BJPsych | The British Journal of Psychiatry (2026)
1–10. doi: 10.1192/bjp.2026.10798

Original Article

Clinical and genetic correlates of a circadian subtype of depression in the Australian Genetics of Depression Study

Emiliana Tonini, Jacob J. Crouse*, Mirim Shin, Joanne S. Carpenter, Brittany L. Mitchell, Enda M. Byrne, Penelope A. Lind, Scott D. Gordon, Richard Parker, Samuel J. Hockey, Timothy To, Andrew Shim, Alex Hill, Anna Treneman, Elizabeth Scott, Jan Scott, Kathleen R. Merikangas, Naomi R. Wray, Nicholas G. Martin, Sarah E. Medland and Ian B. Hickie*

Background

Although commonly accepted depressive subtypes reflect phenotypic differences, there has been minimal progress in identification of discrete pathophysiological pathways, biomarkers or differential therapeutic approaches to effectively guide clinical management.

Aims

To test the biological validity and clinical utility of a circadian subtype of depression on the basis of clinical course, differential medication response (self-reported) and genetic risk profile.

Method

Cross-sectional data were drawn from the nationwide Australian Genetics of Depression Study. Participants were classified as having a 'circadian' or 'non-circadian' subtype of depression on the basis of meeting criteria for at least three binary circadian-associated features: social jetlag, seasonality, delayed sleep midpoint, evening chronotype, morning tiredness and hypersomnia. Clinical course characteristics were compared. Associations with response to commonly prescribed antidepressants and polygenic risk scores for mental disorders and sleep, circadian, metabolic and inflammatory traits were investigated using logistic regression models.

Results

A total of 2604 participants (23%; 80% female; mean age 37.87 ± 13.62 years) had a circadian subtype. They reported an earlier age at onset ($P < 0.001$), more severe clinical features including (hypo)manic-like and psychotic-like experiences, suicidality, psychological distress and somatic complaints (all $P < 0.001$), weight gain during depressive episodes ($P < 0.001$), poorer response to selective serotonin reuptake inhibitors (odds ratio 0.88 [95% CI 0.82, 0.94]) and serotonin–noradrenaline reuptake inhibitors (odds ratio 0.89 [95% CI 0.83, 0.97]), and more side-effects compared with those with a non-circadian subtype. Having a circadian subtype was associated with higher polygenic risk scores for attention-deficit hyperactivity disorder (odds ratio 1.11 [95% CI 1.06, 1.17]), major depression (odds ratio 1.11 [95% CI 1.06, 1.16]), anxiety (odds ratio 1.10 [95% CI 1.04, 1.15]), bipolar disorder (odds ratio 1.09 [95% CI 1.04, 1.14]), body mass index (odds ratio 1.09 [95% CI 1.05, 1.14]), triglycerides (odds ratio 1.10 [95% CI 1.06, 1.16]), interleukin-6 (odds ratio 1.08 [95% CI 1.03, 1.13]), higher insulin resistance (odds ratio 1.08 [95% CI 1.04, 1.13]), later sleep midpoint (odds ratio 1.15 [95% CI 1.10, 1.21]), insomnia (odds ratio 1.08 [95% CI 1.03, 1.13]) and later chronotype (odds ratio 0.68 [95% CI 0.65, 0.71]).

Conclusions

These findings support the face validity and potential clinical utility of a circadian subtype of depression as a clinical profile. Pending independent replication, investigation of its biology and predictive utility are warranted.

Keywords

Depression; circadian; mood disorder; treatment response; chronobiology.

Copyright and usage

© The Author(s), 2026. Published by Cambridge University Press on behalf of Royal College of Psychiatrists. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

Major depressive disorder (MDD) is a heterogeneous condition with highly variable presentations and patterns of treatment response, probably reflecting multiple underlying pathophysiological mechanisms. Despite decades of research, most proposed clinical subtypes of mood disorders show only modest differences in prognosis or treatment response.[1] Consequently, international treatment guidelines largely emphasise dimensions such as severity, persistence or recurrence,[2,3] often resulting in repeated trial-and-error prescribing of common antidepressants.[4] Earlier detection of distinct illness pathways could enable more effective personalised interventions at earlier clinical stages.

Proposed circadian subtype of depression

Accumulating evidence implicates circadian disruption as a pathophysiological mechanism causing depressive symptomatology.[5] Circadian disruption has been proposed as a marker for a distinct profile, termed 'circadian depression',[6] which has garnered attention as a clinical construct.[7] This cross-cutting profile is proposed to preferentially capture cases in which individuals have a circadian pathophysiology as a core contributor to their mental disorder.[6] Phenotypically, this circadian subtype is proposed to be characterised by disrupted 24-h sleep–wake cycles, reduced daytime activity, low energy and weight gain during episodes[6] and to be associated with early age at onset, bipolar-like features, poor response to common antidepressants (e.g. selective serotonin reuptake inhibitors (SSRIs)) and cardiometabolic/inflammatory comorbidities.[8] Objective markers of circadian dysregulation have been reported in emerging mood disorders displaying such circadian-like clinical features.[9–11] Actigraphy-derived circadian measures are heritable,[12] and genetic risk for bipolar disorder (BD) and MDD has been linked to delayed circadian rhythms.[13] Circadian gene variants also seem to contribute to the development of mood disorders,[14] and evening chronotype (a proposed feature of the circadian subtype) has been tied to poorer

*These authors contributed equally.

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

response to SSRIs and serotonin–noradrenaline reuptake inhibitor (SNRIs).[15]

Current study

We leveraged a nationwide genetically informative study of >10 000 adults with depression and aimed to (a) construct a circadian phenotype using a selection of circadian-associated self-reported markers; (b) investigate the correlates of this circadian subtype, including symptoms, clinical course and self-reported treatment response to common antidepressants; and (c) examine associations between this circadian subtype and genetic risk for relevant mental disorders, physical health and sleep/circadian traits. We proposed that the circadian subtype would be associated with more severe features (e.g. earlier age at onset), poorer response to conventional antidepressants, and higher genetic risk for bipolar and metabolic and inflammatory markers, relative to a 'non-circadian' subtype (residual cases) of depression. Our overarching goal was to examine whether this construct could be a valid and clinically useful phenotype that could guide clinical future stratification efforts. This study represents an initial exploration of a provisional set of circadian criteria for definition of a circadian subtype of depression.

Method

Participants

Participants were from the Australian Genetics of Depression Study (AGDS), a nationwide cohort study exploring genetic and psychosocial factors influencing the aetiology of depressive disorders and antidepressant response. The cohort profile has been described elsewhere.[16] Participants were recruited by (a) invitations sent from the Australian government Department of Human Services to individuals on the basis of prescription medication records in the past 4.5 years (obtained through the nationwide Medicare Benefits Scheme or the Pharmaceutical Benefits Scheme); or (b) a media publicity campaign targeting adults who had experienced clinical depression. Individuals who had been diagnosed with depression at some point in their lifetime were eligible. Data from the first freeze (September 2016 to September 2018) were analysed. Ethical approval was granted by the Human Research Ethics Committee of the Queensland Institute of Medical Research Berghofer Medical Research Institute in Brisbane, Australia (HREC EC00278, protocol P2118). Written informed consent was obtained.

Participants completed an online survey comprising a core module on depressive symptomatology and experiences with common antidepressants, and additional modules including one on sleep and circadian-related behaviours. Participants were also asked whether they had ever been diagnosed with any of a set of other mental disorders (e.g. BD). The Composite International Diagnostic Interview Short Form was used to assess MDD according to DSM-5 criteria. The AGDS cohort predominantly comprises adults with severe, recurrent depressive disorders; only 4% reported having had a single depressive episode, with a median of 6 episodes and a median worst-episode duration of 12 weeks.[16] In addition, 65% of the cohort reported lifetime suicidal ideation and 31% reported at least one suicide attempt. Here, we only included participants of genetically inferred European ancestry with complete data on polygenic risk scores (PGS) and on at least three circadian criteria (as described below). A total of 11 380 participants (75% female; mean age 43.8 ± 15.3 years) were included in this study (see Supplementary Fig. 1 available at https://doi.org/10.1192/bjp.2026.10798 for the participant selection process and Supplementary Table 1 for comparison with the excluded sample). Results of sensitivity analyses restricted to participants with complete data on all six circadian criteria ($n = 8728$) are presented in Supplementary Fig. 5 and Supplementary Table 7.

