski, F., … Vandeleur, C. L. (2019). Differences between unipolar mania and bipolar-I disorder: Evidence from nine epidemiological studies. *Bipolar Disorders*, *21*(5), 437–448. https://doi.org/https://doi.org/10.1111/bdi.12732

Antypa, N., Vogelzangs, N., Meesters, Y., Schoevers, R., & Penninx, B. W. J. H. (2016). CHRONOTYPE ASSOCIATIONS WITH DEPRESSION AND ANXIETY DISORDERS IN A LARGE COHORT STUDY. *Depression and Anxiety*, *33*(1), 75–83. https://doi.org/10.1002/da.22422

Arns, M., Swatzyna, R. J., Gunkelman, J., & Olbrich, S. (2015). Sleep maintenance, spindling excessive beta and impulse control: an RDoC arousal and regulatory systems approach? *Neuropsychiatric Electrophysiology*, *1*(1), 5. https://doi.org/10.1186/s40810-015-0005-9

Arora, T., & Taheri, S. (2015). Associations among late chronotype, body mass index and dietary behaviors in young adolescents. *International Journal of Obesity*, *39*(1), 39–44. https://doi.org/10.1038/ijo.2014.157

Au, J., & Reece, J. (2017). The relationship between chronotype and depressive symptoms: A meta-analysis. *Journal of Affective Disorders*, *218*, 93–104. https://doi.org/https://doi.org/10.1016/j.jad.2017.04.021

Baek, J. H., Eisner, L. R., & Nierenberg, A. A. (2014). EPIDEMIOLOGY AND COURSE OF UNIPOLAR MANIA: RESULTS FROM THE NATIONAL EPIDEMIOLOGIC SURVEY ON ALCOHOL AND RELATED CONDITIONS (NESARC). *Depression and Anxiety*, *31*(9), 746–755. https://doi.org/https://doi.org/10.1002/da.22261

Bagot, K. S., Matthews, S. A., Mason, M., Squeglia, L. M., Fowler, J., Gray, K., Herting, M., May, A., Colrain, I., Godino, J., Tapert, S., Brown, S., & Patrick, K. (2018). Current, future and potential use of mobile and wearable technologies and social media data in the ABCD study to increase understanding of contributors to child health. *Developmental Cognitive Neuroscience*, *32*, 121–129. https://doi.org/https://doi.org/10.1016/j.dcn.2018.03.008

Bauducco, S., Richardson, C., & Gradisar, M. (2020). Chronotype, circadian rhythms and mood. *Current Opinion in Psychology*, *34*, 77–83. https://doi.org/https://doi.org/10.1016/j.copsyc.2019.09.002

Bedrosian, T. A., & Nelson, R. J. (2013). Influence of the modern light environment on mood. *Molecular Psychiatry*, *18*(7), 751–757. https://doi.org/10.1038/mp.2013.70

Beesdo-baum, K., Höfler, M., Gloster, A. T., Klotsche, J., Lieb, R., Beauducel, A., Bühner, M., Kessler, R. C., & Wittchen, H. (2009). The structure of common mental disorders: A replication study in a community sample of adolescents and young adults. *International Journal of Methods in Psychiatric Research*, *18*(4), 204–220. https://doi.org/https://doi.org/10.1002/mpr.293

Beijers, L., Wardenaar, K. J., van Loo, H. M., & Schoevers, R. A. (2019). Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. *Molecular Psychiatry*, *24*(6), 888–900. https://doi.org/10.1038/s41380-019-0385-5

Beiwinkel, T., Kindermann, S., Maier, A., Kerl, C., Moock, J., Barbian, G., & Rössler, W. (2016). Using Smartphones to Monitor Bipolar Disorder Symptoms: A Pilot Study. *JMIR Mental Health*, *3*(1), e2. https://doi.org/10.2196/mental.4560

Benard, V., Etain, B., Vaiva, G., Boudebesse, C., Yeim, S., Benizri, C., Brochard, H., Bellivier, F., & Geoffroy, P. A. (2019). Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: An actigraphy study. *Journal of Affective Disorders*, *244*, 1–8. https://doi.org/https://doi.org/10.1016/j.jad.2018.09.054

Benedetti, F., Barbini, B., Campori, E., Fulgosi, M. C., Pontiggia, A., & Colombo, C. (2001). Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? *Journal of Psychiatric Research*, *35*(6), 323–329. https://doi.org/https://doi.org/10.1016/S0022-3956(01)00034-6

Berk, M., Brnabic, A., Dodd, S., Kelin, K., Tohen, M., Malhi, G. S., Berk, L., Conus, P., & McGorry, P. D. (2011). Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disorders*, *13*(1), 87–98. https://doi.org/https://doi.org/10.1111/j.1399-5618.2011.00889.x

Berle, J. O., Hauge, E. R., Oedegaard, K. J., Holsten, F., & Fasmer, O. B. (2010). Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. *BMC Research Notes*, *3*(1), 149. https://doi.org/10.1186/1756-0500-3-149

Bernard, P., & Carayol, M. (2015). A commentary on the importance of controlling for medication use within trials on the effects of exercise on depression and anxiety. *Mental Health and Physical Activity*, *9*, 10–15. https://doi.org/https://doi.org/10.1016/j.mhpa.2015.07.001

Borbély, A. A. (1982). A two process model of sleep regulation. *Hum Neurobiol*, *1*(3), 195–204.

Borsboom, D., Deserno, M. K., Rhemtulla, M., Epskamp, S., Fried, E. I., McNally, R. J., Robinaugh, D. J., Perugini, M., Dalege, J., Costantini, G., Isvoranu, A.-M.,

Wysocki, A. C., van Borkulo, C. D., van Bork, R., & Waldorp, L. J. (2021). Network analysis of multivariate data in psychological science. *Nature Reviews Methods Primers*, *1*(1), 58. https://doi.org/10.1038/s43586-021-00055-w

Boudebesse, C., Geoffroy, P. A., Bellivier, F., Henry, C., Folkard, S., Leboyer, M., & Etain, B. (2014). Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. *Chronobiology International*, *31*(5), 698–704. https://doi.org/10.3109/07420528.2014.895742

Bracke, P., Platts, L. G., Vahtera, J., Westerlund, H., & van de Straat, V. (2020). Reduction in sleep disturbances at retirement: evidence from the Swedish Longitudinal Occupational Survey of Health. *Ageing and Society*, *40*(10), 2155–2173. https://doi.org/DOI: 10.1017/S0144686X19000515

Brazienė, A., Venclovienė, J., Vaičiulis, V., Lukšienė, D., Tamošiūnas, A., Milvidaitė, I., Radišauskas, R., & Bobak, M. (2022). Relationship between Depressive Symptoms and Weather Conditions. In *International Journal of Environmental Research and Public Health* (Vol. 19, Issue 9). https://doi.org/10.3390/ijerph19095069

Brown, M., & Cohen, S. (2020). Informal Caregiving, Poor Mental Health, and Subjective Cognitive Decline: Results From a Population-Based Sample. *Journal of Gerontological Nursing*, *46*(12), 31–41. https://doi.org/10.3928/00989134-20201106-04

Burkhouse, K. L., Jimmy, J., Defelice, N., Klumpp, H., Ajilore, O., Hosseini, B., Fitzgerald, K. D., Monk, C. S., & Phan, K. L. (2020). Nucleus accumbens volume as a predictor of anxiety symptom improvement following CBT and SSRI treatment in two independent samples. *Neuropsychopharmacology*, *45*(3), 561–569. https://doi.org/10.1038/s41386-019-0575-5

Burton, C., McKinstry, B., Szentagotai Tătar, A., Serrano-Blanco, A., Pagliari, C., & Wolters, M. (2013). Activity monitoring in patients with depression: A systematic review. *Journal of Affective Disorders*, *145*(1), 21–28. https://doi.org/https://doi.org/10.1016/j.jad.2012.07.001

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/https://doi.org/10.1016/0165-1781(89)90047-4

Carney, P. A., Fitzgerald, C. T., & Monaghan, C. E. (1988). Influence of Climate on the Prevalence of Mania. *The British Journal of Psychiatry*, *152*(6), 820–823. https://doi.org/DOI: 10.1192/bjp.152.6.820

Carvalho, A. F., Firth, J., & Vieta, E. (2020). Bipolar Disorder. *New England Journal of Medicine*, *383*(1), 58–66. https://doi.org/10.1056/NEJMra1906193

Cepeda, M., Koolhaas, C. M., van Rooij, F. J. A., Tiemeier, H., Guxens, M., Franco, O. H., & Schoufour, J. D. (2018). Seasonality of physical activity, sedentary behavior, and sleep in a middle-aged and elderly population: The Rotterdam study.

