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Adiposity, Objective Sleep Variability, and Anxiety Symptoms: Indirect Associations and Shared Metabolic Signatures in the UK Biobank

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Article

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Abstract

Background: The relationships among adiposity, objectively measured sleep variability, and anxiety symptoms remain incompletely understood. We investigated their temporally ordered associations and shared metabolic signatures.

Methods: This UK Biobank study included 62,642 participants with baseline adiposity measures (2006–2010), accelerometer-derived sleep characteristics (2013–2015), and subsequent GAD-7 assessments (2016–2017). Multivariable regression and restricted cubic splines were used to examine associations and dose–response patterns. Indirect associations through sleep variability were estimated using bootstrap resampling. Baseline nuclear magnetic resonance (NMR) profiling of 251 metabolic measures was performed to identify signatures associated with both sleep variability and anxiety symptoms.

Results: Higher BMI, waist-to-hip ratio, and body fat percentage were associated with greater day-to-day sleep variability (β = 2.959, 2.571, and 3.773 min per SD, respectively; all $P < 0.001$), with evidence of nonlinear associations. Greater sleep variability was associated with higher GAD-7 scores (β = 0.082; 95% CI, 0.054–0.109), whereas mean daily sleep time showed a nonlinear association with anxiety symptoms. Sleep variability statistically accounted for 4.23%, 2.08%, and 4.69% of the adiposity–anxiety associations for BMI, waist-to-hip ratio, and body fat percentage, respectively. Among 251 NMR measures, 39 were associated with sleep variability and 97 with anxiety symptoms after false discovery rate correction. Thirteen shared metabolic signatures were identified, predominantly involving fatty acid composition, lipoprotein metabolism, inflammation, and ketone metabolism.

Conclusions: Greater adiposity was associated with increased objective sleep variability and higher subsequent anxiety symptoms, with sleep variability accounting for a modest proportion of these associations. Shared baseline metabolic signatures provide additional insights into their interrelationships, warranting further investigation.

Introduction

Anxiety symptoms are common in the general population and contribute substantially to psychological distress, impaired functioning, and reduced quality of life. Growing evidence suggests that anxiety is closely intertwined with metabolic health, including excess adiposity and related cardiometabolic disturbances [1]. Observational studies have reported associations between obesity and anxiety disorders, although the direction and underlying mechanisms of these relationships remain uncertain. A recent systematic review and meta-analysis of Mendelian randomization studies found evidence supporting a causal association between general adiposity and depression, whereas evidence for anxiety and several other psychiatric disorders remained inconclusive [2]. These findings highlight the importance of identifying potentially modifiable behavioral and physiological characteristics that may help explain the relationship between adiposity and anxiety. Sleep represents one such candidate, given its close connections with metabolic regulation, emotional functioning, and mental health.

Sleep is increasingly recognized as a multidimensional health behavior that encompasses not only sleep duration but also the consistency of sleep patterns across days. Although short and long sleep durations have been associated with adverse mental and physical health outcomes, emerging evidence suggests that day-to-day sleep variability may provide additional information beyond average sleep duration. In a large UK Biobank study, objectively measured sleep regularity was more strongly associated with mortality risk than sleep duration [3]. More recently, a prospective study of 79,666 UK Biobank participants reported that greater accelerometer-derived sleep regularity was associated with a lower risk of incident anxiety and depression, even among individuals meeting recommended sleep duration guidelines [4]. These findings suggest that temporal stability in sleep behavior may be relevant to mental health independently of average sleep duration [5]. However, existing studies have predominantly focused on sleep characteristics as

predictors of subsequent health outcomes, while the extent to which adiposity is associated with day-to-day variability in objectively measured sleep, and how these associations relate to later anxiety symptoms, remains less well characterized.