Circadian criteria

To identify participants with a circadian subtype, the following criteria were selected on the basis of availability, domain knowledge and clinical expertise.

(a) Seasonality, which has been proposed as a marker of sensitivity of the circadian system to photoperiodic changes in day length and is associated with mood disorders.[17] We calculated the Global Seasonality Score (GSS) using the Seasonal Pattern Assessment Questionnaire.[18] The GSS is composed of six items assessing seasonal change in usual behaviour across sleep length, social activity, mood, weight, appetite and energy. Each item is scored from 0 ('no change') to 4 ('extremely marked change'). Items are summed to calculate the GSS. Following validated cut-offs,[19] a GSS ≥ 11 was coded as indicating seasonality.

(b) Delayed sleep midpoint, the halfway point (clock time) between sleep onset and waking up, is an expression of evening chronotype (the preference for sleep–wake timing) and is influenced by genetics[20] but also by behaviour (e.g. work schedules). Participants reported what time they had usually gone to bed at night and got up in the morning for the majority of the nights and days in the past month. First, sleep midpoint on free (non-working) days was calculated. Then, age-adjusted cut-offs, calculated as the average sleep midpoint of the age group plus one standard deviation, were applied to determine delayed sleep midpoint as follows: for 18- to 24-year-olds, sleep midpoint later than 6 am; for 25- to 34-year-olds, sleep midpoint later than 5:30 am; for 35- to 64-year-olds, sleep midpoint later than 5 am; and for 65-year-olds and older, sleep midpoint later than 4:30 am.

(c) Social jetlag represents the mismatch between biological time and social time and is a marker of circadian disturbance.[21] First, sleep midpoint was calculated on free (non-working) days and on working days. Next, the difference between sleep midpoint on free days and on working days was calculated. Given the wide age range in the AGDS cohort (18–90 years) and the fact that sleep timing changes with age, age-adjusted thresholds for social jetlag were calculated as the average sleep midpoint of the age group plus one standard deviation: for 18- to 24-year-olds, sleep midpoint on free days ≥2.5 h later than on working days; for 25- to 34-year-olds:,sleep midpoint on free days ≥2.25 h later than on working days; for 35- to 64-year-olds, sleep midpoint on free days ≥2 h later than on working days; and for 65-year-olds and older, sleep midpoint on free days ≥1.25 h later than on working days.

(d) Evening chronotype, where chronotype is the genetically influenced preference for daily timing of sleep, waking and other phenomena and is associated with mood disorders.[22,23] Chronotype was defined using item 19 of the Morningness–Eveningness Questionnaire.[24] Reflecting on their usual behaviour, those reporting being 'Definitely an "evening type"' were coded as having an evening chronotype.

(e) Hypersomnia is a common symptom of mood disorders and may plausibly stem from circadian disruption (e.g. weakened circadian signal of alertness leading to increased sleepiness).[25] Using the DSM-5 MDD criterion, those endorsing the item 'sleep much more than usual'

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

Table 1 Circadian features in the whole sample ($N = 11\,380$)

Feature	Variable used	Age group, years	Mean (s.d.)	Cut-off or category used	*n* (%) meeting criteria
Seasonality	SPAQ GSS		6.59 (4.69)	GSS > 11	2190 (19.2)
Social jetlag	Weekend–weekday difference in sleep midpoint	18–24	1.33 (1.11)	>2 h 30 min	1390 (12.2)
		25–34	1.23 (1.01)	>2 h 15 min	
		35–64	0.95 (0.86)	>2 h 00 min	
		65+	0.46 (0.69)	>1 h 30 min	
Evening chronotype	MEQ item 19			'Definitely an "evening" type'	2826 (24.8)
Delayed sleep midpoint	Sleep midpoint	18–24	28.49 (1.36)	>6:00 am	1409 (12.4)
		25–34	28.00 (1.35)	>5:30 am	
		35–64	27.48 (1.29)	>5:00 am	
		65+	27.17 (1.18)	>4:30am	
Hypersomnia	DSM-5 criteria			Reported sleeping more during worst depressive episode	5831 (51.2)
Morning tiredness	MEQ item 8			'Very tired'	4391 (38.6)

SPAQ, Seasonal Pattern Assessment Questionnaire; GSS, General Seasonality Score; MEQ, Morningness–Eveningness Questionnaire.

during the period in which their feelings of depression were the worst were coded as having hypersomnia.

(f) Morning tiredness, relating partly to the construct of sleep inertia, has been proposed as an indirect marker of waking during the biological (circadian) night. Morning tiredness was defined using item 8 of the Morningness–Eveningness Questionnaire.[24] Reflecting on their usual behaviour, those reporting being 'very tired' in the first half-hour after waking in the morning were coded as having morning tiredness.

Table 1 reports the numbers and proportions of participants meeting these circadian criteria. The sum of all criteria was computed and those meeting at least three of the six criteria were coded as the 'circadian subtype' group; those meeting fewer than three were coded as the 'non-circadian group'. The ≥3 circadian criteria cut-off was selected as an optimal balance of a criteria-based set that most closely matched the clinical estimates from our prior actigraphy and controlled chronobiological studies[26,27] and to provide appropriate subgroup sizes that would support statistical power for large-scale clinical research. Further refinement of this provisional subtype in future work may support alternative cut-offs or reweighted and/or additional criteria. Exploratory analyses of clinical correlates by number of circadian criteria are presented in Supplementary Figs. 4 and 10.

Assessments

Clinical variables

Information about demographics, age at onset and clinical course were assessed by self-report questionnaires, including (hypo) manic-like experiences, psychotic-like experiences, psychological and somatic distress, and suicidal ideation. Details on assessments are provided in the Supplementary Materials.

Antidepressants, efficacy and side-effects

Participants' subjective experiences with ten of the most commonly prescribed antidepressants in Australia at the time of the survey were assessed. Efficacy was rated ordinally (0 = not at all well; 1 = moderately well; 2 = very well), excluding 'I don't know' responses, and compared across two major classes: SSRIs (sertraline, escitalopram, citalopram, fluoxetine and paroxetine) and SNRIs (venlafaxine, desvenlafaxine and duloxetine), as well as two additional antidepressants (amitriptyline and mirtazapine). In the case of different ratings for antidepressants within the same class, the highest efficacy rating was used as the class-level rating. Side-effects while taking antidepressants were assessed as a binary variable (0 = no; 1 = yes) across 25 possible (predetermined) symptoms, including rash, runny nose, muscle pain, constipation, diarrhoea, drowsiness, agitation, fatigue, suicidal thoughts, dry mouth, blurred vision, difficulty getting to sleep, weight gain, sweating, vomiting, shaking, increased anxiety, attempted suicide, headache, reduced sexual desire, dizziness, nausea, weight loss and other side-effects. Participants reported side-effects only for antidepressants they had taken.

Polygenic risk scores

DNA samples were collected using saliva kits, genotyped using the Illumina Global Screening Array V.1.0, GSAMD V.1.0 or V.3.0 depending on batch, and processed using standardised quality control measures. Pre-imputation quality control was done using PLINK 1.9[28,29] and involved removal of single nucleotide polymorphisms (SNPs) with a minor allele frequency <0.01, a SNP call rate <95%, and Hardy–Weinberg equilibrium ($P < 1 \times 10^{-6}$). Genotypes were imputed using 1000 Genomes, HRC v1.1 and the TopMed r2 reference panel.[30] Ancestry was inferred using the first two principal components, by projecting principal components on 1000 Genomes data using *smartpca* from EigenSoft 7.2.1.[31] Samples within six standard deviations of the principal components of each ancestry in 1000 Genomes were assigned as the same ancestry. The latest publicly available genome-wide association study results for mental disorders and sleep, circadian, metabolic and inflammatory traits were used as weights in the calculation of each PGS (Supplementary Table 2). Where applicable, leave-one-out summary statistics were used for genome-wide association studies that included AGDS participants to avoid overestimation. SBayesRC was used to generate allele weights for each PGS.[32] The posterior SNP effects for each disorder and/or trait were used to generate PGS for each participant using the PLINK score function.[28] Each PGS was standardised with the sample. Effect sizes were interpretable per standard deviation unit increase in the AGDS PGS.

