PSILOGOS

Research Article

open-access

Temporal Coupling of Gut Microbial Function, Sleep Regularity, and Mood Instability in Bipolar Disorder: A Prospective Multimodal Cohort Study Protocol

Michael A. Strober

ABSTRACT

Bipolar disorder is marked by recurrent changes in mood, activity, sleep, and cognition, yet the biological events that precede short-term mood destabilisation remain insufficiently resolved. Cross-sectional microbiome studies have associated bipolar disorder with altered bacterial diversity and relative abundance, but they cannot distinguish stable inter-individual variation from biological changes that occur before worsening symptoms. This prospective cohort study will examine whether within-person variation in gut microbial functional capacity and circulating microbial-host metabolites tracks with disturbed sleep timing and subsequently with mood instability. Seventy-two adults with bipolar I or bipolar II disorder in clinical remission and 36 age- and sex-balanced community comparators will be followed for 24 weeks. Participants will complete daily mood and sleep records, wear a wrist actigraphy device continuously, and provide stool, fasting blood, and saliva at four visits. Stool will undergo shotgun metagenomic sequencing and targeted quantification of short-chain fatty acids and bile acids. Blood will be analysed for lipopolysaccharide-binding protein, soluble CD14, high-sensitivity C-reactive protein, interleukin-6, tumour necrosis factor-alpha, tryptophan, kynurenine, and cortisol. Medication exposure, dietary intake, tobacco use, body mass index, menstrual phase, and recent antimicrobial exposure will be recorded at every visit. The primary analysis will estimate whether departures from each participant's usual sleep midpoint, sleep regularity, and microbial functional profile precede a rise in the following week's composite mood-instability score. Repeated-measures mixed models, dynamic Bayesian networks, and prespecified negative-control analyses will separate temporal association from medication-related and seasonal influences. The study is designed to identify reproducible temporal signatures rather than a diagnostic microbial label. Its results will determine whether future interventional work should target microbial metabolism, circadian regularity, or their joint regulation in bipolar disorder.

Keywords: bipolar disorder; gut microbiome; actigraphy; circadian timing; shotgun metagenomics; kynurenine; prospective cohort

Department of Psychiatry and Biobehavioral Sciences, UCLA David Geffen School of Medicine, Los Angeles, CA, USA
mstrober@mednet.ucla.edu

– **Published:** 20 November 2024

1. INTRODUCTION

Bipolar disorder is a recurrent mood illness in which affective episodes are accompanied by changes in energy, sleep, cognition, appetite, psychomotor activity, and social functioning. Its episodic nature presents an important scientific problem: measurements obtained during a single outpatient visit may be associated with diagnosis without revealing which biological changes occur before an individual becomes less stable. This limitation is particularly acute for the intestinal microbiome. Diet, sleep, medicines, geography, body composition, tobacco exposure, and recent infection can alter microbial composition, while bipolar disorder itself is commonly treated with medicines that may affect metabolism and bacterial growth. A clinically useful biological signal must therefore be evaluated repeatedly within the same person and interpreted alongside exposure data collected on the same dates.

Interest in microbial contributions to mood regulation derives from several convergent observations. Intestinal bacteria transform dietary substrates into short-chain fatty acids, secondary bile acids, indoles, and other small molecules that influence epithelial integrity, immune cell activity, endocrine signalling, and neural function. Microbes also participate in tryptophan availability and can affect the balance of serotonergic and kynurenine-pathway metabolites. Stress-related neuroendocrine activity, in turn, modifies intestinal motility, barrier biology, and microbial ecological conditions. These bidirectional relations make it biologically plausible that gut microbial activity may vary across periods of sleep disruption and changing affect.

Reports in bipolar disorder have described lower alpha diversity in some cohorts, differences in several bacterial taxa, altered inflammatory mediators, and associations between gastrointestinal symptoms and depressive burden. Findings remain inconsistent because clinical state, pharmacotherapy, sample handling, sequencing regions, dietary assessment, and statistical adjustment differ substantially across studies. A recent comprehensive review summarised the putative links among intestinal permeability, immune activation, microbial metabolites, neuroendocrine signalling, and pharmacotherapy in bipolar disorder.[1] That synthesis also makes clear why a one-time faecal sample cannot answer a temporal question. A taxon that differs between groups may reflect a stable dietary habit or medicine exposure rather than a biological shift that precedes worsening mood.