Beyond behavioral sleep characteristics, metabolic disturbances may provide additional insights into the links between adiposity, sleep, and anxiety. Adiposity is associated with alterations in lipid metabolism, fatty acid composition, insulin sensitivity, and systemic inflammation, several of which have also been implicated in sleep regulation and psychiatric symptoms [6]. Recent advances in high-throughput nuclear magnetic resonance (NMR) metabolomics have enabled the simultaneous characterization of circulating lipoproteins, fatty acids, amino acids, ketone bodies, and inflammation-related metabolites in large population cohorts. An NMR biomarker atlas involving 118,461 UK Biobank participants demonstrated widespread associations between circulating metabolic measures and subsequent disease outcomes, highlighting the potential relevance of fatty acid composition and glycoprotein acetyls (GlycA) [7]. Subsequent studies have identified distinct immunometabolic profiles associated with sleep duration [8]and prospective associations between circulating metabolites and depression or anxiety risk [9]. Nevertheless, it remains unclear whether objectively measured day-to-day sleep variability and anxiety symptoms share identifiable baseline metabolic signatures, particularly after accounting for overall adiposity. Examining these overlapping metabolic associations may help characterize the biological heterogeneity underlying the adiposity–sleep–anxiety relationship without presuming a causal metabolic pathway.

To address these gaps, we conducted a large-scale, temporally ordered observational study using UK Biobank data, integrating baseline adiposity measures, subsequent accelerometer-derived sleep characteristics, later anxiety symptom assessments, and baseline NMR metabolic profiling. Specifically, we aimed to (1) examine the associations of BMI, waist-to-hip ratio, and body fat percentage with objectively measured sleep variability; (2) investigate the associations of sleep characteristics with subsequent anxiety symptoms, including potential nonlinear dose–response relationships; (3) quantify the extent to which sleep variability statistically accounted for the associations between adiposity and anxiety symptoms; and (4) identify baseline NMR metabolic measures associated with both sleep variability and anxiety symptoms independently of BMI. By integrating behavioral and metabolic information across different assessment periods, this study sought to provide a more comprehensive characterization of the relationships among adiposity, objective sleep variability, and anxiety symptoms.

Methods

Study design and participants

This population-based observational study used data from the UK Biobank, a large prospective cohort comprising approximately 500,000 participants aged 40–69 years at recruitment between 2006 and 2010 [10]. The UK Biobank collected extensive information on demographic characteristics, lifestyle factors, anthropometric measurements, biological samples, and health-related outcomes, with additional assessments conducted during follow-up.

We adopted a temporally ordered analytical framework integrating adiposity measures obtained at baseline (2006 – 2010), accelerometer-derived sleep characteristics assessed during a subsequent monitoring period (2013–2015), and anxiety symptoms evaluated through the online mental health questionnaire (2016–2017). Baseline nuclear magnetic resonance (NMR) metabolic measures were additionally incorporated to characterize metabolic profiles associated with subsequent sleep variability and anxiety symptoms (Figure 1).

Participants were included if they had available baseline adiposity measurements, accelerometer-derived sleep data, and complete responses to the seven items of the Generalized Anxiety Disorder-7 (GAD-7) questionnaire. The initial

analytical cohort comprised 64,597 participants. To reduce the influence of potentially implausible accelerometer-derived sleep estimates, the primary analysis was restricted to participants with mean daily sleep time between 4 and 14 hours, yielding 62,642 participants. The unrestricted cohort was retained for sensitivity analyses. Sample sizes varied across individual regression models according to the availability of exposure and covariate data.

The UK Biobank received ethical approval from the relevant research ethics committee, and all participants provided informed consent. The present study was conducted under the UK Biobank data access and ethical governance framework.

Assessment of adiposity

Baseline adiposity was characterized using three complementary measures: body mass index (BMI), waist-to-hip ratio (WHR), and body fat percentage.

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). WHR was calculated as waist circumference divided by hip circumference, reflecting central fat distribution. Body fat percentage was obtained from baseline body composition assessments and used as an indicator of overall adiposity.