Statistical analyses

Analyses were conducted in RStudio (version 2024.9.1.394 for Windows; Posit Team, Boston, Massachusetts, USA; http://www.posit.co/) (R version 4.3.0). Demographic and clinical characteristics of circadian versus non-circadian depressive profiles were compared using Welch's *t*-test for age, analysis of covariance (adjusting for age and sex) for continuous variables and Pearson's chi-squared (χ^2) test for categorical variables. Clinical significance was assessed

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

using Cohen's d for Welch's t-test, partial eta-squared (η^2p) for analysis of covariance and Cramér's V for chi-squared test.

Logistic regression was used to estimate (a) associations between 28 PGS (mental health, physical health, and circadian and sleep-related PGS) and the circadian subtype, adjusting for age, sex and the first four genetically inferred ancestry principal components; and (b) associations between antidepressant efficacy and side-effects and the circadian subtype, adjusting for age and sex. To control for multiple testing, Bonferroni correction was applied at the following threshold and significance level: $P = 0.05/28 = 0.00179$, accounting for seven mental health PGS, 16 physical health PGS, and five sleep and circadian-related PGS. For antidepressant efficacy, the Bonferroni threshold was 0.0125 ($P < 0.05/4$), and for side-effects, the Bonferroni threshold was 0.002 ($P < 0.05/25$).

The following sensitivity analyses are reported in the Supplementary Material: (a) primary analyses controlling for weight gain during depressive episodes to explore clinical overlap with the atypical depression subtype,[33] which is also partially defined by hypersomnia (Supplementary Table 4); (b) analyses controlling for employment status to account for the potential influence of psychosocial circumstances (Supplementary Table 9); (c) analyses of associations between each binary circadian criteria and PGS and antidepressant efficacy (Supplementary Figs. 6–9); and (d) primary analyses restricted to participants meeting MDD criteria (Supplementary Tables 10 and 11).

Results

Distribution of circadian criteria

Of 11 380 participants with non-missing data for ≥3 circadian criteria, a subset of 2604 participants (80% female; mean age 37.87 ± 13.62 years) were classified as having a circadian subtype. Hypersomnia was the most frequently endorsed criterion among participants with the circadian subtype ($n = 2182$; 84%), followed by morning tiredness ($n = 2143$; 83%), evening chronotype ($n = 1774$; 68%), delayed sleep midpoint ($n = 1099$; 42%) and seasonality ($n = 1071$; 41%). The least commonly endorsed criterion was social jetlag ($n = 914$; 35%). The most common combinations of these criteria involved hypersomnia, morning tiredness and evening chronotype ($n = 481$; 18%). The distributions of these criteria are shown in Fig. 1. The numbers of criteria met in the whole sample are reported in Supplementary Fig. 2.

Demographics and clinical characteristics of participants with the circadian subtype

As shown in Table 2, compared with those with the non-circadian subtype of depression ($n = 8{,}776$), participants with the circadian subtype were younger (37.87 ± 13.62 *v.* 45.56 ± 15.30 years; $P < 0.001$) and more often female (80 *v.* 73%, $P < 0.001$). Additionally, participants with the circadian subtype reported an earlier age at onset of depression (18.68 ± 8.40 *v.* 23.20 ± 11.84 years, $P < 0.001$), and greater severity of (hypo)manic-like experiences (2.99 ± 2.06 *v.* 2.46 ± 2.08, $P < 0.001$), psychotic-like experiences (1.18 ± 1.54 *v.* 0.78 ± 1.26, $P < 0.001$), suicidal ideation (8.18 ± 10.65 *v.* 4.96 ± 8.68, $P < 0.001$), psychological distress (5.40 ± 3.72 *v.* 3.56 ± 3.57, $P < 0.001$) and somatic distress (6.33 ± 3.43 *v.* 4.10 ± 3.34, $P < 0.001$). The largest effect sizes were observed for age (Cohen's $d = 0.531$) and age at onset (Cohen's $d = 0.440$). Twelve per cent of those with the circadian subtype self-reported having received a diagnosis of BD, compared with 9% in the non-circadian group (the full list of self-reported diagnoses is summarised in Supplementary Table 8).

Genetic profile of individuals with the circadian subtype

PGS for mental disorders

As shown in Fig. 2a and Supplementary Table 3, the circadian subtype was associated with higher genetic risk (PGS) for attention-deficit hyperactivity disorder (ADHD) (odds ratio 1.11, 95% CI [1.06, 1.17]; Bonferroni-corrected P-value (P_{Bonf}) < 0.001), major depression (odds ratio 1.11, 95% CI [1.06, 1.16]; $P_{Bonf} < 0.001$), anxiety (odds ratio 1.10, 95% CI [1.04, 1.15]; $P_{Bonf} < 0.001$) and BD (odds ratio 1.09, 95% CI [1.04, 1.14]; $P_{Bonf} = 0.005$). The circadian subtype was also associated with higher schizophrenia PGS (odds ratio 1.07, 95% CI [1.02, 1.13]; $P = 0.006$; $P_{Bonf} = 0.162$); however, this association did not survive Bonferroni correction. Neither neuroticism PGS (odds ratio 0.98, 95% CI [0.93, 1.03]; $P = 0.419$; $P_{Bonf} = 1.000$) nor the autism PGS (odds ratio 1.04, 95% CI [0.99, 1.09]; $P = 0.105$; $P_{Bonf} = 1.000$) was associated with the circadian subtype.

PGS for physical health

As shown in Fig. 2b–d and Supplementary Table 3, the circadian subtype was associated with higher PGS for BMI (odds ratio 1.09, 95% CI [1.05, 1.14]; $p_{Bonf} = 0.003$), triglycerides (odds ratio 1.10, 95% CI [1.06, 1.16]; $P_{Bonf} < 0.001$), interleukin-6 (IL-6) (odds ratio 1.08, 95% CI [1.03, 1.13]; $P_{Bonf} = 0.038$) and insulin resistance (odds ratio 1.08, 95% CI [1.04, 1.13]; $P_{Bonf} = 0.011$). The circadian subtype was associated with lower PGS for high-density lipoprotein (odds ratio 0.93, 95% CI [0.89, 0.98]; $P = 0.003$; $p_{Bonf} = 0.078$) and higher PGS for migraine (odds ratio 1.07, 95% CI [1.03, 1.12]; $P = 0.002$; $P_{Bonf} = 0.054$), C-reactive protein (odds ratio 1.06, 95% CI [1.02, 1.11]; $P = 0.008$; $P_{Bonf} = 0.209$), type 2 diabetes (odds ratio 1.07, 95% CI [1.02, 1.13]; $P = 0.006$; $P_{Bonf} = 0.158$), coronary artery disease (odds ratio 1.05, 95% CI [1.00, 1.10]; $P = 0.048$; $P_{Bonf} = 1.000$) and fasting insulin (odds ratio 1.05, 95% CI [1.01, 1.11]; $P = 0.023$; $P_{Bonf} = 0.617$); however, these associations did not survive Bonferroni correction. The PGS for IL-10, IL-1β, IL-12, fasting glucose, tumour necrosis factor alpha and glycated haemoglobin (HbA1c) were not associated with the circadian subtype (all $P > 0.159$; $P_{Bonf} = 1.000$).