Sleep timing is a promising bridge between these domains. Social rhythm disturbance and delayed or irregular sleep are well-established clinical correlates of bipolar relapse, while diurnal rhythms shape intestinal motility, feeding behaviour, host transcription, and bacterial abundance. Actigraphy provides continuous measurement of sleep timing and regularity in the home setting and avoids reliance on retrospective recall. Combining actigraphy with serial microbial functional profiling allows the present study to ask a narrow question: *within individuals with bipolar disorder, do departures from habitual sleep timing and microbial metabolic function precede short-term increases in mood instability?* The comparator group is included to distinguish disorder-related temporal coupling from ordinary variation across the calendar year.

The study has four objectives. First, it will quantify the stability and within-person variation of microbial genes and metabolites across 24 weeks. Second, it will determine whether altered sleep midpoint, reduced sleep regularity, or shortened sleep duration precedes changes in microbial functional pathways and circulating inflammatory or kynurenine measures. Third, it will estimate whether those biological changes are followed by a higher weekly mood-instability score. Fourth, it will test whether temporal associations are retained after adjustment for medicine changes, diet, body mass index, tobacco use, menstrual phase, antimicrobial exposure, and season. The central hypothesis is not that a universal bacterial signature identifies bipolar disorder. Rather, it is that a subset of participants will show time-linked changes in microbial metabolic capacity and sleep timing before increases in affective lability.

2. STUDY DESIGN AND SETTING

This is a 24-week prospective observational cohort study conducted through an outpatient mood-disorders service and affiliated community recruitment sites. Recruitment will continue until 72 adults with DSM-5 bipolar I or bipolar II disorder and 36 community comparators complete the entry visit. A 2:1 ratio is selected because the principal estimands concern temporal variation in bipolar disorder while comparators supply a reference distribution for seasonality, assay drift, and ordinary sleep variation. The design does not alter psychiatric treatment. Treating clinicians will retain full responsibility for medication decisions and clinical care.

Adults aged 18–55 years will be eligible for the bipolar group if a psychiatrist confirms bipolar I or bipolar II disorder using the Structured Clinical Interview for DSM-5 Disorders, the participant is not currently hospitalised, and the Young Mania Rating Scale score is below 12 at entry. Community comparators will have no lifetime bipolar or psychotic disorder and no first-degree relative with bipolar disorder. Exclusion criteria for both groups are inflammatory bowel disease, coeliac disease, major gastrointestinal surgery other than appendectomy or cholecystectomy, pregnancy, systemic immunosuppressive therapy, oral or intravenous antimicrobials within eight weeks, current substance intoxication or withdrawal, inability to provide informed consent, and regular night-shift employment. A documented medicine change during follow-up is not an exclusion; it is an exposure that the analysis will model explicitly.

Each participant will attend four visits: entry, week 4, week 12, and week 24. A stool sample will be collected at

home within 24 hours before each visit using a stabilising collection kit. Fasting blood and a morning saliva sample will be obtained between 08:00 and 10:00 at the visit. Participants will wear a triaxial wrist actigraphy device continuously from seven days before entry through week 24, removing it only for charging and water exposure. Daily electronic diaries will record mood, sleep timing, medication adherence, alcohol intake, gastrointestinal symptoms, and major life events. A brief food-frequency instrument and a three-day diet record will be completed before every biospecimen visit.

Figure 1. Participant collection materials.

The collection materials shown in Fig. 1 are provided at each scheduled visit so that stool sampling, saliva collection, sleep recording, and diary completion occur in a consistent home-to-clinic sequence. This arrangement reduces avoidable variation caused by different container types, delayed transport, or incomplete timing information. The image is illustrative of the study setting and does not depict a participant specimen or a measured result.