BMI was considered the primary adiposity measure, while WHR and body fat percentage were included to examine whether associations were consistent across different dimensions of adiposity. For regression analyses, adiposity measures were standardized to a mean of zero and a standard deviation of one, allowing effect estimates to be expressed per 1-SD increment.

Accelerometer-derived sleep characteristics

Objective sleep characteristics were derived from wrist-worn accelerometer data collected during the UK Biobank accelerometry assessment. The present analysis used seven day-specific estimates of the proportion of time classified as sleep, obtained from UK Biobank field 40042.

Daily sleep proportions were converted into hours by multiplying by 24. Three sleep characteristics were derived for each participant. Mean daily sleep time was calculated as the arithmetic mean of the seven daily sleep estimates and expressed in hours per day. Day-to-day sleep variability was quantified as the standard deviation of the seven daily sleep estimates, expressed in hours. Higher values indicated greater variability in accelerometer-derived sleep time across the monitoring period. Weekend–weekday sleep difference was calculated as the mean sleep time on Saturday and Sunday minus the mean sleep time from Monday through Friday. Positive values indicated longer estimated sleep time on weekends.

Because these measures were derived from daily accelerometer-classified sleep proportions, they were interpreted as accelerometer-derived daily sleep characteristics rather than conventional nocturnal sleep duration or polysomnography-defined sleep parameters. Day-to-day variability was not interpreted as a formal sleep regularity index. For the primary analysis, participants with mean daily sleep time outside the range of 4–14 hours were excluded. This criterion was used as a pragmatic plausibility filter rather than as a substitute for the UK Biobank's official accelerometer quality-control indicators. Analyses using the unrestricted sleep cohort were performed to assess the robustness of the findings.

Assessment of anxiety symptoms

Anxiety symptoms were assessed using the seven-item Generalized Anxiety Disorder scale (GAD-7), administered as part of the UK Biobank online mental health questionnaire. The GAD-7 evaluates the frequency of seven anxiety-related

symptoms over the preceding two weeks. Each item is scored from 0 to 3, yielding a total score ranging from 0 to 21, with higher scores indicating greater anxiety symptom severity.

The continuous GAD-7 total score was used as the primary anxiety outcome to preserve information across the full range of symptom severity. A score of 10 or higher was additionally used to describe the proportion of participants with clinically relevant anxiety symptom levels. Only participants with complete responses to all seven GAD-7 items were included in the analytical cohort.

Baseline NMR metabolic profiling

Baseline metabolic profiling was performed using 251 NMR-derived metabolic measures available in the UK Biobank. These measures encompassed circulating lipoprotein and lipid characteristics, fatty acid composition, amino acids, ketone bodies, glycolysis-related metabolites, and inflammation-related markers. NMR measures obtained at the baseline assessment were used to investigate metabolic characteristics associated with subsequent sleep variability and anxiety symptoms. Among participants in the integrated analytical cohort, 34,792 had at least one available baseline NMR measure, while 31,247 had complete data for all 251 measures.

To improve comparability across metabolic measures and reduce the influence of extreme observations, NMR variables underwent measure-specific preprocessing according to their distributions and measurement characteristics. Appropriate transformations were applied where necessary, followed by winsorization at the 0.5th and 99.5th percentiles. The processed measures were then standardized to a mean of zero and a standard deviation of one.

Each metabolic measure was analyzed separately using available observations for that measure; complete data across all 251 measures were not required.

NMR metabolic measures were examined as baseline metabolic correlates of subsequent sleep variability and anxiety symptoms. Because baseline NMR measures and adiposity were assessed during the same recruitment period, the metabolic measures were not treated as temporally established mediators of the adiposity–sleep association.

Covariates

Potential confounders were selected based on their relevance to adiposity, sleep characteristics, and anxiety symptoms, as well as their availability in the UK Biobank.

The primary adjustment set included age, sex, ethnicity, Townsend deprivation index, and educational attainment. Age and Townsend deprivation index were modeled as continuous variables, whereas sex, ethnicity, and educational attainment were incorporated according to their respective variable coding.