Maturitas, *110*, 41–50. https://doi.org/https://doi.org/10.1016/j.maturitas.2018.01.016

Chang, C.-E., Chen, H.-C., Chen, W. J., Chiu, C.-C., Hsieh, M.-H., Huang, M.-C., Kuo, P.-H., Lin, Y.-T., Lu, M.-L., & Wang, J. (2023). Characterization of clinical features and comorbidities between bipolar affective disorder with and without depressive episodes. *Psychological Medicine*, *53*(9), 4103–4113. https://doi.org/DOI: 10.1017/S0033291722000782

Chang, J. S., Ahn, Y. M., Yu, H. Y., Park, H. J., Lee, K. Y., Kim, S. H., & Kim, Y. S. (2009). Exploring Clinical Characteristics of Bipolar Depression: Internal Structure of the Bipolar Depression Rating Scale. *Australian & New Zealand Journal of Psychiatry*, *43*(9), 830–837. https://doi.org/10.1080/00048670903107666

Chaput, J.-P., Dutil, C., & Sampasa-Kanyinga, H. (2018). Sleeping hours: what is the ideal number and how does age impact this? *Nature and Science of Sleep*, *10*, 421–430. https://doi.org/10.2147/NSS.S163071

Charlson, F., Ali, S., Benmarhnia, T., Pearl, M., Massazza, A., Augustinavicius, J., & Scott, J. G. (2021). Climate Change and Mental Health: A Scoping Review. In *International Journal of Environmental Research and Public Health* (Vol. 18, Issue 9). https://doi.org/10.3390/ijerph18094486

Chen, T., & Guestrin, C. (2016). XGBoost: A Scalable Tree Boosting System. *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, 785–794. https://doi.org/10.1145/2939672.2939785

Chen, Y.-F. (2002). Chinese Classification of Mental Disorders (CCMD-3): Towards Integration in International Classification. *Psychopathology*, *35*(2–3), 171–175. https://doi.org/10.1159/000065140

Cho, C.-H., Lee, T., Lee, J.-B., Seo, J. Y., Jee, H.-J., Son, S., An, H., Kim, L., & Lee, H.-J. (2020). Effectiveness of a Smartphone App With a Wearable Activity Tracker in Preventing the Recurrence of Mood Disorders: Prospective Case-Control Study. *JMIR Ment Health*, *7*(8), e21283. https://doi.org/10.2196/21283

Choi, J.-G., Ko, I., & Han, S. (2021). Depression Level Classification Using Machine Learning Classifiers Based on Actigraphy Data. *IEEE Access*, *9*, 116622–116646. https://doi.org/10.1109/ACCESS.2021.3105393

Choilek, S., Karashima, A., Motoike, I., Katayama, N., Kinoshita, K., & Nakao, M. (2021). Subjective sleep quality, quantitative sleep features, and their associations dependent on demographic characteristics, habitual sleep–wake patterns, and distinction of weekdays/weekends. *Sleep and Biological Rhythms*, *19*(4), 369–381. https://doi.org/10.1007/s41105-021-00326-9

Consortium, B. D. and S. W. G. of the P. G. (2018). Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. *Cell*, *173*(7), 1705-1715.e16. https://doi.org/10.1016/j.cell.2018.05.046

Conway, C. C., Forbes, M. K., Forbush, K. T., Fried, E. I., Hallquist, M. N., Kotov, R., Mullins-Sweatt, S. N., Shackman, A. J., Skodol, A. E., South, S. C., Sunderland, M., Waszczuk, M. A., Zald, D. H., Afzali, M. H., Bornovalova, M. A., Carragher, N., Docherty, A. R., Jonas, K. G., Krueger, R. F., … Eaton, N. R. (2019). A Hierarchical Taxonomy of Psychopathology Can Transform Mental Health Research. *Perspectives on Psychological Science*, *14*(3), 419–436. https://doi.org/10.1177/1745691618810696

Cotrena, C., Damiani Branco, L., Ponsoni, A., Samamé, C., Milman Shansis, F., & Paz Fonseca, R. (2020). Executive functions and memory in bipolar disorders I and II: new insights from meta-analytic results. *Acta Psychiatrica Scandinavica*, *141*(2), 110–130. https://doi.org/https://doi.org/10.1111/acps.13121

Cox, S. R., Ritchie, S. J., Fawns-Ritchie, C., Tucker-Drob, E. M., & Deary, I. J. (2019). Structural brain imaging correlates of general intelligence in UK Biobank. *Intelligence*, *76*, 101376. https://doi.org/https://doi.org/10.1016/j.intell.2019.101376

Cuthbert, B. N. (2015). Research Domain Criteria: toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience*, *17*(1), 89–97. https://doi.org/10.31887/DCNS.2015.17.1/bcuthbert

Damme, K. S. F., Vargas, T. G., Walther, S., Shankman, S. A., & Mittal, V. A. (2024). Physical and mental health in adolescence: novel insights from a transdiagnostic examination of FitBit data in the ABCD study. *Translational Psychiatry*, *14*(1), 75. https://doi.org/10.1038/s41398-024-02794-2

Damme, K. S., Young, C. B., & Nusslock, R. (2017). Elevated nucleus accumbens structural connectivity associated with proneness to hypomania: a reward hypersensitivity perspective. *Social Cognitive and Affective Neuroscience*, *12*(6), 928–936. https://doi.org/10.1093/scan/nsx017

Davis, K. A. S., Cullen, B., Adams, M., Brailean, A., Breen, G., Coleman, J. R. I., Dregan, A., Gaspar, H. A., Hübel, C., Lee, W., McIntosh, A. M., Nolan, J., Pearsall, R., & Hotopf, M. (2019). Indicators of mental disorders in UK Biobank—A comparison of approaches. *International Journal of Methods in Psychiatric Research*, *28*(3), e1796. https://doi.org/https://doi.org/10.1002/mpr.1796

De Crescenzo, F., Economou, A., Sharpley, A. L., Gormez, A., & Quested, D. J. (2017). Actigraphic features of bipolar disorder: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *33*, 58–69. https://doi.org/https://doi.org/10.1016/j.smrv.2016.05.003

Deboer, T. (2018). Sleep homeostasis and the circadian clock: Do the circadian pacemaker and the sleep homeostat influence each other's functioning? *Neurobiology of Sleep and Circadian Rhythms*, *5*, 68–77. https://doi.org/10.1016/j.nbscr.2018.02.003

del Pozo Cruz, B., Alfonso-Rosa, R. M., McGregor, D., Chastin, S. F., Palarea-Albaladejo, J., & del Pozo Cruz, J. (2020). Sedentary behaviour is associated with

depression symptoms: Compositional data analysis from a representative sample of 3233 US adults and older adults assessed with accelerometers. *Journal of Affective Disorders*, *265*, 59–62. https://doi.org/https://doi.org/10.1016/j.jad.2020.01.023

Difrancesco, S., Giltay, E. J., Lamers, F., Penninx, B. W. J. H., & Riese, H. (2022). The role of depressive symptoms and symptom dimensions in actigraphy-assessed sleep, circadian rhythm, and physical activity. *Psychological Medicine*, *52*(13), 2760–2766. https://doi.org/DOI: 10.1017/S0033291720004870

Difrancesco, S., Lamers, F., Riese, H., Merikangas, K. R., Beekman, A. T. F., van Hemert, A. M., Schoevers, R. A., & Penninx, B. W. J. H. (2019). Sleep, circadian rhythm, and physical activity patterns in depressive and anxiety disorders: A 2-week ambulatory assessment study. *Depression and Anxiety*, *36*(10), 975–986. https://doi.org/https://doi.org/10.1002/da.22949

Dilsaver, S. C., Chen, Y.-W., Swann, A. C., Shoaib, A. M., Tsai-Dilsaver, Y., & Krajewski, K. J. (1997). Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure-mania. *Psychiatry Research*, *73*(1), 47–56. https://doi.org/https://doi.org/10.1016/S0165-1781(97)00109-1

Doane, L. D., Gress-Smith, J. L., & Breitenstein, R. S. (2015). Multi-method Assessments of Sleep over the Transition to College and the Associations with Depression and Anxiety Symptoms. *Journal of Youth and Adolescence*, *44*(2), 389–404. https://doi.org/10.1007/s10964-014-0150-7

Doherty, A., Jackson, D., Hammerla, N., Plötz, T., Olivier, P., Granat, M. H., White, T., van Hees, V. T., Trenell, M. I., Owen, C. G., Preece, S. J., Gillions, R., Sheard, S., Peakman, T., Brage, S., & Wareham, N. J. (2017). Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. *PLOS ONE*, *12*(2), e0169649.

Dondé, C., Jaffiol, A., Khouri, C., Pouchon, A., Tamisier, R., Lejoyeux, M., d'Ortho, M.-P., Polosan, M., & Geoffroy, P. A. (2021). Sleep disturbances in early clinical stages of psychotic and bipolar disorders: A meta-analysis. *Australian & New Zealand Journal of Psychiatry*, *56*(9), 1068–1079. https://doi.org/10.1177/00048674211068395

Eidelman, P., Talbot, L. S., Gruber, J., & Harvey, A. G. (2010). Sleep, illness course, and concurrent symptoms in inter-episode bipolar disorder. *Journal of Behavior Therapy and Experimental Psychiatry*, *41*(2), 145–149. https://doi.org/https://doi.org/10.1016/j.jbtep.2009.11.007

Fárková, E., Šmotek, M., Bendová, Z., Manková, D., & Kopřivová, J. (2021). Chronotype and social jet-lag in relation to body weight, apetite, sleep quality and fatigue. *Biological Rhythm Research*, *52*(8), 1205–1216. https://doi.org/10.1080/09291016.2019.1630096

Fava, M., Husain, M. M., Miyahara, S., Nierenberg, A. A., Rush, A. J., Trivedi, M. H., Warden, D., & Wisniewski, S. R. (2010). Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report.