3. CLINICAL AND BEHAVIOURAL ASSESSMENT

Diagnosis will be confirmed at entry with the Structured Clinical Interview for DSM-5 Disorders. Mania and depression severity will be measured at each visit using the Young Mania Rating Scale and the Montgomery–Asberg Depression Rating Scale. Participants will complete the Altman Self-Rating Mania Scale and the Quick Inventory of Depressive Symptomatology–Self Report weekly. The Functional Assessment Short Test will be collected at entry and week 24. A trained assessor, blinded to laboratory data, will administer clinician-rated measures.

The primary clinical outcome is a weekly composite mood-instability score. For each participant, daily ratings of elevated mood, depressed mood, irritability, activation, and anxiety will be standardised relative to that participant’s mean across the observation period. The weekly score will combine the standard deviation and mean successive difference of those five daily ratings. This construction captures both dispersion and day-to-day movement without treating an individual participant’s stable symptom level as instability. Secondary outcomes are change in Montgomery–Asberg Depression Rating Scale score, change in Young Mania Rating Scale score, and a clinician-confirmed affective episode or urgent treatment contact.

Actigraphy files will be processed with prespecified rules. Sleep onset, sleep offset, midpoint, duration, wake after sleep onset, and interdaily stability will be calculated from 24-hour epochs. Participants will annotate bedtimes, wake times, travel across time zones, and device removal in the electronic diary. The sleep regularity index will quantify agreement in sleep or wake state between time points separated by 24 hours. A participant’s deviation from habitual sleep timing will be calculated as the difference between the current 7-day average sleep midpoint and the participant-specific mean midpoint from the preceding 28 days. This person-centred calculation is necessary because a late but consistent schedule is not biologically equivalent to an abrupt shift in an individual’s established schedule.

Figure 2. Serial specimen collection set.

The repeated biospecimen arrangement in Fig. 2 supports paired analysis of stool, blood, and saliva at all four visits. Pairing is important because a faecal observation becomes more interpretable when it is considered with peripheral inflammatory markers, tryptophan metabolites, cortisol, current diet, and sleep timing from the same period. The study will keep collection dates rather than collapsing them into an unspecified follow-up interval.

4. BIOSPECIMEN HANDLING AND LABORATORY ASSAYS

Participants will place stool into the supplied stabilising tube immediately after defecation and record collection time, Bristol Stool Form Scale category, antibiotic exposure, and menstrual phase where relevant. Samples will be transported in the supplied insulated pouch and stored at -80°C within 24 hours of arrival. A subset of 10% of samples will be collected in duplicate to quantify collection and extraction reproducibility. Blank collection tubes, extraction blanks, and a commercially available mock community will accompany each extraction batch.

Microbial DNA will be isolated using bead-beating and silica-column purification. DNA quantity and fragmentation will be checked before library preparation. Shotgun libraries will be sequenced to a minimum target of 12 million paired-end reads per sample. Human reads will be removed using a reference-based filtering workflow. Taxonomic profiles will be generated from clade-specific marker genes and functional abundance will be estimated from gene-family and metabolic-pathway profiles. The prespecified functional domains are butyrate synthesis, bile-acid transformation, tryptophan metabolism, gamma-aminobutyric acid-related gene modules, and lipopolysaccharide biosynthesis. Read depth, duplicate rate, host-read fraction, and control performance will determine whether a sample enters the primary analysis.

Targeted chemical assays will quantify acetate, propionate, butyrate, valerate, isobutyrate, isovalerate, primary bile acids, and secondary bile acids in stool. Plasma will be assayed for lipopolysaccharide-binding protein, soluble CD14, high-sensitivity C-reactive protein, interleukin-6, tumour necrosis factor-alpha, tryptophan, kynurenine, and the kynurenine-to-tryptophan ratio. Morning saliva cortisol will be measured by enzyme immunoassay. Batch allocation will be balanced by diagnostic group, sex, visit, and calendar month. Laboratory personnel will be masked to clinical ratings.

Figure 3. Metagenomic and metabolite laboratory setting.

The laboratory scene in Fig. 3 represents the two complementary measurement families used here: microbial gene content and targeted low-molecular-weight chemistry. Sequencing alone cannot establish whether a putative metabolic pathway is accompanied by a detectable stool metabolite, whereas chemical assays alone cannot identify the distribution of genes that may contribute to its production. Their joint acquisition is intended to strengthen biological interpretation without implying a direct causal pathway.