PGS for sleep and circadian traits

As shown in Fig. 2e and Supplementary Table 3, the circadian subtype was associated with lower PGS for chronotype (i.e. higher liability for eveningness) (odds ratio 0.68, 95% CI [0.65, 0.71]; $P_{Bonf} < 0.001$) and higher PGS for insomnia (odds ratio 1.08, 95% CI [1.03, 1.13]; $P_{Bonf} = 0.043$) and sleep midpoint (i.e. higher liability for later sleep midpoint) (odds ratio 1.15, 95% CI [1.10, 1.21]; $P_{Bonf} < 0.001$). The circadian subtype was associated with higher PGS for low relative amplitude (i.e. higher liability for weaker behavioural rest–activity amplitude) (odds ratio 1.06, 95% CI [1.02, 1.11]; $P = 0.008$; $P_{Bonf} = 0.225$) and lower sleep duration (odds ratio 0.95, 95% CI [0.91, 0.99]; $P = 0.029$; $P_{Bonf} = 1.783$); however, these associations did not survive Bonferroni correction.

Treatment response outcomes

Finally, as shown in Fig. 2f and Supplementary Table 3, the circadian subtype was associated with lower efficacy of SSRIs (odds ratio 0.88, 95% CI [0.82, 0.94]; $P_{Bonf} < 0.001$) and SNRIs (odds ratio 0.89, 95% CI [0.83, 0.97]; $P_{Bonf} = 0.023$) but not with efficacy of mirtazapine (odds ratio 0.96, 95% CI [0.82, 1.12]; $P = 0.608$; $P_{Bonf} = 1.000$) or amitriptyline (odds ratio 0.97, 95% CI [0.81, 1.16]; $P = 0.722$; $P_{Bonf} = 1.000$). Within-class comparisons of antidepressant efficacy are reported in the Supplementary Materials. The circadian subtype was associated with a broad profile of

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

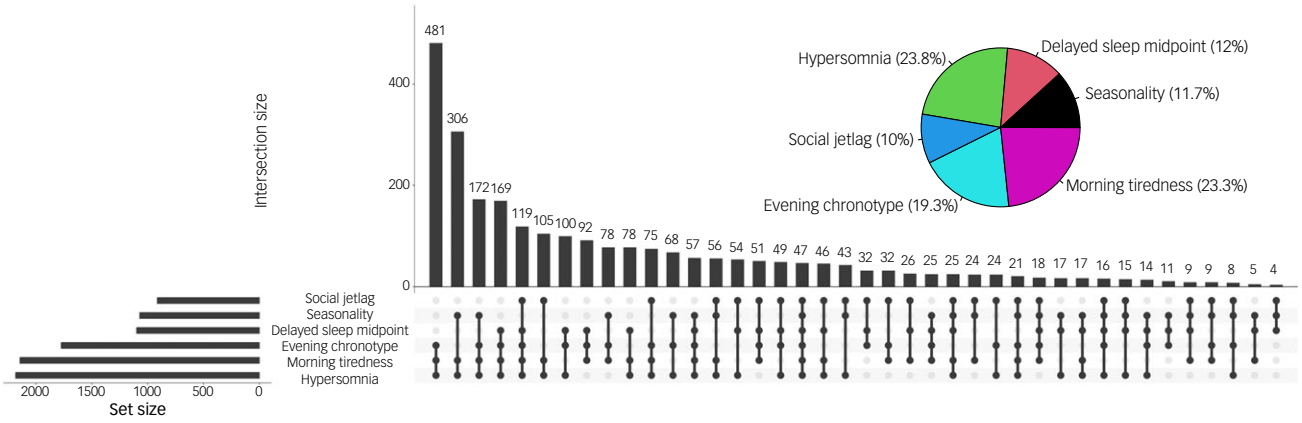


Fig. 1 Distribution of circadian criteria among participants with the circadian subtype of depression ($N = 2604$). UpSet plot of intersection between circadian criteria. Each row represents one circadian criterion, and each column indicates a specific combination of criteria. Filled dots denote which criteria were included in each intersection. The bar height above each column shows the number of participants meeting that combination of criteria. The pie chart illustrates the relative proportion of each circadian criterion.

self-reported antidepressant side-effects, including runny nose, muscle pain, blurred vision, constipation, drowsiness, diarrhoea, fatigue, difficulty sleeping, sweating, agitation, attempted suicide, shaking, dry mouth, headache, weight gain, suicidal thoughts, anxiety, reduced sexual desire, dizziness and nausea. No significant association was found with self-reported 'rash', 'other side-effects', 'no side-effects' or 'weight loss' (Supplementary Fig. 3 and Supplementary Table 5).

Discussion

In a large genetically informative cohort of adults with severe recurrent forms of depressive disorders, 23% of participants were classified as having a 'circadian subtype' of depression. These participants were younger, more commonly female, had an earlier age at onset, and reported a more severe clinical profile in terms of number of depressive episodes and severity of symptom dimensions. The circadian subtype was associated with lower reported efficacy of SSRIs and SNRIs and more side-effects, suggestive of its clinical utility. As greater depression severity is typically considered to be a predictor of enhanced response to antidepressant medications,[2,3] our finding of the opposite may be of clinical significance and supportive of the hypothesis of this circadian subtype being underpinned by a unique pathophysiological mechanism, in contrast to other forms of severe or persistent depressive disorder. Genetically, circadian cases had higher genetic risk for some neurodevelopmental conditions (ADHD) and mood disorders (major depression, anxiety and BD); sleep–wake cycle phenotypes including delayed sleep midpoint, insomnia and evening preference; and metabolic (insulin resistance, BMI, triglycerides) and inflammatory (IL-6) markers. These clinical, treatment response and genetic findings support the notion that a circadian subtype represents a distinct and clinically relevant profile of depressive disorders.

The increased genetic risk for ADHD, major depression and BD in circadian cases warrants further exploration. Delayed phase of circadian markers, such as dim-light melatonin onset, sleep–wake timing and evening chronotype are common in individuals with ADHD.[34] Specific circadian SNPs have been linked to ADHD symptoms,[35] and genetic risk of dysregulation of melatonin seems to be correlated with ADHD.[36] In addition, another study conducted in the AGDS cohort observed an association between the ADHD PGS and increased likelihood of having an earlier age at onset, greater recurrence of depressive episodes and atypical depression.[37] Circadian disruption is also a hallmark of BD,[38] often preceding the onset of episodes,[17] and has been potentially implicated in the switch between depressive and manic states.[39] Shared genetic pathways further support circadian involvement in BD, with dysregulated clock genes in BD[40] and BD PGS predicting later timing of circadian activity peaks.[13] In addition to higher PGS for BD, we observed greater enrichment for self-reported lifetime diagnoses of BD in the circadian cases but noted that ~700 cases of BD were assigned as non-circadian cases.

The circadian subtype was also associated with genetic risk for metabolic and inflammatory markers. This was consistent with evidence linking circadian disruption to metabolic dysregulation and chronic inflammation[41]; for example, adolescents with delayed sleep–wake cycles exhibit metabolic abnormalities,[42] and insulin resistance has been linked to abnormal melatonin sleep timing.[43] Circadian disruption may contribute to cardiometabolic dysfunction,[44] with genetic vulnerability in metabolic and inflammatory pathways worsening outcomes and potentially leading to treatment resistance. The circadian subtype was also associated with higher PGS for later sleep midpoint, insomnia and evening chronotype; these findings provide suggestive evidence that the circadian subtype captures a biologically meaningful subset, as opposed to these features being epiphenomena. Clinically, individuals in circadian cases reported lower SSRI and SNRI efficacy and more side-effects, consistent with evidence that circadian misalignment may respond less favourably to standard pharmacotherapies[15] or the notion that conventional antidepressants do not adequately correct sleep–wake/circadian disturbance.