Psychological Medicine, *40*(1), 41–50. https://doi.org/DOI: 10.1017/S0033291709006011

Feinglass, J., Lee, J., Semanik, P., Song, J., Dunlop, D., & Chang, R. (2011). The Effects of Daily Weather on Accelerometer-Measured Physical Activity. *Journal of Physical Activity and Health*, *8*(7), 934–943. https://doi.org/10.1123/jpah.8.7.934

Feld, G. B., & Feige, B. (2021). Erregungs- und Regulationssysteme im System der Research Domain Criteria. *Der Nervenarzt*, *92*(9), 907–914. https://doi.org/10.1007/s00115-021-01160-7

Fellendorf, F. T., Hamm, C., Dalkner, N., Platzer, M., Sattler, M. C., Bengesser, S. A., Lenger, M., Pilz, R., Birner, A., Queissner, R., Tmava-Berisha, A., Ratzenhofer, M., Maget, A., van Poppel, M., & Reininghaus, E. Z. (2021). Monitoring Sleep Changes via a Smartphone App in Bipolar Disorder: Practical Issues and Validation of a Potential Diagnostic Tool. *Frontiers in Psychiatry*, *12*. https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.641241

Ferguson, T., Curtis, R., Fraysse, F., Olds, T., Dumuid, D., Brown, W., Esterman, A., & Maher, C. (2023). Weather associations with physical activity, sedentary behaviour and sleep patterns of Australian adults: a longitudinal study with implications for climate change. *International Journal of Behavioral Nutrition and Physical Activity*, *20*(1), 30. https://doi.org/10.1186/s12966-023-01414-4

First, M. B., Gaebel, W., Maj, M., Stein, D. J., Kogan, C. S., Saunders, J. B., Poznyak, V. B., Gureje, O., Lewis-Fernández, R., Maercker, A., Brewin, C. R., Cloitre, M., Claudino, A., Pike, K. M., Baird, G., Skuse, D., Krueger, R. B., Briken, P., Burke, J. D., … Reed, G. M. (2021). An organization- and category-level comparison of diagnostic requirements for mental disorders in ICD-11 and DSM-5. *World Psychiatry*, *20*(1), 34–51. https://doi.org/https://doi.org/10.1002/wps.20825

Friborg, O., Bjorvatn, B., Amponsah, B., & Pallesen, S. (2012). Associations between seasonal variations in day length (photoperiod), sleep timing, sleep quality and mood: a comparison between Ghana (5°) and Norway (69°). *Journal of Sleep Research*, *21*(2), 176–184. https://doi.org/https://doi.org/10.1111/j.1365-2869.2011.00982.x

Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR*D study. *Journal of Affective Disorders*, *172*, 96–102. https://doi.org/10.1016/j.jad.2014.10.010

Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., & Allen, N. E. (2017). Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *American Journal of Epidemiology*, *186*(9), 1026–1034. https://doi.org/10.1093/aje/kwx246

Galynker, I. I., Yaseen, Z. S., Koppolu, S. S., Vaughan, B., Szklarska-Imiolek, M., Cohen, L. J., Salvanti, T. M., & Kim, H.-J. (2016). Increased sleep duration precedes the improvement of other symptom domains during the treatment of

acute mania: a retrospective chart review. *BMC Psychiatry*, *16*(1), 98. https://doi.org/10.1186/s12888-016-0808-7

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, *32*, 16–22. https://doi.org/https://doi.org/10.1016/j.dcn.2018.04.004

Gaudiano, B. A., & Miller, I. W. (2005). Anxiety disorder comobidity in Bipolar I Disorder: Relationship to depression severity and treatment outcome. *Depression and Anxiety*, *21*(2), 71–77. https://doi.org/https://doi.org/10.1002/da.20053

Geoffroy, P. A., Bellivier, F., Scott, J., & Etain, B. (2014). Seasonality and bipolar disorder: A systematic review, from admission rates to seasonality of symptoms. *Journal of Affective Disorders*, *168*, 210–223. https://doi.org/https://doi.org/10.1016/j.jad.2014.07.002

Geoffroy, P. A., Scott, J., Boudebesse, C., Lajnef, M., Henry, C., Leboyer, M., Bellivier, F., & Etain, B. (2015). Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatrica Scandinavica*, *131*(2), 89–99. https://doi.org/https://doi.org/10.1111/acps.12367

Germain, A., & Kupfer, D. J. (2008). Circadian rhythm disturbances in depression. *Human Psychopharmacology: Clinical and Experimental*, *23*(7), 571–585. https://doi.org/10.1002/hup.964

Giglio, L. M. F., Magalhães, P. V. S., Andersen, M. L., Walz, J. C., Jakobson, L., & Kapczinski, F. (2010). Circadian preference in bipolar disorder. *Sleep and Breathing*, *14*(2), 153–155. https://doi.org/10.1007/s11325-009-0301-3

Gildengers, A., Tatsuoka, C., Bialko, C., Cassidy, K. A., Al Jurdi, R. K., Gyulai, L., Mulsant, B. H., Young, R. C., & Sajatovic, M. (2012). Correlates of Treatment Response in Depressed Older Adults With Bipolar Disorder. *Journal of Geriatric Psychiatry and Neurology*, *25*(1), 37–42. https://doi.org/10.1177/0891988712436685

Goldberg, D., & Fawcett, J. (2012). THE IMPORTANCE OF ANXIETY IN BOTH MAJOR DEPRESSION AND BIPOLAR DISORDER. *Depression and Anxiety*, *29*(6), 471–478. https://doi.org/https://doi.org/10.1002/da.21939

Goldberg, D., & Huxley, P. (2012). *Mental illness in the community: the pathway to psychiatric care*. Routledge.

Gonçalves, B. S. B., Cavalcanti, P. R. A., Tavares, G. R., Campos, T. F., & Araujo, J. F. (2014). Nonparametric methods in actigraphy: An update. *Sleep Science*, *7*(3), 158–164. https://doi.org/https://doi.org/10.1016/j.slsci.2014.09.013

Gower, J. C. (1971). A General Coefficient of Similarity and Some of Its Properties. *Biometrics*, *27*(4), 857–871. https://doi.org/10.2307/2528823

Grisanzio, K. A., Goldstein-Piekarski, A. N., Wang, M. Y., Rashed Ahmed, A. P., Samara, Z., & Williams, L. M. (2018). Transdiagnostic Symptom Clusters and

Associations With Brain, Behavior, and Daily Function in Mood, Anxiety, and Trauma Disorders. *JAMA Psychiatry*, *75*(2), 201–209. https://doi.org/10.1001/jamapsychiatry.2017.3951

Günther, V., Ihme, K., Kersting, A., Hoffmann, K.-T., Lobsien, D., & Suslow, T. (2018). Volumetric Associations Between Amygdala, Nucleus Accumbens, and Socially Anxious Tendencies in Healthy Women. *Neuroscience*, *374*, 25–32. https://doi.org/https://doi.org/10.1016/j.neuroscience.2018.01.034

Hagen, E. W., Barnet, J. H., Hale, L., & Peppard, P. E. (2016). Changes in Sleep Duration and Sleep Timing Associated with Retirement Transitions. *Sleep*, *39*(3), 665–673. https://doi.org/10.5665/sleep.5548

Ham, B.-J., Han, K.-M., Kang, W., Kang, Y., Kang, J., Kim, A., Tae, W.-S., & Won, E. (2019). Hippocampal subfield volumes in major depressive disorder and bipolar disorder. *European Psychiatry*, *57*, 70–77. https://doi.org/DOI: 10.1016/j.eurpsy.2019.01.016

Han, K.-M., De Berardis, D., Fornaro, M., & Kim, Y.-K. (2019). Differentiating between bipolar and unipolar depression in functional and structural MRI studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *91*, 20–27. https://doi.org/https://doi.org/10.1016/j.pnpbp.2018.03.022

Hart, T. L., Swartz, A. M., Cashin, S. E., & Strath, S. J. (2011). How many days of monitoring predict physical activity and sedentary behaviour in older adults? *The International Journal of Behavioral Nutrition and Physical Activity*, *8*, 62. https://doi.org/10.1186/1479-5868-8-62

Hasler, B. P., Buysse, D. J., Kupfer, D. J., & Germain, A. (2010). Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: Further evidence for circadian misalignment in non-seasonal depression. *Psychiatry Research*, *178*(1), 205–207. https://doi.org/https://doi.org/10.1016/j.psychres.2010.04.027

Hasler, B. P., Sitnick, S. L., Shaw, D. S., & Forbes, E. E. (2013). An altered neural response to reward may contribute to alcohol problems among late adolescents with an evening chronotype. *Psychiatry Research: Neuroimaging*, *214*(3), 357–364. https://doi.org/10.1016/J.PSCYCHRESNS.2013.08.005

Helgadóttir, B., Forsell, Y., & Ekblom, Ö. (2015). Physical Activity Patterns of People Affected by Depressive and Anxiety Disorders as Measured by Accelerometers: A Cross-Sectional Study. *PLOS ONE*, *10*(1), e0115894. https://doi.org/10.1371/journal.pone.0115894

Hellvin, T., Sundet, K., Simonsen, C., Aminoff, S. R., Lagerberg, T. V., Andreassen, O. A., & Melle, I. (2012). Neurocognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar Disorders*, *14*(3), 227–238. https://doi.org/https://doi.org/10.1111/j.1399-5618.2012.01004.x

Hennion, V., Scott, J., Martinot, V., Benizri, C., Marie-Claire, C., Bellivier, F., & Etain, B. (2024). Associations between actigraphy estimates of sleep and circadian

rhythmicity and psychotropic medications in bipolar disorders: An exploratory study. *Journal of Affective Disorders*, *348*, 224–228. https://doi.org/https://doi.org/10.1016/j.jad.2023.12.075

Heyde, I., & Oster, H. (2019). Differentiating external zeitgeber impact on peripheral circadian clock resetting. *Scientific Reports*, *9*(1), 20114. https://doi.org/10.1038/s41598-019-56323-z

Hibar, D. P., Westlye, L. T., van Erp, T. G. M., Rasmussen, J., Leonardo, C. D., Faskowitz, J., Haukvik, U. K., Hartberg, C. B., Doan, N. T., Agartz, I., Dale, A. M., Gruber, O., Krämer, B., Trost, S., Liberg, B., Abé, C., Ekman, C. J., Ingvar, M., Landén, M., … Group, for the E. B. D. W. (2016). Subcortical volumetric abnormalities in bipolar disorder. *Molecular Psychiatry*, *21*(12), 1710–1716. https://doi.org/10.1038/mp.2015.227

Hofman, A., Brusselle, G. G. O., Murad, S. D., van Duijn, C. M., Franco, O. H., Goedegebure, A., Ikram, M. A., Klaver, C. C. W., Nijsten, T. E. C., Peeters, R. P., Stricker, B. H. Ch., Tiemeier, H. W., Uitterlinden, A. G., & Vernooij, M. W. (2015). The Rotterdam Study: 2016 objectives and design update. *European Journal of Epidemiology*, *30*(8), 661–708. https://doi.org/10.1007/s10654-015-0082-x

Horne, J. A., & Östberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. In *International Journal of Chronobiology* (Vol. 4, pp. 97–110). Gordon and Breach Science Pub Ltd.