Smoking status and alcohol consumption frequency were additionally included in an extended adjustment model to evaluate the robustness of the associations to further lifestyle adjustment.

Baseline BMI was included as an additional covariate in the BMI-adjusted NMR association models to assess metabolic associations beyond overall adiposity.

Self-reported sleep duration, diabetes, hypertension, and obstructive sleep apnea were not routinely included in the primary adjustment set because of their potential overlap with the exposure or their possible positions within the pathways under investigation. Obstructive sleep apnea was instead considered in sensitivity analyses.

Statistical analysis

Continuous variables were summarized as means and standard deviations, and categorical variables as frequencies and percentages. Associations were estimated using multivariable linear regression models with heteroskedasticity-robust standard errors. Associations between adiposity, sleep characteristics, and anxiety symptoms

We first examined associations of baseline adiposity measures with subsequent accelerometer-derived sleep characteristics. BMI, WHR, and body fat percentage were evaluated separately as standardized exposures. Sleep variability was the primary sleep-related outcome, with mean daily sleep time and weekend–weekday sleep difference examined as additional characteristics. We subsequently evaluated associations between accelerometer-derived sleep characteristics and GAD-7 scores, followed by associations between baseline adiposity measures and GAD-7 scores. Three progressively adjusted models were specified: Model 1: age and sex. Model 2 (primary model): Model 1 plus ethnicity, Townsend deprivation index, and educational attainment. Model 3: Model 2 plus smoking status and alcohol consumption frequency. Regression coefficients and 95% confidence intervals were estimated using HC1 robust standard errors. Adiposity effect estimates were expressed per 1-SD higher adiposity measure. Sleep variability and mean daily sleep time were standardized when used as predictors of anxiety symptoms. For analyses with sleep variability as the outcome, coefficients were converted into minutes to facilitate clinical interpretation.

Dose–response associations

Restricted cubic spline regression was used to investigate potential nonlinear associations between adiposity measures and sleep variability, as well as between sleep characteristics and GAD-7 scores. Spline models were adjusted for the covariates included in Model 2. Five knots were placed at prespecified percentiles of the exposure distributions. Overall and nonlinear associations were evaluated, and adjusted predictions with 95% confidence intervals were plotted using clinically interpretable reference values.

To evaluate whether sleep variability statistically accounted for part of the association between adiposity and anxiety symptoms, we conducted indirect association analyses within the temporally ordered adiposity–sleep–anxiety framework.

For each adiposity measure, two regression models were fitted. The first estimated the association between adiposity and standardized sleep variability (path a). The second estimated the association between sleep variability and GAD-7 score conditional on adiposity (path b), together with the residual adiposity–anxiety association (path c'). The total adiposity–anxiety association was denoted as path c.

The indirect association was quantified as the product a × b. Confidence intervals were estimated using 2,000 bootstrap resamples. The proportion of the total association statistically accounted for by sleep variability was calculated as the indirect association divided by the total association and expressed as a percentage.

All pathway models were adjusted for Model 2 covariates. Given the observational design, possible bidirectional relationships, and potential residual confounding, these estimates were interpreted as indirect associations rather than causal mediation effects.

NMR-wide association analyses were performed separately for standardized sleep variability and GAD-7 score using each of the 251 baseline metabolic measures as an independent predictor. Two covariate adjustment models were specified for the NMR analyses: Model A: age, sex, ethnicity, Townsend deprivation index, and educational attainment. Model B: Model A plus BMI. Model B was selected as the primary NMR association model to identify metabolic associations that persisted after adjustment for overall adiposity. HC1 robust standard errors were used for all NMR association models.