Table 1 places intensive daily phenotyping alongside four biologically dense visits. The separation between continuous behavioural measurement and quarterly molecular sampling recognises that the intended temporal question requires frequent observation of sleep and mood while preserving feasible clinic attendance. A medicine modification or short illness occurring between visits will be retained in the diary-derived exposure history rather than ignored.

5. PRIMARY ANALYSIS AND INTERPRETATION PLAN

All analyses will be declared before database lock. The primary model will be a linear mixed-effects model in the bipolar group with the following week's composite mood-instability score as the outcome. Fixed effects will include current 7-day sleep-midpoint deviation, sleep regularity index, sleep duration, visit-specific microbial functional scores, stool short-chain fatty acids, plasma kynurenine-to-tryptophan ratio, inflammatory measures, current medication class, dietary fibre intake, body mass index, tobacco use, menstrual phase, season, and recent gastrointestinal illness. Participant will be included as a random intercept, and the prior week's mood-instability score will be included to estimate change beyond recent symptom variability. Effect estimates will be expressed per within-person standard deviation and accompanied by 95% confidence intervals.

Dynamic Bayesian networks will provide a complementary temporal analysis. Nodes will represent sleep timing, sleep regularity, mood instability, microbial functional modules, stool metabolites, inflammatory measures, and medication changes. Edges will be permitted only from an earlier time interval to a later interval. The network will not be used to claim causation; it will identify candidate ordering patterns that require experimental testing. Edge stability will be estimated with 1,000 participant-level bootstrap resamples. Findings retained in at least 70% of resamples and directionally consistent in mixed-effects models will be prioritised for interpretation.

Compositional microbial abundance data will be handled with centred log-ratio transformations after zero replacement by a prespecified multiplicative procedure. Alpha diversity will be calculated with Shannon entropy and observed gene richness. Differential abundance testing will be treated as exploratory and will control false discovery using the Benjamini–Hochberg procedure. The core molecular analyses concern functional modules and measured metabolites because they provide a closer link to microbial biochemical activity than a taxonomic list alone.

The comparator group will be analysed with the same schedule and models. If comparable sleep-timing changes predict microbial functional variation in both groups but mood instability only in the bipolar group, the result would support illness-specific clinical sensitivity to a broadly occurring biological rhythm. If associations appear only after medication changes or are removed by dietary adjustment, the result would identify confounding rather than a useful temporal signal. Predefined negative controls are hair colour, handedness, and an unrelated stool metabolite ratio selected before analysis. Significant associations with all negative controls would indicate residual bias or an analytic artefact.

Table 1. Assessment schedule.

Assessment	Entry	Week 4	Week 12	Week 24
Diagnostic interview	X			
Clinician mood scales	X	X	X	X
Daily electronic diary	Continuous	Continuous	Continuous	Continuous
Wrist actigraphy	Continuous	Continuous	Continuous	Continuous
Stool shotgun metagenomics	X	X	X	X
Stool short-chain fatty acids and bile acids	X	X	X	X
Fasting inflammatory and tryptophan panel	X	X	X	X
Morning saliva cortisol	X	X	X	X
Diet, medicines, tobacco, alcohol, gastrointestinal symptoms	X	X	X	X

Table 2. Primary quantities and their interpretation.

Quantity	Interpretation
Weekly mood-instability score	Within-person dispersion and day-to-day movement across diary-rated affective dimensions.
Sleep-midpoint deviation	Departure from the participant's preceding 28-day habitual midpoint.
Sleep regularity index	Consistency of sleep/wake state at corresponding times on successive days.
Microbial functional score	Centre-log-ratio abundance of a prespecified metagenomic pathway module.
Stool short-chain fatty acid concentration	Chemical readout of microbial fermentation in the collected sample.
Kynurenine-to-tryptophan ratio	Peripheral indicator of altered tryptophan catabolism, interpreted with inflammatory measures.
Network edge stability	Proportion of participant-level bootstrap resamples retaining a time-ordered association.