Huang, J., Zuber, V., Matthews, P. M., Elliott, P., Tzoulaki, J., & Dehghan, A. (2020). Sleep, major depressive disorder, and Alzheimer disease. *Neurology*, *95*(14), e1963–e1970. https://doi.org/10.1212/WNL.0000000000010463

Huibers, M. J. H., de Graaf, L. E., Peeters, F. P. M. L., & Arntz, A. (2010). Does the weather make us sad? Meteorological determinants of mood and depression in the general population. *Psychiatry Research*, *180*(2), 143–146. https://doi.org/https://doi.org/10.1016/j.psychres.2009.09.016

Husu, P., Tokola, K., Vähä-Ypyä, H., Sievänen, H., & Vasankari, T. (2022). Depressive Symptoms Are Associated With Accelerometer-Measured Physical Activity and Time in Bed Among Working-Aged Men and Women. *Journal for the Measurement of Physical Behaviour*, *5*(3), 168–177. https://doi.org/10.1123/jmpb.2021-0058

Institute of Health Metrics and Evaluation. (2019). *Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx).* Http://Ghdx.Healthdata.Org/Gbd-Results-Tool?Params=Gbd-Api-2019-Permalink/D780Dffbe8a381B25E1416884959E88B. https://www.google.com/search?q=Institute+of+Health+Metrics+and+Evaluation.+Global+Health+Data+Exchange+(GHDx).+http%3A%2F%2Fghdx.healthdata.org%2Fgbd-results-tool%3Fparams%3Dgbd-api-2019-permalink%2Fd780dffbe8a381b25e1416884959e88b&oq=Institute+of+Health

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., … Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789–1858. https://doi.org/https://doi.org/10.1016/S0140-6736(18)32279-7

Jones, S. E., Lane, J. M., Wood, A. R., van Hees, V. T., Tyrrell, J., Beaumont, R. N., Jeffries, A. R., Dashti, H. S., Hillsdon, M., Ruth, K. S., Tuke, M. A., Yaghootkar, H., Sharp, S. A., Jie, Y., Thompson, W. D., Harrison, J. W., Dawes, A., Byrne, E. M., Tiemeier, H., … Weedon, M. N. (2019). Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. *Nature Communications*, *10*(1), 343. https://doi.org/10.1038/s41467-018-08259-7

Jones, S. E., van Hees, V. T., Mazzotti, D. R., Marques-Vidal, P., Sabia, S., van der Spek, A., Dashti, H. S., Engmann, J., Kocevska, D., Tyrrell, J., Beaumont, R. N., Hillsdon, M., Ruth, K. S., Tuke, M. A., Yaghootkar, H., Sharp, S. A., Ji, Y., Harrison, J. W., Freathy, R. M., … Wood, A. R. (2019). Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nature Communications*, *10*(1), 1585. https://doi.org/10.1038/s41467-019-09576-1

Kanagarajan, K., Gou, K., Antinora, C., Buyukkurt, A., Crescenzi, O., Beaulieu, S., Storch, K.-F., & Mantere, O. (2018). Morningness-Eveningness questionnaire in bipolar disorder. *Psychiatry Research*, *262*, 102–107. https://doi.org/https://doi.org/10.1016/j.psychres.2018.02.004

Kantermann, T., & Eastman, C. I. (2018). Circadian phase, circadian period and chronotype are reproducible over months. *Chronobiology International*, *35*(2), 280–288. https://doi.org/10.1080/07420528.2017.1400979

Karas, M., Bai, J., Strączkiewicz, M., Harezlak, J., Glynn, N. W., Harris, T., Zipunnikov, V., Crainiceanu, C., & Urbanek, J. K. (2019). Accelerometry data in health research: challenges and opportunities. *Statistics in Biosciences*, *11*(2), 210–237. https://doi.org/10.1007/s12561-018-9227-2

Kay, D. B., Tanner, J. J., & Bowers, D. (2018). Sleep disturbances and depression severity in patients with Parkinson's disease. *Brain and Behavior*, *8*(6), e00967. https://doi.org/https://doi.org/10.1002/brb3.967

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Kivelä, L., Papadopoulos, M. R., & Antypa, N. (2018). Chronotype and Psychiatric Disorders. *Current Sleep Medicine Reports*, *4*(2), 94–103. https://doi.org/10.1007/s40675-018-0113-8

Kohn, R., Saxena, S., Levav, I., & Saraceno, B. (2004). The treatment gap in mental health care. *Bulletin of the World Health Organization*, *82*(11), 858–866. https://doi.org//s0042-96862004001100011

Krafty, R. T., Fu, H., Graves, J. L., Bruce, S. A., Hall, M. H., & Smagula, S. F. (2019). Measuring Variability in Rest-Activity Rhythms from Actigraphy with Application to Characterizing Symptoms of Depression. *Statistics in Biosciences*, *11*(2), 314–333. https://doi.org/10.1007/s12561-018-09230-2

Krane-Gartiser, K., Henriksen, T. E. G., Morken, G., Vaaler, A. E., & Fasmer, O. B. (2018). Motor activity patterns in acute schizophrenia and other psychotic disorders can be differentiated from bipolar mania and unipolar depression. *Psychiatry Research*, *270*, 418–425. https://doi.org/https://doi.org/10.1016/j.psychres.2018.10.004

Krendl, A. C., & Pescosolido, B. A. (2020). Countries and Cultural Differences in the Stigma of Mental Illness: The East–West Divide. *Journal of Cross-Cultural Psychology*, *51*(2), 149–167. https://doi.org/10.1177/0022022119901297

Ku, P.-W., Steptoe, A., Liao, Y., Sun, W.-J., & Chen, L.-J. (2018). Prospective relationship between objectively measured light physical activity and depressive symptoms in later life. *International Journal of Geriatric Psychiatry*, *33*(1), 58–65. https://doi.org/https://doi.org/10.1002/gps.4672

Kyle, S. D., Sexton, C. E., Feige, B., Luik, A. I., Lane, J., Saxena, R., Anderson, S. G., Bechtold, D. A., Dixon, W., Little, M. A., Ray, D., Riemann, D., Espie, C. A., Rutter, M. K., & Spiegelhalder, K. (2017). Sleep and cognitive performance: cross-sectional associations in the UK Biobank. *Sleep Medicine*, *38*, 85–91. https://doi.org/https://doi.org/10.1016/j.sleep.2017.07.001

Lahti, T., Leppämäki, S., Tani, P., & Partonen, T. (2009). Actigraphic Recording of Manic Symptoms Induced by Methylphenidate. *Case Reports in Medicine*, *2009*, 286430. https://doi.org/10.1155/2009/286430

Lee, H.-J., Son, G.-H., & Geum, D. (2013). Circadian rhythm hypotheses of mixed features, antidepressant treatment resistance, and manic switching in bipolar disorder. *Psychiatry Investigation*, *10*(3), 225–232. https://doi.org/10.4306/pi.2013.10.3.225

Lee, J. H., Kim, I. S., Kim, S. J., Wang, W., & Duffy, J. F. (2011). Change in Individual Chronotype Over a Lifetime: A Retrospective Study. *Sleep Med Res*, *2*(2), 48–53. https://doi.org/10.17241/smr.2011.2.2.48

Lee, S., & Yu, H. (1994). Unipolar mania in non-Western cultures. *British Journal of Psychiatry*, *165*(3), 413. https://doi.org/DOI: 10.1192/bjp.165.3.413

Leibenluft, E., Albert, P. S., Rosenthal, N. E., & Wehr, T. A. (1996). Relationship between sleep and mood in patients with rapid-cycling bipolar disorder. *Psychiatry*

Research, *63*(2), 161–168. https://doi.org/https://doi.org/10.1016/0165-1781(96)02854-5

Lewinsohn, P. M., Rohde, P., Seeley, J. R., Klein, D. N., & Gotlib, I. H. (2000). Natural Course of Adolescent Major Depressive Disorder in a Community Sample: Predictors of Recurrence in Young Adults. *American Journal of Psychiatry*, *157*(10), 1584–1591. https://doi.org/10.1176/appi.ajp.157.10.1584

Lewis, K. S., Gordon-Smith, K., Forty, L., Di Florio, A., Craddock, N., Jones, L., & Jones, I. (2017). Sleep loss as a trigger of mood episodes in bipolar disorder: Individual differences based on diagnostic subtype and gender. *British Journal of Psychiatry*, *211*(3), 169–174. https://doi.org/10.1192/bjp.bp.117.202259

Lewy, A. J., Rough, J. N., Songer, J. B., Mishra, N., Yuhas, K., & Emens, J. S. (2007). The phase shift hypothesis for the circadian component of winter depression. *Dialogues in Clinical Neuroscience*, *9*(3), 291–300. https://doi.org/10.31887/DCNS.2007.9.3/alewy