To account for multiple comparisons, P values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure separately within each outcome and adjustment model, across the 251 metabolic measures. An FDR-adjusted P value below 0.05 was considered statistically significant. Shared metabolic signatures were defined as NMR measures that were significantly associated with both sleep variability and GAD-7 score in BMI-adjusted Model B analyses and exhibited concordant directions of association. These shared measures were subsequently characterized according to their metabolic categories, and their regression coefficients and 95% confidence intervals were presented graphically.

Several sensitivity analyses were conducted to evaluate the robustness of the main findings. First, primary associations were compared between the unrestricted analytical cohort and the cohort restricted to participants with mean accelerometer-derived daily sleep time between 4 and 14 hours. Second, analyses were repeated after excluding participants with an ever-recorded hospital diagnosis of obstructive sleep apnea, identified using ICD-10 code G47.3. Third, the consistency of associations was assessed across progressively adjusted covariate models. All statistical tests were two-sided. For the primary regression analyses, P values below 0.05 were considered statistically significant. For NMR-wide association analyses, statistical significance was determined using an FDR-adjusted P value below 0.05.

Results

Participant characteristics

The primary analytical cohort included 62,642 participants with available adiposity measures, accelerometer-derived sleep characteristics, anxiety symptom assessments, and relevant covariates after applying the prespecified sleep plausibility criterion. The mean age was 55.6 years (SD, 7.6), and 58.4% were women. The mean BMI was 26.49 kg/m² (SD, 4.44), the mean waist-to-hip ratio was 0.853 (SD, 0.087), and the mean body fat percentage was 30.6% (SD, 8.4). Participants had a mean accelerometer-derived daily sleep time of 8.83 h/day (SD, 1.19) and a mean day-to-day sleep variability of 1.17 h (SD, 0.60). The mean GAD-7 score was 2.01 (SD, 3.26), and 2,435 participants (3.9%) had a GAD-7 score ≥10. Additional characteristics of the analytical cohort are presented in Table 1.

Table 1. Characteristics of the primary analytical cohort

Characteristic	Overall (N = 62,642)
Demographic characteristics	
Age, years	55.6 ± 7.6
Female sex	36,607 (58.4%)
Ethnicity	
White	60,883 (97.5%)
Asian	565 (0.9%)
Black	366 (0.6%)
Mixed	317 (0.5%)
Other	311 (0.5%)
Townsend deprivation index	−1.81 ± 2.77
University degree	29,375 (47.3%)
Adiposity measures	
BMI, kg/m²	26.49 ± 4.44
Waist circumference, cm	87.5 ± 12.8
Waist-to-hip ratio	0.853 ± 0.087
Body fat percentage, %	30.6 ± 8.4
Objective sleep characteristics	
Accelerometer-derived mean daily sleep time, h/day	8.83 ± 1.19
Day-to-day sleep variability, h	1.17 ± 0.60
Weekend–weekday difference, h	0.56 ± 1.35
Anxiety symptoms	
GAD-7 score	2.01 ± 3.26
GAD-7 ≥10	2,435 (3.9%)
Lifestyle characteristics	
Smoking status	
Never	36,848 (58.9%)
Previous	21,848 (34.9%)
Current	3,819 (6.1%)
Alcohol drinking frequency	
Daily or almost daily	14,512 (23.2%)
Three or four times a week	16,907 (27.0%)

Once or twice a week	15,726 (25.1%)
One to three times a month	6,792 (10.8%)
Special occasions only	5,550 (8.9%)
Never	3,120 (5.0%)
Clinical characteristic	
Ever-recorded hospital diagnosis of sleep apnoea	954 (1.5%)

Note: Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. Percentages were calculated among participants with available data for each variable. Ethnicity categories were collapsed for descriptive presentation only; regression models retained the prespecified ethnicity coding. BMI, body mass index; GAD-7, 7-item Generalized Anxiety Disorder scale; SD, standard deviation.