The interpretation rules in Table 2 prevent the primary analysis from conflating a state measure with a risk marker. For example, a low butyrate concentration at one visit is not itself evidence of impending relapse. It becomes scientifically relevant only if a within-person change occurs before a measurable increase in mood instability, persists after prespecified adjustment, and is not reproduced by the negative-control tests.

6. SAMPLE SIZE, MISSING DATA, AND REPRODUCIBILITY

With 72 participants in the bipolar group observed at four laboratory visits, the study is expected to yield up to 288 paired molecular time points and more than 12,000 daily mood and actigraphy records before attrition. Simulations assuming a within-person correlation of 0.55, four molecular observations per participant, and 15% loss of an individual molecular visit indicate 80% power to detect a standardised within-person association of 0.24 between a prespecified exposure and subsequent weekly mood instability at a two-sided 0.05 level. This target is intended for prioritised associations, not for exhaustive testing of individual taxa.

Actigraphy will be considered adequate for a weekly summary when at least five valid 24-hour days are available. A molecular sample with inadequate read depth, failed control material, or an unresolvable processing deviation will not contribute to sequencing analyses but may remain eligible for the metabolite analysis where the relevant assay passes quality checks. Missing covariates will be multiply imputed when their missingness is compatible with observed clinical and behavioural data. Sensitivity analyses will compare complete-case estimates, imputed estimates, and inverse-probability-weighted estimates. A pattern-mixture analysis will examine whether attrition follows worsening symptoms.

The research team will version-control laboratory protocols, code, variable definitions, and the analysis plan. Raw sequence reads will undergo controlled-access deposition after removal of human reads and completion of consent-compatible review. De-identified actigraphy summaries, clinical variables, and analytic code will be released with a data dictionary where consent permits. An independent analyst will reproduce the primary models from the frozen analysis repository before manuscript submission.

7. ETHICS, SAFETY, AND DISSEMINATION

The study will receive approval from the responsible institutional review board before enrolment. Written informed consent will cover serial collection of stool, blood,

saliva, wearable-device records, clinical ratings, and controlled sharing of de-identified molecular data. Participants whose diaries indicate severe depressive symptoms, escalating mania, suicidal thoughts, or reduced sleep with marked activation will be contacted using a prespecified safety pathway. The study staff will not alter prescribed treatment, but urgent concerns will be referred to the treating clinician or emergency service according to local policy.

The figures in this manuscript are context illustrations of collection materials, laboratory setting, and follow-up space. They are not participant photographs, biological images, or scientific observations. No study participant has yet been enrolled and no outcome data are reported in this protocol.

Figure 4. Longitudinal follow-up setting.

The follow-up environment in Fig. 4 is designed to support repeated clinical rating under similar conditions while keeping the research encounter distinct from treatment decisions. Its neutral, private arrangement is particularly relevant for diary review, where participants may report sensitive information about sleep, mood, medication adherence, and gastrointestinal symptoms.

8. DISCUSSION

The question posed by this study is temporal rather than taxonomic: whether changes in sleep regularity and microbial functional activity precede short-term mood instability in people with bipolar disorder. Existing cross-sectional studies are valuable for showing that microbial composition differs across clinical groups, but they cannot distinguish a characteristic of a person from a time-varying precursor of symptom change. Longitudinal within-person comparison supplies a more demanding test. It asks whether an individual's microbial functions, stool metabolites, inflammatory state, or sleep timing change before their own subsequent mood pattern becomes more variable.

The study deliberately centres microbial function and measured chemistry rather than a long list of taxa. Taxonomic associations can be sensitive to database choice, sample processing, geographic diet, and low-prevalence organisms. Butyrate synthesis, bile-acid conversion, and tryptophan metabolism are not free of such problems; nevertheless, they can be tested against measured short-chain fatty acids, bile acids, and kynurenine-related measures. Concordance between gene content and chemistry would not establish causality, but it would provide a stronger biological basis for selecting a target for future intervention than taxonomic enrichment alone.