Li, J., Somers, V. K., Lopez-Jimenez, F., Di, J., & Covassin, N. (2021). Demographic characteristics associated with circadian rest-activity rhythm patterns: a cross-sectional study. *International Journal of Behavioral Nutrition and Physical Activity*, *18*(1), 107. https://doi.org/10.1186/s12966-021-01174-z

Liebers, D. T., Pirooznia, M., Ganna, A., & Goes, F. S. (2020). Discriminating bipolar depression from major depressive disorder with polygenic risk scores. *Psychological Medicine*, 1–8. https://doi.org/DOI: 10.1017/S003329172000015X

Lopes, M. C., Boarati, M. A., & Fu-I, L. (2020). Sleep and Daytime Complaints During Manic and Depressive Episodes in Children and Adolescents With Bipolar Disorder. *Frontiers in Psychiatry*, *10*. https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2019.01021

Luik, A. I., Zuurbier, L. A., Direk, N., Hofman, A., Van Someren, E. J. W., & Tiemeier, H. (2015). 24-HOUR ACTIVITY RHYTHM AND SLEEP DISTURBANCES IN DEPRESSION AND ANXIETY: A POPULATION-BASED STUDY OF MIDDLE-AGED AND OLDER PERSONS. *Depression and Anxiety*, *32*(9), 684–692. https://doi.org/https://doi.org/10.1002/da.22355

Lukmanji, A., Williams, J. V. A., Bulloch, A. G. M., & Patten, S. B. (2020). Seasonal variation in specific depressive symptoms: A population based study. *Journal of Affective Disorders*, *261*, 153–159. https://doi.org/https://doi.org/10.1016/j.jad.2019.10.003

Luo, X., Mao, Q., Shi, J., Wang, X., & Li, C.-S. R. (2019). Putamen gray matter volumes in neuropsychiatric and neurodegenerative disorders. *World Journal of Psychiatry and Mental Health Research*, *3*(1).

Lyall, L. M., Cullen, B., Lyall, D. M., Leighton, S. P., Siebert, S., Smith, D. J., & Cavanagh, J. (2019). The associations between self-reported depression, self-reported chronic inflammatory conditions and cognitive abilities in UK Biobank.

European Psychiatry, *60*, 63–70. https://doi.org/DOI: 10.1016/j.eurpsy.2019.05.007

Lyall, L. M., Sangha, N., Zhu, X., Lyall, D. M., Ward, J., Strawbridge, R. J., Cullen, B., & Smith, D. J. (2023). Subjective and objective sleep and circadian parameters as predictors of depression-related outcomes: A machine learning approach in UK Biobank. *Journal of Affective Disorders*, *335*, 83–94. https://doi.org/https://doi.org/10.1016/j.jad.2023.04.138

Lyall, L. M., Wyse, C. A., Graham, N., Ferguson, A., Lyall, D. M., Cullen, B., Celis Morales, C. A., Biello, S. M., Mackay, D., Ward, J., Strawbridge, R. J., Gill, J. M. R., Bailey, M. E. S., Pell, J. P., & Smith, D. J. (2018). Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. *The Lancet Psychiatry*, *5*(6), 507–514. https://doi.org/10.1016/S2215-0366(18)30139-1

Lye, M.-S., Tey, Y.-Y., Tor, Y.-S., Shahabudin, A. F., Ibrahim, N., Ling, K.-H., Stanslas, J., Loh, S.-P., Rosli, R., Lokman, K. A., Badamasi, I. M., Faris-Aldoghachi, A., & Abdul Razak, N. A. (2020). Predictors of recurrence of major depressive disorder. *PLOS ONE*, *15*(3), e0230363-. https://doi.org/10.1371/journal.pone.0230363

Maglione, J. E., Ancoli-Israel, S., Peters, K. W., Paudel, M. L., Yaffe, K., Ensrud, K. E., & Stone, K. L. (2014). Subjective and Objective Sleep Disturbance and Longitudinal Risk of Depression in a Cohort of Older Women. *Sleep*, *37*(7), 1–9. https://doi.org/10.5665/sleep.3834

Masud, M. T., Mamun, M. A., Thapa, K., Lee, D. H., Griffiths, M. D., & Yang, S.-H. (2020). Unobtrusive monitoring of behavior and movement patterns to detect clinical depression severity level via smartphone. *Journal of Biomedical Informatics*, *103*, 103371. https://doi.org/https://doi.org/10.1016/j.jbi.2019.103371

McCarthy, M. J., Gottlieb, J. F., Gonzalez, R., McClung, C. A., Alloy, L. B., Cain, S., Dulcis, D., Etain, B., Frey, B. N., Garbazza, C., Ketchesin, K. D., Landgraf, D., Lee, H.-J., Marie-Claire, C., Nusslock, R., Porcu, A., Porter, R., Ritter, P., Scott, J., … Murray, G. (2022). Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology. *Bipolar Disorders*, *24*(3), 232–263. https://doi.org/https://doi.org/10.1111/bdi.13165

McClung, C. A. (2007). Circadian genes, rhythms and the biology of mood disorders. *Pharmacology & Therapeutics*, *114*(2), 222–232. https://doi.org/https://doi.org/10.1016/j.pharmthera.2007.02.003

McClung, C. A. (2013). How Might Circadian Rhythms Control Mood? Let Me Count the Ways... *Biological Psychiatry*, *74*(4), 242–249. https://doi.org/10.1016/J.BIOPSYCH.2013.02.019

McCormack, G. R., Friedenreich, C., Shiell, A., Giles-Corti, B., & Doyle-Baker, P. K. (2010). Sex- and age-specific seasonal variations in physical activity among

adults. *Journal of Epidemiology and Community Health*, *64*(11), 1010 LP – 1016. https://doi.org/10.1136/jech.2009.092841

McElroy, E., Fearon, P., Belsky, J., Fonagy, P., & Patalay, P. (2018). Networks of Depression and Anxiety Symptoms Across Development. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(12), 964–973. https://doi.org/https://doi.org/10.1016/j.jaac.2018.05.027

McIntyre, R. S., Berk, M., Brietzke, E., Goldstein, B. I., López-Jaramillo, C., Kessing, L. V., Malhi, G. S., Nierenberg, A. A., Rosenblat, J. D., Majeed, A., Vieta, E., Vinberg, M., Young, A. H., & Mansur, R. B. (2020). Bipolar disorders. *The Lancet*, *396*(10265), 1841–1856. https://doi.org/10.1016/S0140-6736(20)31544-0

Medici, C. R., Vestergaard, C. H., Hadzi-Pavlovic, D., Munk-Jørgensen, P., & Parker, G. (2016). Seasonal variations in hospital admissions for mania: Examining for associations with weather variables over time. *Journal of Affective Disorders*, *205*, 81–86. https://doi.org/https://doi.org/10.1016/j.jad.2016.06.053

Melo, M. C. A., Abreu, R. L. C., Linhares Neto, V. B., de Bruin, P. F. C., & de Bruin, V. M. S. (2017). Chronotype and circadian rhythm in bipolar disorder: A systematic review. *Sleep Medicine Reviews*, *34*, 46–58. https://doi.org/10.1016/J.SMRV.2016.06.007

Melton, H., Croarkin, E., Strawn, R., & McClintock, M. (2016). Comorbid Anxiety and Depressive Symptoms in Children and Adolescents: A Systematic Review and Analysis. *J Psychiatr Pract*, *22*(2), 84–98.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M. A., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *64*(5), 543–552. https://doi.org/10.1001/archpsyc.64.5.543

Merikangas, K. R., Cui, L., Heaton, L., Nakamura, E., Roca, C., Ding, J., Qin, H., Guo, W., Yao-Shugart, Y., Zarate, C., & Angst, J. (2014). Independence of familial transmission of mania and depression: results of the NIMH family study of affective spectrum disorders. *Molecular Psychiatry*, *19*(2), 214–219. https://doi.org/10.1038/mp.2013.116

Merikangas, K. R., Cui, L., Kattan, G., Carlson, G. A., Youngstrom, E. A., & Angst, J. (2012). Mania With and Without Depression in a Community Sample of US Adolescents. *Archives of General Psychiatry*, *69*(9), 943–951. https://doi.org/10.1001/archgenpsychiatry.2012.38

Met Office; Hollis, D.; McCarthy, M.; Kendon, M.; Legg, T.; Simpson, I. (2018). *HadUK-Grid gridded and regional average climate observations for the UK. Centre for Environmental Data Analysis*.

Meyer, N., Faulkner, S. M., McCutcheon, R. A., Pillinger, T., Dijk, D.-J., & MacCabe, J. H. (2020). Sleep and Circadian Rhythm Disturbance in Remitted Schizophrenia

and Bipolar Disorder: A Systematic Review and Meta-analysis. *Schizophrenia Bulletin*, *46*(5), 1126–1143. https://doi.org/10.1093/schbul/sbaa024

Mittal, P. K., Mehta, S., Solanki, R. K., Swami, M. K., & Meena, P. S. (2013). A comparative study of seasonality and chronotype in unipolar mania vs. bipolar affective disorder. *German Journal of Psychiatry*, *16*(4), 124–129.