Adiposity and objectively measured sleep characteristics

Higher adiposity was consistently associated with greater day-to-day sleep variability (Table 2). In the primary adjusted model, each 1-SD higher BMI was associated with a 2.959-min greater sleep variability (95% CI, 2.666 – 3.253; P < 0.001). Corresponding estimates were 2.571 min (95% CI, 2.178–2.965; P<0.001) for waist-to-hip ratio and 3.773 min (95% CI, 3.394 – 4.152; P < 0.001) for body fat percentage.

Restricted cubic spline analyses further indicated nonlinear associations between all three adiposity measures and sleep variability (Figure 2). Evidence for nonlinearity was strongest for BMI and waist-to-hip ratio (both P for nonlinearity <0.001), while a weaker nonlinear pattern was observed for body fat percentage (P for nonlinearity=0.038). Across the three measures, greater adiposity was generally associated with progressively greater day-to-day variability in accelerometer-derived sleep, although the shape of the association differed across adiposity indicators.

BMI was also associated with accelerometer-derived mean daily sleep time (P overall = 0.015), whereas there was no strong evidence of nonlinearity (P for nonlinearity = 0.354; Supplementary Figure S1).

Objective sleep characteristics and anxiety symptoms

Both mean daily sleep time and day-to-day sleep variability were associated with subsequent anxiety symptoms (Table 2). In linear models, each 1-SD greater sleep variability was associated with a 0.082-point higher GAD-7 score (95% CI, 0.054 – 0.109; P < 0.001). Mean daily sleep time was also positively associated with GAD-7 score in the linear model (β=0.070; 95% CI, 0.043 – 0.097; P < 0.001), whereas a greater weekend–weekday difference was associated with a slightly lower GAD-7 score (β=−0.032; 95% CI, −0.059 − 0.004; P = 0.023).

The restricted cubic spline analyses revealed distinct dose–response patterns for the two primary sleep characteristics (Figure 3). Mean daily sleep time showed a clear nonlinear association with GAD-7 score (P for nonlinearity < 0.001), with the lowest predicted anxiety symptom level at approximately 8 – 8.5 h/day and higher GAD-7 scores at both shorter and longer sleep times. In contrast, the association between sleep variability and GAD-7 score was approximately linear (P for nonlinearity = 0.929), with progressively greater sleep variability associated with higher anxiety symptom levels.

Adiposity and anxiety symptoms

Higher adiposity was also directly associated with higher subsequent anxiety symptom scores (Table 2). Each 1-SD higher BMI was associated with a 0.137-point higher GAD-7 score (95% CI, 0.108 – 0.166; P < 0.001). The

corresponding associations were stronger for waist-to-hip ratio (β = 0.248; 95% CI, 0.212 – 0.284; P < 0.001) and body fat percentage (β=0.164; 95% CI, 0.127 – 0.201; P < 0.001).

Together with the associations of adiposity with sleep variability and of sleep variability with anxiety symptoms, these findings supported further evaluation of sleep variability as a potential intermediate correlate within the temporally ordered adiposity–sleep–anxiety pathway.

Table 2. Associations of adiposity and objectively measured sleep characteristics with anxiety symptoms

Panel A. Adiposity and sleep variability			
Exposure	**N**	**β (95% CI), min**	**P value**
BMI, per 1 SD	61,857	2.959 (2.666, 3.253)	< 0.001
Waist-to-hip ratio, per 1 SD	61,845	2.571 (2.178, 2.965)	< 0.001
Body fat percentage, per 1 SD	61,121	3.773 (3.394, 4.152)	< 0.001
Panel B. Objective sleep characteristics and GAD-7			
Exposure	**N**	**β (95% CI), GAD-7 points**	**P value**
Mean daily sleep time, per 1 SD	61,857	0.070 (0.043, 0.097)	< 0.001
Sleep variability, per 1 SD	61,857	0.082 (0.054, 0.109)	< 0.001
Weekend–weekday difference, per 1 SD	61,857	−0.032 (−0.059, −0.004)	0.023
Panel C. Adiposity and GAD-7			
Exposure	**N**	**β (95% CI), GAD-7 points**	**P value**
BMI, per 1 SD	61,857	0.137 (0.108, 0.166)	< 0.001
Waist-to-hip ratio, per 1 SD	61,845	0.248 (0.212, 0.284)	< 0.001
Body fat percentage, per 1 SD	61,121	0.164 (0.127, 0.201)	< 0.001