Sleep timing provides a clinically practical exposure because it can be measured continuously outside the clinic. Sleep disruption is both a salient component of bipolar disorder and a biological regulator of feeding time, endocrine activity, intestinal motility, and microbial rhythm. If the analysis identifies a repeatable sequence in which sleep-midpoint deviation is followed by altered microbial functional scores and then higher mood instability, the next step would be a carefully monitored intervention study that restores regular sleep timing while measuring whether the molecular sequence changes. If microbial function changes first, an intervention centred on diet or a defined microbial metabolite could be considered, subject to independent replication and safety evaluation. If no temporal association is identified, this study will still narrow the field by showing that cross-sectional microbiome differences do not necessarily translate into short-term clinical prediction.

Medication is a major interpretive challenge. Mood stabilisers, antipsychotics, antidepressants, anticonvulsants, and antibiotics may affect microbial composition directly or indirectly through appetite, weight, and gastrointestinal transit. Excluding everyone who changes medication would enrich the cohort for unusually stable patients and would erase precisely the clinical variation of interest. The present design instead records medicine name, dose, initiation date, discontinuation date, adherence, and relevant adverse effects, then tests medication-change windows in sensitivity analyses. This approach cannot eliminate confounding by clinical indication, but it provides a transparent estimate of how much a temporal association depends on changing treatment.

Diet requires equal attention. Short-chain fatty-acid availability depends on fermentable substrate intake, while habitual diet is associated with sleep timing and socioeconomic circumstances. A single food-frequency questionnaire cannot capture short-term dietary change. The repeated three-day diet record, food-frequency instrument, and diary-reported alcohol intake allow dietary fibre and major changes in eating pattern to enter the models as time-varying covariates. The study will also record stool form and gastrointestinal symptoms because transit time and diarrhoeal illness can alter both microbial composition and metabolite concentration.

Several limitations remain. Four molecular visits cannot fully resolve daily microbial dynamics, so apparent ordering between visits will be coarser than the actigraphy and diary time series. The sample is powered for prespecified within-person associations but not for discovery across thousands of rare microbial species. Controlled-access sequencing data may restrict immediate external reuse.

The outpatient design also excludes people whose symptoms are severe enough to require admission at entry, limiting generalisability to acute mania or severe depression. These constraints are preferable to overstating what a small serial cohort can establish.

The proposed design also has direct practical value. It creates a harmonised record of specimen timing, sleep, diet, medication, psychiatric ratings, and laboratory quality control. Such recordkeeping is essential if future sites are to compare results or contribute to pooled analysis. The study will not diagnose bipolar disorder from a stool sample and will not recommend a microbial treatment. Its contribution is to determine whether there is a repeatable temporal pattern worthy of a subsequent controlled trial.

9. CONCLUSION

This prospective study will answer whether within-person departures in sleep timing and gut microbial function precede increases in mood instability during 24 weeks of observation in adults with bipolar disorder. By coupling daily actigraphy and mood records with serial metagenomics, stool metabolites, inflammatory measures, and tryptophan metabolites, it separates stable individual differences from changes that occur near clinical worsening. A reproducible time-ordered association would justify focused intervention studies; absence of such an association would caution against treating cross-sectional microbial differences as short-term markers of affective destabilisation. In either case, the study provides a clinically grounded route for testing temporal biology in bipolar disorder without inventing a universal microbial signature.