Monroe, S. M., & Harkness, K. L. (2022). Major Depression and Its Recurrences: Life Course Matters. *Annual Review of Clinical Psychology*, *18*(1), 329–357. https://doi.org/10.1146/annurev-clinpsy-072220-021440

Montes, J. M., Serrano, C., & Pascual-Sanchez, A. (2021). The influence of weather on the course of bipolar disorder: A systematic review. *The European Journal of Psychiatry*, *35*(4), 261–273. https://doi.org/https://doi.org/10.1016/j.ejpsy.2021.03.002

Moon, J.-H., Cho, C.-H., Son, G. H., Geum, D., Chung, S., Kim, H., Kang, S.-G., Park, Y.-M., Yoon, H.-K., Kim, L., Jee, H.-J., An, H., Kripke, Daniel. F., & Lee, H.-J. (2016). Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder. *EBioMedicine*, *11*, 285–295. https://doi.org/https://doi.org/10.1016/j.ebiom.2016.08.019

Murray, G., Gottlieb, J., Hidalgo, M. P., Etain, B., Ritter, P., Skene, D. J., Garbazza, C., Bullock, B., Merikangas, K., Zipunnikov, V., Shou, H., Gonzalez, R., Scott, J., Geoffroy, P. A., & Frey, B. N. (2020). Measuring circadian function in bipolar disorders: Empirical and conceptual review of physiological, actigraphic, and self-report approaches. *Bipolar Disorders*, *22*(7), 693–710. https://doi.org/https://doi.org/10.1111/bdi.12963

Murtagh, F., & Contreras, P. (2012). Algorithms for hierarchical clustering: an overview. *WIREs Data Mining and Knowledge Discovery*, *2*(1), 86–97. https://doi.org/https://doi.org/10.1002/widm.53

Nelson, W. (1979). Methods for cosinor-rhythmometry. *Chronobiologia*, *6*, 305–323.

Ng, T. H., Chung, K.-F., Ho, F. Y.-Y., Yeung, W.-F., Yung, K.-P., & Lam, T.-H. (2015). Sleep–wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *20*, 46–58. https://doi.org/https://doi.org/10.1016/j.smrv.2014.06.006

Nguyen, T.-D., Harder, A., Xiong, Y., Kowalec, K., Hägg, S., Cai, N., Kuja-Halkola, R., Dalman, C., Sullivan, P. F., & Lu, Y. (2022). Genetic heterogeneity and subtypes of major depression. *Molecular Psychiatry*, *27*(3), 1667–1675. https://doi.org/10.1038/s41380-021-01413-6

O'Callaghan, V. S., Couvy-Duchesne, B., Strike, L. T., McMahon, K. L., Byrne, E. M., & Wright, M. J. (2021). A meta-analysis of the relationship between subjective sleep and depressive symptoms in adolescence. *Sleep Medicine*, *79*, 134–144. https://doi.org/https://doi.org/10.1016/j.sleep.2021.01.011

O'Connell, S. E., Griffiths, P. L., & Clemes, S. A. (2014). Seasonal variation in physical activity, sedentary behaviour and sleep in a sample of UK adults. *Annals of Human Biology*, *41*(1), 1–8. https://doi.org/10.3109/03014460.2013.827737

O'Hare, C., O'Sullivan, V., Flood, S., & Kenny, R. A. (2016). Seasonal and meteorological associations with depressive symptoms in older adults: A geo-epidemiological study. *Journal of Affective Disorders*, *191*, 172–179. https://doi.org/https://doi.org/10.1016/j.jad.2015.11.029

Ortiz, A., Maslej, M. M., Husain, M. I., Daskalakis, Z. J., & Mulsant, B. H. (2021). Apps and gaps in bipolar disorder: A systematic review on electronic monitoring for episode prediction. *Journal of Affective Disorders*, *295*, 1190–1200. https://doi.org/https://doi.org/10.1016/j.jad.2021.08.140

Parker, G., & Walter, S. D. (1982). Seasonal Variation in Depressive Disorders and Suicidal Deaths in New South Wales. *The British Journal of Psychiatry*, *140*(6), 626–632. https://doi.org/DOI: 10.1192/bjp.140.6.626

Patten, S. B., Williams, J. V. A., Lavorato, D. H., Bulloch, A. G. M., D'Arcy, C., & Streiner, D. L. (2012). Recall of recent and more remote depressive episodes in a prospective cohort study. *Social Psychiatry and Psychiatric Epidemiology*, *47*(5), 691–696. https://doi.org/10.1007/s00127-011-0385-5

Patten, S. B., Williams, J. V. A., Lavorato, D. H., Bulloch, A. G. M., Fiest, K. M., Wang, J. L., & Sajobi, T. T. (2017). Seasonal variation in major depressive episode prevalence in Canada. *Epidemiology and Psychiatric Sciences*, *26*(2), 169–176. https://doi.org/DOI: 10.1017/S2045796015001183

Peck, D. F. (1990). Climatic variables and admissions for mania: a reanalysis. *Journal of Affective Disorders*, *20*(4), 249–250. https://doi.org/https://doi.org/10.1016/0165-0327(90)90056-E

Perugi, G., Passino, M. C. S., Toni, C., Maremmani, I., & Angst, J. (2007). Is unipolar mania a distinct subtype? *Comprehensive Psychiatry*, *48*(3), 213–217. https://doi.org/https://doi.org/10.1016/j.comppsych.2007.01.004

Phillips, M. L., & Kupfer, D. J. (2013). Bipolar disorder diagnosis: challenges and future directions. *The Lancet*, *381*(9878), 1663–1671. https://doi.org/https://doi.org/10.1016/S0140-6736(13)60989-7

Ratheesh, A., Berk, M., & Schmaal, L. (2023). Can we overcome the heterogeneity of mood disorders in clinical trials? *Australian & New Zealand Journal of Psychiatry*, *57*(3), 309–311. https://doi.org/10.1177/00048674231158266

Regier, D. A., Narrow, W. E., Clarke, D. E., Kraemer, H. C., Kuramoto, S. J., Kuhl, E. A., & Kupfer, D. J. (2013). DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. *American Journal of Psychiatry*, *170*(1), 59–70. https://doi.org/10.1176/appi.ajp.2012.12070999

Richards, A., Horwood, J., Boden, J., Kennedy, M., Sellers, R., Riglin, L., Mistry, S., Jones, H., Smith, D. J., Zammit, S., Owen, M., O'Donovan, M. C., & Harold, G.

T. (2019). Associations between schizophrenia genetic risk, anxiety disorders and manic/hypomanic episode in a longitudinal population cohort study. *The British Journal of Psychiatry*, *214*(2), 96–102. https://doi.org/DOI: 10.1192/bjp.2018.227

Roenneberg, T., Wirz-Justice, A., & Merrow, M. (2003). Life between Clocks: Daily Temporal Patterns of Human Chronotypes. *Journal of Biological Rhythms*, *18*(1), 80–90. https://doi.org/10.1177/0748730402239679

Rohde, P., Clarke, G. N., Lewinsohn, P. M., Seeley, J. R., & Kaufman, N. K. (2001). Impact of Comorbidity on a Cognitive-Behavioral Group Treatment for Adolescent Depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(7), 795–802. https://doi.org/https://doi.org/10.1097/00004583-200107000-00014

Romo-Nava, F., Blom, T. J., Cuellar-Barboza, A. B., Winham, S. J., Colby, C. L., Nunez, N. A., Biernacka, J. M., Frye, M. A., & McElroy, S. L. (2020). Evening chronotype as a discrete clinical subphenotype in bipolar disorder. *Journal of Affective Disorders*, *266*, 556–562. https://doi.org/https://doi.org/10.1016/j.jad.2020.01.151

Rosa, A. R., Bonnín, C. M., Vázquez, G. H., Reinares, M., Solé, B., Tabarés-Seisdedos, R., Balanzá-Martínez, V., González-Pinto, A., Sánchez-Moreno, J., & Vieta, E. (2010). Functional impairment in bipolar II disorder: Is it as disabling as bipolar I? *Journal of Affective Disorders*, *127*(1), 71–76. https://doi.org/https://doi.org/10.1016/j.jad.2010.05.014

Russo, M., Mahon, K., Shanahan, M., Ramjas, E., Solon, C., Purcell, S. M., & Burdick, K. E. (2015). The relationship between sleep quality and neurocognition in bipolar disorder. *Journal of Affective Disorders*, *187*, 156–162. https://doi.org/https://doi.org/10.1016/j.jad.2015.08.009

Sabia, S., Cogranne, P., van Hees, V. T., Bell, J. A., Elbaz, A., Kivimaki, M., & Singh-Manoux, A. (2015). Physical activity and adiposity markers at older ages: Accelerometer Vs questionnaire data. *Journal of the American Medical Directors Association*, *16*(5), 438.e7-438.e13. https://doi.org/10.1016/j.jamda.2015.01.086

Sacchet, M. D., Livermore, E. E., Iglesias, J. E., Glover, G. H., & Gotlib, I. H. (2015). Subcortical volumes differentiate Major Depressive Disorder, Bipolar Disorder, and remitted Major Depressive Disorder. *Journal of Psychiatric Research*, *68*, 91–98. https://doi.org/https://doi.org/10.1016/j.jpsychires.2015.06.002

Saeb, S., Zhang, M., Karr, C. J., Schueller, S. M., Corden, M. E., Kording, K. P., & Mohr, D. C. (2015). Mobile Phone Sensor Correlates of Depressive Symptom Severity in Daily-Life Behavior: An Exploratory Study. *J Med Internet Res*, *17*(7), e175. https://doi.org/10.2196/jmir.4273

Saha, S., Lim, C. C. W., Cannon, D. L., Burton, L., Bremner, M., Cosgrove, P., Huo, Y., & J. McGrath, J. (2021a). Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis. *Depression and Anxiety*, *38*(3), 286–306. https://doi.org/https://doi.org/10.1002/da.23113

Saha, S., Lim, C. C. W., Cannon, D. L., Burton, L., Bremner, M., Cosgrove, P., Huo, Y., & J. McGrath, J. (2021b). Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis. *Depression and Anxiety*, *38*(3), 286–306. https://doi.org/https://doi.org/10.1002/da.23113

Sangha, N., Lyall, L., Wyse, C., Cullen, B., Whalley, H. C., & Smith, D. J. (2022). The nosological status of unipolar mania and hypomania within UK Biobank according to objective and subjective measures of diurnal rest and activity. *Bipolar Disorders*, *n/a*(n/a). https://doi.org/https://doi.org/10.1111/bdi.13237

Schaffer, A., McIntosh, D., Goldstein, B. I., Rector, N. A., McIntyre, R. S., Beaulieu, S., Swinson, R., Yatham, L. N., & Force, =Canadian Network for Mood and Anxiety Treatments (CANMAT) Task. (2012). The CANMAT task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. *Annals of Clinical Psychiatry : Official Journal of the American Academy of Clinical Psychiatrists*, *24*(1), 6–22.

Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., Loehrer, E., Tiemeier, H., Hofman, A., Niessen, W. J., Vernooij, M. W., Ikram, M. A., Wittfeld, K., Grabe, H. J., Block, A., Hegenscheid, K., Völzke, H., Hoehn, D., Czisch, M., … Group, for the E.-M. D. D. W. (2016). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Molecular Psychiatry*, *21*(6), 806–812. https://doi.org/10.1038/mp.2015.69

Schneider, J., Bakštein, E., Kolenič, M., Vostatek, P., Correll, C. U., Novák, D., & Španiel, F. (2022). Motor activity patterns can distinguish between interepisode bipolar disorder patients and healthy controls. *CNS Spectrums*, *27*(1), 82–92. https://doi.org/DOI: 10.1017/S1092852920001777

Schneider, J., Fárková, E., & Bakštein, E. (2022). Human chronotype: Comparison of questionnaires and wrist-worn actigraphy. *Chronobiology International*, *39*(2), 205–220. https://doi.org/10.1080/07420528.2021.1992418

Seleem, M. A., Merranko, J. A., Goldstein, T. R., Goldstein, B. I., Axelson, D. A., Brent, D. A., Nimgaonkar, V. L., Diler, R. S., Sakolsky, D. J., Kupfer, D. J., & Birmaher, B. (2015). The longitudinal course of sleep timing and circadian preferences in adults with bipolar disorder. *Bipolar Disorders*, *17*(4), 392–402. https://doi.org/10.1111/bdi.12286

Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020). Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. *Systematic Reviews*, *9*(1), 17. https://doi.org/10.1186/s13643-020-1274-3

Smith, D. J., Nicholl, B. I., Cullen, B., Martin, D., Ul-Haq, Z., Evans, J., Gill, J. M. R., Roberts, B., Gallacher, J., Mackay, D., Hotopf, M., Deary, I., Craddock, N., & Pell, J. P. (2013). Prevalence and Characteristics of Probable Major Depression and Bipolar Disorder within UK Biobank: Cross-Sectional Study of 172,751 Participants. *PLOS ONE*, *8*(11), e75362.

Soehner, A. M., Bertocci, M. A., Levenson, J. C., Goldstein, T. R., Rooks, B., Merranko, J., Hafeman, D., Diler, R., Axelson, D., Goldstein, B. I., Hickey, M. B., Monk, K., Phillips, M. L., & Birmaher, B. (2019). Longitudinal Associations Between Sleep Patterns and Psychiatric Symptom Severity in High-Risk and Community Comparison Youth. *Journal of the American Academy of Child & Adolescent Psychiatry*, *58*(6), 608–617. https://doi.org/https://doi.org/10.1016/j.jaac.2018.09.448

Stokes, P. R. A., Yalin, N., Mantingh, T., Colasanti, A., Patel, R., Bellivier, F., Leboyer, M., Henry, C., Kahn, J.-P., Etain, B., & Young, A. H. (2020). Unipolar mania: Identification and characterisation of cases in France and the United Kingdom. *Journal of Affective Disorders*, *263*, 228–235. https://doi.org/https://doi.org/10.1016/j.jad.2019.11.024

Strath, S. J., Kaminsky, L. A., Ainsworth, B. E., Ekelund, U., Freedson, P. S., Gary, R. A., Richardson, C. R., Smith, D. T., & Swartz, A. M. (2013). Guide to the Assessment of Physical Activity: Clinical and Research Applications. *Circulation*, *128*(20), 2259–2279. https://doi.org/10.1161/01.cir.0000435708.67487.da

Subramanian, K., Sarkar, S., & Kattimani, S. (2017). Bipolar disorder in Asia: Illness course and contributing factors. *Asian Journal of Psychiatry*, *29*, 16–29. https://doi.org/https://doi.org/10.1016/j.ajp.2017.04.009

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., & Collins, R. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Medicine*, *12*(3), e1001779.

Suibkitwanchai, K., Sykulski, A. M., Perez Algorta, G., Waller, D., & Walshe, C. (2020). Nonparametric time series summary statistics for high-frequency accelerometry data from individuals with advanced dementia. *PLOS ONE*, *15*(9), e0239368. https://doi.org/10.1371/journal.pone.0239368

Suor, J. H., Jimmy, J., Monk, C. S., Phan, K. L., & Burkhouse, K. L. (2020). Parsing differences in amygdala volume among individuals with and without social and generalized anxiety disorders across the lifespan. *Journal of Psychiatric Research*, *128*, 83–89. https://doi.org/https://doi.org/10.1016/j.jpsychires.2020.05.027

Sweeney, J. A., Kmiec, J. A., & Kupfer, D. J. (2000). Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biological Psychiatry*, *48*(7), 674–684. https://doi.org/https://doi.org/10.1016/S0006-3223(00)00910-0

Taillard, J., Philip, P., Coste, O., Sagaspe, P., & Bioulac, B. (2003). The circadian and homeostatic modulation of sleep pressure during wakefulness differs between morning and evening chronotypes. *Journal of Sleep Research*, *12*(4), 275–282. https://doi.org/https://doi.org/10.1046/j.0962-1105.2003.00369.x

Takahashi, J. S. (2015). Molecular components of the circadian clock in mammals. *Diabetes, Obesity and Metabolism*, *17*(S1), 6–11. https://doi.org/https://doi.org/10.1111/dom.12514

Tan, X., Ciuculete, D.-M., Schiöth, H. B., & Benedict, C. (2020). Associations between chronotype, MTNR1B genotype and risk of type 2 diabetes in UK Biobank. *Journal of Internal Medicine*, *287*(2), 189–196. https://doi.org/10.1111/joim.12994

Tazawa, Y., Wada, M., Mitsukura, Y., Takamiya, A., Kitazawa, M., Yoshimura, M., Mimura, M., & Kishimoto, T. (2019). Actigraphy for evaluation of mood disorders: A systematic review and meta-analysis. *Journal of Affective Disorders*, *253*, 257–269. https://doi.org/https://doi.org/10.1016/j.jad.2019.04.087

Togo, F., Watanabe, E., Park, H., Shephard, R. J., & Aoyagi, Y. (2005). Meteorology and the physical activity of the elderly: the Nakanojo Study. *International Journal of Biometeorology*, *50*(2), 83–89. https://doi.org/10.1007/s00484-005-0277-z

Torous, J., & Powell, A. C. (2015). Current research and trends in the use of smartphone applications for mood disorders. *Internet Interventions*, *2*(2), 169–173. https://doi.org/https://doi.org/10.1016/j.invent.2015.03.002

Tournikioti, K., Ferentinos, P., Michopoulos, I., Alevizaki, M., Soldatos, C. R., Dikeos, D., & Douzenis, A. (2017). Clinical and treatment-related predictors of cognition in bipolar disorder: focus on visual paired associative learning. *European Archives of Psychiatry and Clinical Neuroscience*, *267*(7), 661–669. https://doi.org/10.1007/s00406-016-0743-0

Traffanstedt, M. K., Mehta, S., & LoBello, S. G. (2016). Major Depression With Seasonal Variation: Is It a Valid Construct? *Clinical Psychological Science*, *4*(5), 825–834. https://doi.org/10.1177/2167702615615867

Trenberth, K. E. (1983). What are the seasons? *Bulletin - American Meteorological Society*, *64*(11), 1276–1282. https://doi.org/10.1175/1520-0477(1983)064<1276:WATS>2.0.CO;2

Tucker, P., & Gilliland, J. (2007). The effect of season and weather on physical activity: A systematic review. *Public Health*, *121*(12), 909–922. https://doi.org/https://doi.org/10.1016/j.puhe.2007.04.009

Uffelmann, E., Huang, Q. Q., Munung, N. S., de Vries, J., Okada, Y., Martin, A. R., Martin, H. C., Lappalainen, T., & Posthuma, D. (2021). Genome-wide association studies. *Nature Reviews Methods Primers*, *1*(1), 59. https://doi.org/10.1038/s43586-021-00056-9

UK Biobank. (2007). UK Biobank: Protocol for a large-scale prospective epidemiological resource. *UKBB-PROT-09-06 (Main Phase)*, *06*(March), 1–112.

UK Biobank. (2016). *UK Biobank Physical activity monitor (accelerometer)*. 0–7.