Other proposed subtypes of depression, such as atypical depression, immunometabolic depression and bipolar depression, share some features with the circadian subtype of depression. Notably, atypical depression, which is defined by mood reactivity, weight gain, somatic symptoms and hypersomnia and was initially linked to preferential response to monoamine oxidase inhibitors,[45] also shows poorer response to SSRIs and SNRIs and includes sleep-related features (i.e. hypersomnia) in its definition. However, its strong reliance on weight gain during episodes or longitudinally as a criterion is likely to conflate heterogeneous and potentially unrelated factors, including anxiety and neuroticism, alongside circadian characteristics. We note that although our circadian subtype was enriched for cases that also met criteria for atypical depression, ~1400 cases with atypical depression were assigned to

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

Table 2 Demographic and clinical characteristics of the analytic sample

Characteristics	Total sample $N = 11\,380$	Circadian subtype $n = 2604$ (23%)	Non-circadian subtype $n = 8776$ (77%)	*P*-value	Effect size[a]
Age	43.80 (15.28)	37.87 (13.62)	45.56 (15.30)	<0.001	0.531
Sex, *n* (%)				<0.001	0.068
Female	8509 (75)	2090 (80)	6419 (73)		
Male	2861 (25)	513 (20)	2348 (27)		
Information not provided	10 (<1)	1 (<1)	9 (<1)		
BMI	28.49 (7.28)	29.66 (8.06)	28.15 (6.99)	<0.001	0.201
Working regular hours, 'Yes', *n* (%)	6708 (59)	1427 (55)	5281 (60)	<0.001	0.048
Number of working days per week	3.61 (2.26)	3.5 (2.2)	3.65 (2.27)	0.004	0.001
Marital status, *n* (%)				<0.001	0.184
Married or *de facto*	6183 (54)	1102 (42)	5081 (58)		
Separated or divorced	1676 (15)	373 (14)	1303 (15)		
Widowed	192 (2)	25 (1)	167 (2)		
Never married	3311 (29)	1102 (42)	2209 (25)		
Information not provided	18 (<1)	2 (<1)	16 (<1)		
Highest level of education, *n* (%)				<0.001	0.062
Degree	4047 (36)	1,014 (40)	3033 (35)		
Postgraduate	3194 (28)	602 (23)	2592 (29)		
Certificate or diploma	2637 (23)	638 (24)	1999 (23)		
Senior high school (year 11–12)	870 (8)	226 (9)	644 (7)		
Junior high school or less (year 1–10)	623 (5)	122 (4)	501 (6)		
No formal education	4 (<1)	1 (<1)	3 (<1)		
Information not provided	5 (<1)	1 (<1)	4 (<1)		
Meeting MDD criteria					
'Yes', *n* (%)	10 043 (88)	2513 (97)	7530 (86)	<0.001	
'No', *n* (%)	414 (4)	21 (<1)	393 (4)		
Information not provided	923 (8)	70 (3)	853 (10)		
Weight gain during episode, 'Yes', *n* (%)	3815 (36)	1,061 (41)	2754 (31)	<0.001	0.058
Depressive episodes, *n* (%)				<0.001	0.130
1–2 episodes	1275 (11)	182 (7)	1093 (12)		
3–4 episodes	2301 (20)	445 (17)	1856 (21)		
5–6 episodes	1655 (15)	400 (15)	1255 (14)		
7–9 episodes	579 (5)	159 (6)	420 (5)		
10 or more episodes	4529 (40)	1354 (52)	3175 (36)		
Information not provided	1041 (9)	64 (2)	977 (11)		
Duration of worst episode, *n* (%)				0.330	0.018
2 weeks	477 (5)	114 (5)	363 (5)		
2–4 weeks	1597 (16)	421 (17)	1176 (16)		
1–3 months	3611 (36)	871 (35)	2740 (36)		
3–6 months	1814 (18)	429 (17)	1385 (18)		
6–12 months	1379 (14)	332 (13)	1047 (14)		
1–2 years	589 (6)	152 (6)	437 (6)		
More than 2 years	600 (6)	163 (7)	437 (6)		
Age at onset	22.09 (11.26)	18.68 (8.40)	23.20 (11.84)	<0.001	0.440
Mania (ASRM)[b]	2.58 (2.09)	2.99 (2.06)	2.46 (2.08)	<0.001	0.011
Psychosis (CAPE)[b]	0.87 (1.34)	1.18 (1.54)	0.78 (1.26)	<0.001	0.016
Suicidality (SIDAS)[b]	5.69 (9.27)	8.18 (10.65)	4.96 (8.68)	<0.001	0.022
Psychological distress (SPHERE)[b]	3.40 (3.69)	5.40 (3.72)	3.56 (3.57)	<0.001	0.046
Somatic complaints (SPHERE)[b]	4.61 (3.49)	6.33 (3.43)	4.10 (3.34)	<0.001	0.073
Atypical depression, 'Yes', *n* (%)	2344 (21)	940 (36)	1404 (16)	<0.001	0.195
Bipolar disorder[c], 'Yes', *n* (%)	1006 (9)	309 (12)	697 (8)	<0.001	0.057
Medication use, taking, *n* (%)					
SSRI	9333 (82)	2251 (86)	7082 (81)	<0.001	0.062
SNRI	5536 (49)	1421(55)	4115 (47)	<0.001	0.064
Mirtazapine	1739 (15)	404 (16)	1335 (15)	0.729	0.000
Amitriptyline	1447 (13)	369 (14)	1078 (12)	0.012	0.022
Lithium	764 (7)	193 (7)	571 (7)	0.115	0.012

BMI, body mass index; MDD, major depressive disorder; ASRM, Altman Self-Rating Mania Scale; CAPE, Community Assessment of Psychic Experiences; SIDAS, Suicidal Ideation Attributes Scale; SPHERE, Somatic and Psychological Health Report; SSRI, Selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor.
All characteristics are presented as mean (s.d.), unless otherwise specified.
a. Effect sizes were calculated using Cohen's *d* for age and age of onset, partial eta-squared (η^2p) for continuous measures and Cramér's *V* for categorical measures.
b. Comparisons of clinical scores were corrected for the effect of age and sex.
c. Participants self-reported receiving a diagnosis of bipolar disorder.

the non-circadian subtype group (Table 1). This indicates that these phenotypes are partly overlapping but separable constructs. In another AGDS study,[34] we showed that when the definition of atypical depression was restricted to reliably reported features (i.e. weight gain and hypersomnia), important differences emerged compared with the circadian subtype, notably higher PGS for neuroticism (the full comparison is reported in Supplementary Table 6). By contrast, our circadian phenotype was defined specifically by 24-h sleep–wake and circadian-related markers, arguably providing stronger specificity to circadian disturbance as an underlying pathophysiology. Similarly, immunometabolic depression is characterised by a cluster of energy-related depressive symptoms and related biomarkers, including systemic low-grade inflammation and metabolic abnormalities.[46] Immunometabolic