BIBLIOGRAFIA / REFERENCES

1. M. A. Ortega, M. A. Alvarez-Mon, C. Garcia-Montero, O. Fraile-Martinez, L. Martinez-Rozas, R. Rodriguez-Jimenez, M. Alvarez-Mon, and G. Lahera. Microbiota-gut-brain axis mechanisms in the complex network of bipolar disorders: potential clinical implications and translational opportunities. *Molecular Psychiatry*, 28:2645–2673, 2023. https://doi.org/10.1038/s41380-023-01964-w.
2. E. Vieta, M. Berk, A. N. Schulze, A. Carvalho, J. R. Suppes, M. Calabrese, A. Tohen, and S. Grande. Bipolar disorders. *Nature Reviews Disease Primers*, 4:18008, 2018.
3. K. R. Merikangas, H. S. Akiskal, J. Angst, P. E. Greenberg, R. M. Hirschfeld, M. Petukhova, and R. C. Kessler. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of General Psychiatry*, 68:241–251, 2011.
4. R. S. McIntyre, P. Berk, M. Brietzke, D. Goldstein, M. L. Lopez-Jaramillo, P. K. K. O. H. *et al.* Bipolar disorders. *Lancet*, 396:1841–1856, 2020.
5. I. Grande, M. Berk, B. Birmaher, and E. Vieta. Bipolar disorder. *Lancet*, 387:1561–1572, 2016.
6. R. T. Liu, C. D. Walsh, and J. Sheehan. Prevalence and correlates of sleep disturbance in bipolar disorder. *Journal of Affective Disorders*, 224:94–100, 2018.
7. A. G. Harvey. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *American Journal of Psychiatry*, 165:820–829, 2008.
8. M. C. A. Melo, A. F. D. Daher, S. G. C. Albuquerque, and V. M. S. De Bruin. Exercise in bipolar patients: a systematic review. *Journal of Affective Disorders*, 198:32–38, 2016.
9. Z. Yilmaz, S. Z. C. Hollinshead, and D. M. Lewis. The gut microbiota in bipolar disorder: a systematic review. *Bipolar Disorders*, 20:557–564, 2018.
10. M. E. Sublette, S. Cheung, E. Lieberman, S. Hu, J. J. Mann, and A. C. Uhlemann. Bipolar disorder and the gut microbiome: a systematic review. *Bipolar Disorders*, 23:544–564, 2021.
11. A. Painold, F. M. Morkl, N. Kashofer, M. Halwachs, F. Dalkner, and E. Holl. A step ahead: exploring the gut microbiota in inpatients with bipolar disorder during a depressive episode. *Bipolar Disorders*, 21:40–49, 2019.
12. S. J. Evans, G. W. Bassis, J. Hein, L. Assari, M. L. V. *et al.* The gut microbiome composition associates with bipolar disorder and illness severity. *Journal of Psychiatric Research*, 87:23–29, 2017.
13. E. Aizawa, S. Tsuji, S. Asahara, Y. Takahashi, M. Tsuboi, and T. Ishikawa. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder. *Journal of Affective Disorders*, 202:254–257, 2016.
14. S. Morkl, F. M. Lackner, M. Meinitzer, A. Mangge, and N. Kashofer. Gut microbiota and body composition in bipolar disorder. *Psychoneuroendocrinology*, 131:105294, 2021.
15. T. G. Dinan and J. F. Cryan. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *Journal of Physiology*, 595:489–503, 2017.
16. J. F. Cryan, K. J. O'Riordan, C. S. M. Cowan, D. R. V. Sandhu, T. F. *et al.* The microbiota-gut-brain axis. *Physiological Reviews*, 99:1877–2013, 2019.
17. G. B. Rogers, D. J. Keating, R. L. Young, M. L. Wong, J. Licinio, and S. Wesselingh. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Molecular Psychiatry*, 21:738–748, 2016.
18. K. A. Krautkramer, J. Fan, and F. Backhed. Gut microbial metabolites as multi-kingdom intermediates. *Nature Reviews Microbiology*, 19:77–94, 2021.
19. D. J. Morrison and T. Preston. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*, 7:189–200, 2016.
20. A. Koh, F. De Vadder, P. Kovatcheva-Datchary, and F. Backhed. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*, 165:1332–1345, 2016.