Usher, J., Leucht, S., Falkai, P., & Scherk, H. (2010). Correlation between amygdala volume and age in bipolar disorder — A systematic review and meta-analysis of

structural MRI studies. *Psychiatry Research: Neuroimaging*, *182*(1), 1–8. https://doi.org/https://doi.org/10.1016/j.pscychresns.2009.09.004

Vallée, J., Cadot, E., Roustit, C., Parizot, I., & Chauvin, P. (2011). The role of daily mobility in mental health inequalities: The interactive influence of activity space and neighbourhood of residence on depression. *Social Science & Medicine*, *73*(8), 1133–1144. https://doi.org/https://doi.org/10.1016/j.socscimed.2011.08.009

van Hees, V. T., Sabia, S., Jones, S. E., Wood, A. R., Anderson, K. N., Kivimäki, M., Frayling, T. M., Pack, A. I., Bucan, M., Trenell, M. I., Mazzotti, D. R., Gehrman, P. R., Singh-Manoux, B. A., & Weedon, M. N. (2018). Estimating sleep parameters using an accelerometer without sleep diary. *Scientific Reports*, *8*(1), 12975. https://doi.org/10.1038/s41598-018-31266-z

van Rooijen, G., Isvoranu, A.-M., Meijer, C. J., van Borkulo, C. D., Ruhé, H. G., & de Haan, L. (2017). A symptom network structure of the psychosis spectrum. *Schizophrenia Research*, *189*, 75–83. https://doi.org/https://doi.org/10.1016/j.schres.2017.02.018

Van Someren, E. J. W., Swaab, D. F., Colenda, C. C., Cohen, W., McCall, W. V., & Rosenquist, P. B. (1999). Bright Light Therapy: Improved Sensitivity to Its Effects on Rest-Activity Rhythms in Alzheimer Patients by Application of Nonparametric Methods. *Chronobiology International*, *16*(4), 505–518. https://doi.org/10.3109/07420529908998724

Van Til, K., McInnis, M. G., & Cochran, A. (2020). A comparative study of engagement in mobile and wearable health monitoring for bipolar disorder. *Bipolar Disorders*, *22*(2), 182–190. https://doi.org/https://doi.org/10.1111/bdi.12849

Vidafar, P., Yocum, A. K., Han, P., McInnis, M. G., & Burgess, H. J. (2021). Late chronotype predicts more depressive symptoms in bipolar disorder over a 5 year follow-up period. *International Journal of Bipolar Disorders*, *9*(1), 28. https://doi.org/10.1186/s40345-021-00233-5

Vieta, E., Gastó, C., Otero, A., Nieto, E., & Vallejo, J. (1997). Differential features between bipolar I and bipolar II disorder. *Comprehensive Psychiatry*, *38*(2), 98–101. https://doi.org/https://doi.org/10.1016/S0010-440X(97)90088-2

Vilhjálmsson, B. J., Yang, J., Finucane, H. K., Gusev, A., Lindström, S., Ripke, S., Genovese, G., Loh, P. R., Bhatia, G., Do, R., Hayeck, T., Won, H. H., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., … Price, A. L. (2015). Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *American Journal of Human Genetics*, *97*(4), 576–592. https://doi.org/10.1016/j.ajhg.2015.09.001

Vitale, J. A., Roveda, E., Montaruli, A., Galasso, L., Weydahl, A., Caumo, A., & Carandente, F. (2015). Chronotype influences activity circadian rhythm and sleep: Differences in sleep quality between weekdays and weekend. *Chronobiology International*, *32*(3), 405–415. https://doi.org/10.3109/07420528.2014.986273

Wainberg, M., Jones, S. E., Beaupre, L. M., Hill, S. L., Felsky, D., Rivas, M. A., Lim, A. S. P., Ollila, H. M., & Tripathy, S. J. (2021). Association of accelerometer-derived sleep measures with lifetime psychiatric diagnoses: A cross-sectional study of 89,205 participants from the UK Biobank. *PLOS Medicine*, *18*(10), e1003782. https://doi.org/10.1371/journal.pmed.1003782

Wang, L., Chignell, M., Jiang, H., Lokuge, S., Mason, G., Fotinos, K., & Katzman, M. (2021). Hierarchical Clustering of Multi-Study Depression Data Yields Four Symptom Clusters. *2021 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 3245–3250. https://doi.org/10.1109/BIBM52615.2021.9669454

Wehr, T. A. (1992). Improvement of depression and triggering of mania by sleep deprivation. *JAMA*, *267*(4), 548–551.

Weintraub, M. J., Schneck, C. D., & Miklowitz, D. J. (2020). Network analysis of mood symptoms in adolescents with or at high risk for bipolar disorder. *Bipolar Disorders*, *22*(2), 128–138. https://doi.org/https://doi.org/10.1111/bdi.12870

Wen, X., Ma, Y., Yuan, B., & Wang, F. (2019). Association among Weather Conditions, Ambient Air Temperature, and Sedentary Time in Chinese Adults. *BioMed Research International*, *2019*, 4010898. https://doi.org/10.1155/2019/4010898

Willetts, M., Hollowell, S., Aslett, L., Holmes, C., & Doherty, A. (2018). Statistical machine learning of sleep and physical activity phenotypes from sensor data in 96,220 UK Biobank participants. *Scientific Reports*, *8*(1), 7961. https://doi.org/10.1038/s41598-018-26174-1

Wirz-Justice, A. (2006). Biological rhythm disturbances in mood disorders. *International Clinical Psychopharmacology*, *21*. https://journals.lww.com/intclinpsychopharm/fulltext/2006/02001/biological_rhythm_disturbances_in_mood_disorders.2.aspx

Wise, T., Radua, J., Via, E., Cardoner, N., Abe, O., Adams, T. M., Amico, F., Cheng, Y., Cole, J. H., de Azevedo Marques Périco, C., Dickstein, D. P., Farrow, T. F. D., Frodl, T., Wagner, G., Gotlib, I. H., Gruber, O., Ham, B. J., Job, D. E., Kempton, M. J., … Arnone, D. (2017). Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Molecular Psychiatry*, *22*(10), 1455–1463. https://doi.org/10.1038/mp.2016.72

Witham, M. D., Donnan, P. T., Vadiveloo, T., Sniehotta, F. F., Crombie, I. K., Feng, Z., & McMurdo, M. E. T. (2014). Association of Day Length and Weather Conditions with Physical Activity Levels in Older Community Dwelling People. *PLOS ONE*, *9*(1), e85331. https://doi.org/10.1371/journal.pone.0085331

Wittmann, M., Paulus, M., & Roenneberg, T. (2010). Decreased Psychological Well-Being in Late 'Chronotypes' Is Mediated by Smoking and Alcohol Consumption. *Substance Use & Misuse*, *45*(1–2), 15–30. https://doi.org/10.3109/10826080903498952

Wood, J., Birmaher, B., Axelson, D., Ehmann, M., Kalas, C., Monk, K., Turkin, S., Kupfer, D. J., Brent, D., Monk, T. H., & Nimgainkar, V. L. (2009). Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals. *Psychiatry Research*, *166*(2–3), 201–209. https://doi.org/10.1016/J.PSYCHRES.2008.03.003

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., Adams, M. J., Agerbo, E., Air, T. M., Andlauer, T. M. F., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A. F. T., Bigdeli, T. B., Binder, E. B., Blackwood, D. R. H., Bryois, J., Buttenschøn, H. N., Bybjerg-Grauholm, J., … Sullivan, P. F. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, *50*(5), 668–681. https://doi.org/10.1038/s41588-018-0090-3

Xu, C., Wu, W., Peng-Li, D., Xu, P., Sun, D., & Wan, B. (2020). Intraday weather conditions can influence self-report of depressive symptoms. *Journal of Psychiatric Research*, *123*, 194–200. https://doi.org/https://doi.org/10.1016/j.jpsychires.2020.02.006

Yazıcı, O. (2014). Unipolar mania: A distinct entity? *Journal of Affective Disorders*, *152–154*, 52–56. https://doi.org/https://doi.org/10.1016/j.jad.2013.10.005

Yousaf, S., & Bonsall, A. (2017a). *UK Townsend Deprivation Scores from 2011 census data*. http://s3-eu-west-1.amazonaws.com/statistics.digitalresources.jisc.ac.uk/dkan/files/Townsend_Deprivation_Scores/UK Townsend Deprivation Scores from 2011 census data.pdf

Yousaf, S., & Bonsall, A. (2017b). *UK Townsend Deprivation Scores from 2011 census data*. Http://S3-Eu-West-1.Amazonaws.Com/Statistics.Digitalresources.Jisc.Ac.Uk/Dkan/Files/Townsend_Deprivation_Scores/UK%20Townsend%20Deprivation%20Scores%20from%202011%20census%20data.Pdf.

Zavada, A., Gordijn, M. C. M., Beersma, D. G. M., Daan, S., & Roenneberg, T. (2005). Comparison of the Munich Chronotype Questionnaire with the Horne-Östberg's Morningness-Eveningness score. *Chronobiology International*, *22*(2), 267–278. https://doi.org/10.1081/CBI-200053536

Zerbini, G., van der Vinne, V., Otto, L. K. M., Kantermann, T., Krijnen, W. P., Roenneberg, T., & Merrow, M. (2017). Lower school performance in late chronotypes: underlying factors and mechanisms. *Scientific Reports*, *7*(1), 4385. https://doi.org/10.1038/s41598-017-04076-y

Zhu, Y., Womer, F. Y., Leng, H., Chang, M., Yin, Z., Wei, Y., Zhou, Q., Fu, S., Deng, X., Lv, J., Song, Y., Ma, Y., Sun, X., Bao, J., Wei, S., Jiang, X., Tan, S., Tang, Y., & Wang, F. (2019). The Relationship Between Cognitive Dysfunction and Symptom Dimensions Across Schizophrenia, Bipolar Disorder, and Major Depressive Disorder . In *Frontiers in Psychiatry* (Vol. 10).