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

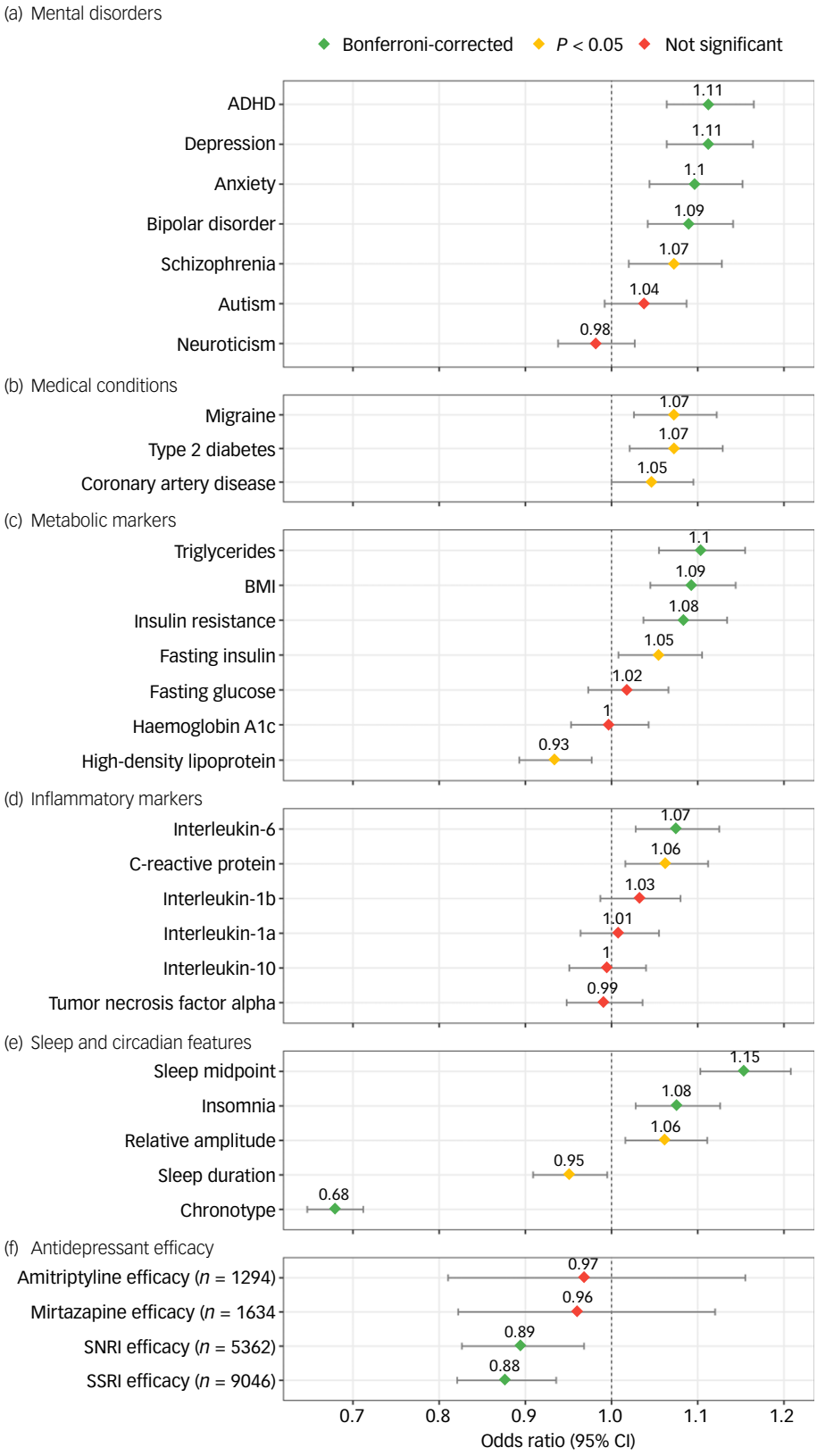


Fig. 2 Associations between the circadian subtype and (a) polygenic risk scores (PGS) for mental disorders; (b) PGS for medical conditions; (c) PGS for metabolic markers; (d) PGS for inflammatory-related markers); (e) PGS for sleep and circadian-related measures; and (f) treatment response ($n = 2604$ [23%] for circadian cases; $n = 8776$ [77%] for non-circadian cases). Results shown are from separate logistic regression models for each variable for the circadian subtype, with covariates of age and sex for all models, and also the first four genetically inferred ancestry principal components for PGS models. Significance levels are indicated as follows: green, Bonferroni-corrected (at alpha level $P < 0.0019$ [0.05/28] for seven mental disorder PGS, 16 physical health PGS, and five sleep and circadian-related measures PGS; and at alpha level $P < 0.0125$ [0.05/4] for treatment response); yellow, uncorrected ($P < 0.05$); red, not significant. Error bars represent 95% confidence intervals. ADHD, attention-deficit hyperactivity disorder; BMI, body mass index; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

depression is also characterised by a poor response to standard psychopharmacology, and evidence suggests that interventions targeting inflammation, metabolism or lifestyle factors may prove more effective.[47] However, immunometabolic depression may result from a range of different and confounding factors, including age, chronicity of illness, weight gain, medication exposure and other comorbidities.[48] Thus, at this stage of research, immunometabolic depression has limited utility with respect to early identification of and intervention in emerging depressive disorders.

Circadian disruptions have also been reported in bipolar depression,[49] alongside mixed efficacy of SSRIs and SNRIs[50] and probable metabolic–inflammatory factors.[51] However, around half of BD cases initially present with depressive episodes that are difficult to distinguish from unipolar depression, with (hypo)manic episodes often emerging after several depressive episodes.[52] This renders early identification of bipolar depression challenging.[53] Other common subtypes of depression include treatment-resistant depression, with limited utility to guide preferential first treatment priority by definition, and melancholic depression, which can be regarded as a marker of severe or difficult-to treat MDD conditions.[54] Overall, distinctions between depressive phenotypes are key to informing different treatments approaches, notably first-line interventions. Compared with other depressive subtypes, our proposed circadian subtype demonstrates clear genetic, clinical and treatment (self-rated) correlates, which support formal evaluation of a stratification approach based on circadian factors to guide early intervention strategies. In addition, circadian disturbances have been associated with transition to more severe clinical stages, suggesting predictive value for illness progression in early intervention.[55]

Overall, we argue that our proposed circadian subtype of depression is a transdiagnostic phenotype that encompasses a subset of individuals currently classified as having other depressive, bipolar or somatic disorders, in which circadian disturbances may be the primary pathophysiological mechanism. From a clinical perspective, defining a circadian subtype of depression may support more personalised care options. Specifically, we propose that individuals with the circadian subtype may benefit preferentially from chronotherapies, that is, behavioural or pharmacological treatments that explicitly target the circadian system.[56] There is growing evidence that daytime light exposure, reduced night-time light, regular sleep–wake timing, or melatonin or melatonergic-targeted agonists may benefit individuals with depression and circadian disturbances.[57]

Limitations and future work

Several limitations need to be acknowledged. First, the data were collected through a self-report survey; although this approach allowed richer access to the lived experience of depression, it may have been subject to biases (e.g. recall bias). For example, a subset of cases did not meet self-rated criteria for MDD and comprised a less clinically severe group; whereas sensitivity analyses excluding these cases attenuated three genetic and one treatment outcome finding (no longer being significant under Bonferroni correction), the pattern of results was otherwise unchanged. Second, the data presented were cross-sectional, rendering causal inferences challenging. Third, although the ten most commonly reported antidepressants were recorded, their classification in broader categories may have masked important sources of heterogeneity. Fourth, individuals in this sample were limited to those of genetically inferred European ancestry, which may limit generalisability. Fourth, although the self-reported nature of these circadian criteria represented an advantage for investigation in large-scale studies, the criteria did not directly capture internal physiological circadian markers (e.g. phase, amplitude, misalignment). Fifth, the circadian subtype was conceptualised as a trait-like vulnerability; accordingly, most criteria were assessed as habitual (trait-like) behaviours. Hypersomnia was the single exception, as it was assessed during the episode, and was selected as a criterion on the basis that circadian disruption may predispose individuals to episodic hypersomnia;[58] we therefore interpreted it as a state expression of the same underlying circadian vulnerability rather than a distinct construct. Overall, we expect the selected features to be largely traits, although they may also be exacerbated during a depressive episode. As traits, we expect that these features reflect (largely) an underlying neurobiological vulnerability, with some genetic determinants, and not simply non-specific perturbations that emerge during the depressive episode. Sixth, the provisional circadian criteria examined in this study were exploratory rather than definitive. Accordingly, all criteria were weighted equally, and no prespecified cut-offs were applied. Further work, including replication in other independent data-sets and exploration of weighted solutions, is needed to validate our criteria. The findings should therefore be interpreted as an initial exploration. Seven, although 'morning tiredness' was used as a label for one of our criteria, in the future, a construct more closely resembling sleep inertia (and capturing people more likely to have woken in their biological night and thus have a problem with misalignment) would be of strong relevance to our proposed circadian subtype of depression.

Despite these limitations, this study strengthens the evidence base for a circadian subtype of depression as a biologically valid and clinically useful phenotype of depression associated with differential treatment response, clinical course characteristics and genetic profile. Future studies are needed to replicate our findings in diverse samples, to investigate whether the phenotype has predictive utility, and to explore whether the circadian subtype indeed preferentially captures cases with circadian disruption as a major pathophysiology.