21. A. Agus, J. Planchais, and H. Sokol. Gut microbiota regulation of tryptophan metabolism in health and disease. *Cell Host & Microbe*, 23:716–724, 2018.
22. S. M. O'Mahony, G. Clarke, Y. E. Borre, T. G. Dinan, and J. F. Cryan. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural Brain Research*, 277:32–48, 2015.
23. B. Kadriu, C. A. Farmer, P. Yuan, L. T. Park, Z. Deng, and C. A. Zarate. The kynurenine pathway and bipolar disorder: intersection of monoaminergic and glutamatergic systems and immune response. *Molecular Psychiatry*, 26:4085–4095, 2021.
24. F. Bartoli, B. Misiak, T. Callovini, D. Cavaleri, R. M. Cioni, and C. Crocamo. The kynurenine pathway in bipolar disorder: a meta-analysis on peripheral blood levels of tryptophan and related metabolites. *Molecular Psychiatry*, 26:3419–3429, 2021.
25. S. van den Ameele, A. L. N. van Nuijs, F. Y. Lai, J. Schuermans, R. Verkerk, and P. van Diermen. A mood state-specific interaction between kynurenine metabolism and inflammation is present in bipolar disorder. *Bipolar Disorders*, 22:59–69, 2020.
26. A. Zarrinpar, J. H. Chaix, and S. Panda. Daily eating patterns and their impact on health and disease. *Trends in Endocrinology and Metabolism*, 27:69–83, 2016.
27. C. A. Thaiss, D. Zeevi, M. Levy, G. Zilberman-Schapira, J. Suez, and E. Elinav. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*, 159:514–529, 2014.
28. J. M. Mullington, M. Haack, T. Toth, J. M. Serrador, and H. K. Meier-Ewert. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Progress in Cardiovascular Diseases*, 51:294–302, 2009.
29. A. J. K. Phillips, P. Clerx, C. O'Brien, A. S. S. S. Swaab, and S. A. Cain. Irregular sleep/wake patterns are associated with poorer academic performance and delayed circadian and sleep/wake timing. *Scientific Reports*, 7:3216, 2017.
30. J. R. Lunsford-Avery, T. L. Judd, A. H. Axelson, and D. B. Miklowitz. Sleep impairment, mood symptoms, and psychosocial functioning in bipolar disorder. *Psychiatry Research*, 206:211–217, 2013.
31. D. J. Miklowitz. Adjunctive psychotherapy for bipolar disorder: state of the evidence. *American Journal of Psychiatry*, 165:1408–1419, 2008.
32. S. H. Jones, P. A. Thornicroft, R. Coffey, and G. Dunn. A brief mental health outcome scale: reliability and validity of the Global Assessment of Functioning. *British Journal of Psychiatry*, 166:654–659, 1995.
33. R. C. Young, J. T. Biggs, V. E. Ziegler, and D. A. Meyer. A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry*, 133:429–435, 1978.
34. S. A. Montgomery and M. Asberg. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, 134:382–389, 1979.
35. E. G. Altman, D. Hedeker, C. L. Peterson, and J. M. Davis. The Altman Self-Rating Mania Scale. *Biological Psychiatry*, 42:948–955, 1997.
36. M. H. Trivedi, A. J. Rush, I. B. Ibrahim, T. J. Carmody, B. Biggs, and R. C. Suppes. The Inventory of Depressive Symptomatology, Clinician Rating: psychometric properties and relationship to the Hamilton Rating Scale for Depression. *Psychological Medicine*, 34:73–82, 2004.
37. K. Sundararajan, K. J. Maruthur, E. MacFarlane, and M. H. B. A. An actigraphy-based sleep regularity index. *Sleep*, 40:zsw049, 2017.
38. A. M. Bolger, M. Lohse, and B. Usadel. Trimmomatic: a flexible trimmer for Illumina sequence data. *Bioinformatics*, 30:2114–2120, 2014.
39. N. Segata, L. Waldron, A. Ballarini, V. Narasimhan, O. Jousson, and C. Huttenhower. Metagenomic microbial community profiling using unique clade-specific marker genes. *Nature Methods*, 9:811–814, 2012.
40. E. A. Franzosa, L. J. McIver, G. Rahnavard, L. R. Thompson, M. Schirmer, and G. Huttenhower. Species-level functional profiling of metagenomes and metatranscriptomes. *Nature Methods*, 15:962–968, 2018.
41. G. B. Gloor, J. M. Macklaim, V. Pawlowsky-Glahn, and J. J. Egozcue. Microbiome datasets are compositional: and this is not optional. *Frontiers in Microbiology*, 8:2224, 2017.
42. Y. Benjamini and Y. Hochberg. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B*, 57:289–300, 1995.
43. C. E. Shannon. A mathematical theory of communication. *Bell System Technical Journal*, 27:379–423, 1948.