Emiliana Tonini, Brain and Mind Centre, The University of Sydney, Australia; **Jacob J. Crouse**, Brain and Mind Centre, The University of Sydney, Australia; **Mirim Shin**, Brain and Mind Centre, The University of Sydney, Australia; **Joanne S. Carpenter**, Brain and Mind Centre, The University of Sydney, Australia; **Brittany L. Mitchell**, QIMR Berghofer Medical Research Institute, Australia; School of Biomedical Sciences, The University of Queensland, Australia; and School of Biomedical Sciences, Queensland University of Technology, Australia; **Enda M. Byrne**, Child Health Research Centre, The University of Queensland, Australia; **Penelope A. Lind**, QIMR Berghofer Medical Research Institute, Australia; School of Biomedical Sciences, The University of Queensland, Australia; and School of Biomedical Sciences, Queensland University of Technology, Australia; **Scott D. Gordon**, QIMR Berghofer Medical Research Institute, Australia; **Richard Parker**, QIMR Berghofer Medical Research Institute, Australia; **Samuel J. Hockey**, Brain and Mind Centre, The University of Sydney, Australia; and Lived Experience Working Group, Youth Mental Health & Technology Team, Brain and Mind Centre, The University of Sydney, Australia; **Timothy To**, Lived Experience Working Group, Youth Mental Health & Technology Team, Brain and Mind Centre, The University of Sydney, Australia; **Andrew Shim**, Lived Experience Working Group, Youth Mental Health & Technology Team, Brain and Mind Centre, The University of Sydney, Australia; **Alex Hill**, Lived Experience Working Group, Youth Mental Health & Technology Team, Brain and Mind Centre, The University of Sydney, Australia; **Anna Treneman**, Lived Experience Working Group, Youth Mental Health & Technology Team, Brain and Mind Centre, The University of Sydney, Australia; **Elizabeth Scott**, Brain and Mind Centre, The University of Sydney, Australia; **Jan Scott**, Academic Psychiatry, Institute of Neuroscience, Newcastle University, UK; **Kathleen R. Merikangas**, Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland, USA; **Naomi R. Wray**, Institute for Molecular Bioscience, The University of Queensland, Australia; Department of Psychiatry, University of Oxford, UK; and Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, UK; **Nicholas G. Martin**, QIMR Berghofer Medical Research Institute, Australia; **Sarah E. Medland**, QIMR Berghofer Medical Research Institute, Australia; School of Psychology, The University of Queensland, Australia; and School of Psychology and Counselling, Queensland University of Technology, Australia; **Ian B. Hickie**, Brain and Mind Centre, The University of Sydney, Australia

Correspondence: Emiliana Tonini. Email: emiliana.tonini@sydney.edu.au

First received 4 Mar 2026 UTC, final revision 31 Jul 2026 UTC, accepted 12 Aug 2026 UTC

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

Supplementary material

The supplementary material is available online at https://doi.org/10.1192/bjp.2026.10798

Acknowledgements

We thank all the AGDS participants for giving their time to contribute to this study. We also thank all the people who helped with conception, implementation, beta testing, the media campaign and data cleaning, as well as the research participants and employees of the 23andMe Research Institute for making this work possible. Artificial Intelligence use: No artificial intelligence tools have been used in the research or writing process for this manuscript.

Data availability

The data that support the findings of this study are available on request from the corresponding author, E.T. The data are not publicly available owing to their containing information that could compromise the privacy of research participants. The analytic code used in this study is available upon request from the corresponding author.

Author contributions

E.T., J.J.C., M.S., J.S.C. and I.B.H. conceptualised the study and formulated the research questions. E.T. formally analysed the data, generated visualisations, and drafted the first and subsequent versions of the manuscript. E.M.B., S.E.M., R.P., N.R.W., I.B.H. and N.G.M. designed the AGDS study. S.J.H., T.T., A.S., A.H. and A.T. provided lived experience expertise. B.L.M. generated the PGS. E.T., J.J.C., M.S., J.S.C., B.L.M., E.M.B., P.A.L., S.D.G., R.P., S.J.H., T.T., A.S., A.H., A.T., E.S., J.S., K.R.M., N.R.W., N.G.M., S.E.M. and I.B.H. critically reviewed the first version of the manuscript and provided approval for the final version.

Funding

The AGDS was primarily funded by grant 1086683 from the National Medical Health and Research Council (NHMRC) of Australia. This work was further supported by philanthropic donations from families who are affected by mental illness (who would like to be left anonymous) awarded to M.S.; NHMRC EL1 Investigator Grants awarded to J.J.C. and B.L.M. (GNT2008196 and GNT2017176, respectively); a Wellcome Trust Mental Health Award (227089/Z/23/Z); NHMRC L1 and L2 Investigator Grants (APP117291, APP2025674) awarded to S.E.M.; and an NHMRC L3 Investigator Grant (GNT2016346) awarded to I.B.H.

Declaration of interest

I.B.H. is the Co-Director of Health and Policy at the Brain and Mind Centre, University of Sydney, Australia. The Brain and Mind Centre operates early intervention youth services at Camperdown under contract to headspace. I.B.H has also previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca, Janssen Cilag) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to and a 3.2% equity shareholder in InnoWell Pty Ltd., which aims to transform mental health services through use of innovative technologies.

References

1 Kessing LV, Bukh JD. The clinical relevance of qualitatively distinct subtypes of depression. *World Psychiatry* 2017; **16**: 318.

2 Malhi GS, Bell E, Bassett D, Boyce P, Bryant R, Hazell P, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Austr N Z J Psychiatry* 2021; **55**: 7–117.

3 National Institute for Health and Care Excellence. *Depression in Adults: Treatment and Management*. NICE, 2022.

4 Pigott HE, Kim T, Xu C, Kirsch I, Amsterdam J. What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR*D study's patient-level data with fidelity to the original research protocol. *BMJ Open* 2023; **13**: e063095.

5 Smith DJ, McGlashan E, Gottlieb J, Meyer N, Jones MW. Chronopsychiatry. *Br J Psychiatry* 2024; **225**: 526–8.

6 Carpenter JS, Crouse JJ, Scott EM, Naismith SL, Wilson C, Scott J, et al. Circadian depression: a mood disorder phenotype. *Neurosci Biobehav Rev* 2021; **126**: 79–101.

7 Wescott DL, Hasler BP, Foust JE, Roecklein KA. Circadian realignment and depressed mood: a systematic review. *Sleep Med Rev* 2025; **79**: 102022.

8 Godin O, Henry C, Leboyer M, Azorin J-M, Aubin V, Bellivier F, et al. Sleep quality, chronotype and metabolic syndrome components in bipolar disorders during the remission period: results from the FACE-BD cohort. *Chronobiol Int* 2017; **34**: 1114–24.

9 Arns M, Kooij JJS, Coogan AN. Review: identification and management of circadian rhythm sleep disorders as a transdiagnostic feature in child and adolescent psychiatry. *J Am Acad Child Adolesc Psychiatry* 2021; **60**: 1085–95.

10 Shin M, Carpenter JS, Park SH, Janiszewski C, Tonini E, McKenna S, et al. Twenty-four-hour skin temperature rhythms in young people with emerging mood disorders: relationships with illness subtypes and clinical stage. *J Biol Rhythms* 2025; **40**: 262–74.

11 Carpenter JS, Crouse JJ, Park SH, Shin M, Tonini E, Guo W, et al. Actigraphy-derived circadian rhythms, sleep-wake patterns, and physical activity across clinical stages and pathophysiological subgroups in young people presenting for mental health care. *J Psychiatr Res* 2025; **186**: 396–406.

12 Gehrman PR, Ghorai A, Goodman M, McCluskey R, Barilla H, Almasy L, et al. Twin-based heritability of actimetry traits. *Genes Brain Behav* 2019; **18**: e12569.

13 Hennion V, Scott J, Martinot V, Godin O, Marie-Claire C, Bellivier F, et al. Polygenic risk scores for mood disorders and actigraphy estimates of sleep and circadian rhythms: a preliminary study in bipolar disorders. *J Sleep Res* 2025; **34**: e14307.

14 Etain B, Milhiet V, Bellivier F, Leboyer M. Genetics of circadian rhythms and mood spectrum disorders. *Eur Neuropsychopharmacol* 2011; **21**: S676–82.

15 Crouse JJ, Park SH, Byrne EM, Mitchell BL, Chan K, Scott J, et al. Evening chronotypes with depression report poorer outcomes of selective serotonin reuptake inhibitors: a survey-based study of self-ratings. *Biol Psychiatry* 2024; **96**: 4–14.

16 Byrne EM, Kirk KM, Medland SE, McGrath JJ, Colodro-Conde L, Parker R, et al. Cohort profile: the Australian Genetics of Depression Study. *BMJ Open* 2020; **10**: e032580.

17 Geoffroy PA, Maruani J. Chronobiology of mood disorders: the role of the biological clock in depression and bipolar disorder. *Biol Psychiatry* 2025; **98**: 830–41.

18 Rosenthal NE. Seasonal pattern assessment questionnaire. *J Affect Disord* 1984; **41**: 72–80.

19 Kasper S, Wehr TA, Bartko JJ, Gaist PA, Rosenthal NE. Epidemiological findings of seasonal changes in mood and behavior: a telephone survey of Montgomery County. *Maryland Arch Gen Psychiatry* 1989; **46**: 823–33.

20 Jones SE, van Hees VT, Mazzotti DR, Marques-Vidal P, Sabia S, van der Spek A, et al. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nat Commun* 2019; **10**: 1585.

21 Roenneberg T. How can social jetlag affect health? *Nat Rev Endocrinol* 2023; **19**: 383–4.

22 Daghlas I, Lane JM, Saxena R, Vetter C. Genetically proxied diurnal preference, sleep timing, and risk of major depressive disorder. *JAMA Psychiatry* 2021; **78**: 903–10.

23 Merikanto I, Lahti T, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, et al. Evening types are prone to depression. *Chronobiol Int* 2013; **30**: 719–25.

24 Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976; **4**: 97–110.

25 Landzberg D, Trotti LM. Is idiopathic hypersomnia a circadian rhythm disorder? *Curr Sleep Med Rep* 2019; **5**: 201–6.

26 Carpenter JS, Robillard R, Hermens DF, Naismith SL, Gordon C, Scott EM, et al. Sleep-wake profiles and circadian rhythms of core temperature and melatonin in young people with affective disorders. *J Psychiatr Res* 2017; **94**: 131–8.

27 Carpenter JS, Crouse JJ, Shin M, Tonini E, Hindmarsh G, de Haan Z, et al. Evidence for internal misalignment of circadian rhythms in youth with emerging mood disorders. *J Biol Rhythms* 2025; **40**: 424–40.

28 Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007; **81**: 559–75.

29 Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience* 2015; **4**: 7.

30 Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature* 2021; **590**: 290–9.

31 Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006; **38**: 904–9.

32 Zheng Z, Liu S, Sidorenko J, Wang Y, Lin T, Yengo L, et al. Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. *Nat Genet* 2024; **56**: 767–77.

33 Shin M, Crouse JJ, Lin T, Byrne EM, Mitchell BL, Lind PA, et al. Atypical depression is associated with a distinct clinical, neurobiological, treatment response, and polygenic risk profile. *Biol Psychiatry* 2026; **100**: 525–35.

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press

34 Coogan AN, McGowan NM. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Atten Defic Hyperact Disord* 2017; **9**: 129–47.

35 Korman M, Palm D, Uzoni A, Faltraco F, Tucha O, Thome J, et al. ADHD 24/7: circadian clock genes, chronotherapy and sleep/wake cycle insufficiencies in ADHD. *World J Biol Psychiatry* 2020; **21**: 156–71.

36 Takahashi N, Nishimura T, Okumura A, Harada T, Iwabuchi T, Rahman MS, et al. Association between genetic risk of melatonin secretion and attention deficit hyperactivity disorder. *Psychiatry Res Commun* 2024; **4**: 100188.

37 Mitchell BL, Campos AI, Whiteman DC, Olsen CM, Gordon SD, Walker AJ, et al. The Australian Genetics of Depression Study: new risk loci and dissecting heterogeneity between subtypes. *Biol Psychiatry* 2022; **92**: 227–35.

38 McCarthy MJ, Gottlieb JF, Gonzalez R, McClung CA, Alloy LB, Cain S, et al. 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 Disord* 2022; **24**: 232–63.

39 Hickie IB, Merikangas KR, Carpenter JS, Iorfino F, Scott EM, Scott J, et al. Does circadian dysrhythmia drive the switch into high- or low-activation states in bipolar I disorder? *Bipolar Disord* 2023; **25**: 191–9.

40 Yegin Z, Sarisoy G, Erguner Aral A, Koc H. For whom the circadian clock ticks? Investigation of PERIOD and CLOCK gene variants in bipolar disorder. *Chronobiol Int* 2021; **38**: 1109–19.

41 Zielinski MR, Gibbons AJ. Neuroinflammation, sleep, and circadian rhythms. *Front Cell Infect Microbiol* 2022; **12**: 853096.

42 Toyoura M, Miike T, Tajima S, Matsuzawa S, Konishi Y. Inadequate sleep as a contributor to impaired glucose tolerance: a cross-sectional study in children, adolescents, and young adults with circadian rhythm sleep-wake disorder. *Pediatr Diabetes* 2020; **21**: 557–64.

43 Kumar A, Chauhan R, Devi S. Biological connection of circadian rhythm and insulin resistance: a review. *Biol Rhythm Res* 2025; **56**: 524–40.

44 Ansu Baidoo V, Knutson KL. Associations between circadian disruption and cardiometabolic disease risk: a review. *Obesity* 2023; **31**: 615–24.

45 Henkel V, Mergl R, Allgaier A-K, Kohnen R, Möller H-J, Hegerl U. Treatment of depression with atypical features: a meta-analytic approach. *Psychiatry Res* 2006; **141**: 89–101.

46 Penninx BWJH, Lamers F, Jansen R, Berk M, Khandaker GM, De Picker L, et al. Immuno-metabolic depression: from concept to implementation. *Lancet Reg Health Eur* 2025; **48**: 101166.

47 Drevets WC, Wittenberg GM, Bullmore ET, Manji HK. Immune targets for therapeutic development in depression: towards precision medicine. *Nat Rev Drug Discov* 2022; **21**: 224–44.

48 Berk M, Köhler-Forsberg O, Turner M, Penninx BWJH, Wrobel A, Firth J, et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World Psychiatry* 2023; **22**: 366–87.

49 Tonon AC, Nexha A, Mendonça da Silva M, Gomes FA, Hidalgo MP, Frey BN. Sleep and circadian disruption in bipolar disorders: from psychopathology to digital phenotyping in clinical practice. *Psychiatry Clin Neurosci* 2024; **78**: 654–66.

50 Gitlin MJ. Antidepressants in bipolar depression: an enduring controversy. *Int J Bipolar Disord* 2018; **6**: 25.

51 McElroy SL, Keck PE. Metabolic syndrome in bipolar disorder: a review with a focus on bipolar depression. *J Clin Psychiatry* 2014; **75**: 11779.

52 O'Donovan C, Alda M. Depression preceding diagnosis of bipolar disorder. *Front Psychiatry* 2020; **11**: 500.

53 Rolin D, Whelan J, Montano CB. Is it depression or is it bipolar depression? *J Am Assoc Nurse Pract* 2020; **32**: 703–13.

54 Dold M, Bartova L, Fugger G, Kautzky A, Mitschek MMM, Fabbri C, et al. Melancholic features in major depression: a European multicenter study. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **110**: 110285.

55 Iorfino F, Scott EM, Carpenter JS, Cross SP, Hermens DF, Killedar M, et al. Clinical stage transitions in persons aged 12 to 25 years presenting to early intervention mental health services with anxiety, mood, and psychotic disorders. *JAMA Psychiatry* 2019; **76**: 1167–75.

56 Crouse JJ, Carpenter JS, Song YJC, Hockey SJ, Naismith SL, Grunstein RR, et al. Circadian rhythm sleep-wake disturbances and depression in young people: implications for prevention and early intervention. *Lancet Psychiatry* 2021; **8**: 813–23.

57 Kang S-G, Kim Y-K. Chronotherapy in the treatment of major depression. In *Understanding Depression: Contemporary Issues and Dilemmas* (ed. Y-K Kim): 415–28. Springer Nature Singapore, 2026.

58 Moderie C, Boivin DB. Pathophysiological models of hypersomnolence associated with depression. *Biol Psychiatry Glob Open Sci* 2025; **5**: 100445.

https://doi.org/10.1192/bjp.2026.10798 Published online by Cambridge University Press