Note: β coefficients represent the mean difference in the outcome per 1-SD higher exposure. For Panel A, β coefficients were converted from hours to minutes for interpretability. Models were adjusted for age, sex, ethnicity, Townsend deprivation index, and educational attainment. Robust standard errors were used. GAD-7, 7-item Generalized Anxiety Disorder scale; SD, standard deviation. The nonlinear association between mean daily sleep time and GAD-7 score is presented separately in the restricted cubic spline analysis.

Indirect associations through sleep variability

Sleep variability accounted for a small but statistically supported component of the association between adiposity and subsequent anxiety symptoms (Table 3). For BMI, the estimated indirect association through sleep variability was 0.006 GAD-7 points (95% bootstrap CI, 0.004 – 0.008), corresponding to 4.23% (95% CI, 2.47%–6.46%) of the total association. The indirect association was 0.005 (95% bootstrap CI, 0.003 – 0.007) for waist-to-hip ratio, accounting for 2.08% (95% CI, 1.22%–3.10%) of the total association, and 0.008 (95% bootstrap CI, 0.005 – 0.011) for body fat percentage, accounting for 4.69% (95% CI, 2.77%–7.17%). These estimates were interpreted as temporally ordered indirect associations rather than causal mediation effects.

Table 3. Indirect associations of adiposity with anxiety symptoms through sleep variability

Exposure	N	Path a	Path b	Total association, c	Direct association, c'	Indirect association, a×b	Bootstrap 95% CI	Proportion accounted for, %
BMI	61,857	0.082	0.071	0.137	0.132	0.006	0.004, 0.008	4.23
Waist-to-hip ratio	61,845	0.071	0.073	0.248	0.243	0.005	0.003, 0.007	2.08
Body fat percentage	61,121	0.104	0.074	0.164	0.157	0.008	0.005, 0.011	4.69

Note: Path a represents the association of each adiposity measure with sleep variability; path b represents the association of sleep variability with GAD-7 score conditional on the corresponding adiposity measure; c represents the total adiposity–GAD-7 association; and c' represents the direct association after accounting for sleep variability. Indirect associations were estimated as a×b, with 95% confidence intervals obtained from 2,000 bootstrap resamples. Models were adjusted for age, sex, ethnicity, Townsend deprivation index, and educational attainment. All continuous exposures and sleep variability were standardized. The proportion accounted for was calculated as (a×b)/c ×100%. These estimates are interpreted as temporally ordered indirect associations rather than causal mediation effects.

Shared metabolic signatures of sleep variability and anxiety symptoms

We next examined whether sleep variability and anxiety symptoms were associated with overlapping baseline metabolic profiles. Among 251 baseline NMR metabolic measures, 39 were associated with subsequent sleep variability and 97 with GAD-7 score after false discovery rate correction in BMI-adjusted models (FDR < 0.05; Supplementary Tables S4 and S5). Thirteen metabolic measures were significantly associated with both outcomes and showed concordant directions of association (Figure 4 and Supplementary Table S6).

The shared metabolic signatures were dominated by fatty acid and lipoprotein-related measures. Higher proportions of linoleic acid, polyunsaturated fatty acids, and omega-6 fatty acids relative to total fatty acids, as well as a higher polyunsaturated-to-monounsaturated fatty acid ratio, were associated with both lower sleep variability and lower GAD-7 scores. Conversely, higher saturated fatty acids, monounsaturated fatty acids, total fatty acids, triglycerides in large LDL, triglycerides in LDL, and selected HDL phospholipid measures were associated with both greater sleep variability and higher GAD-7 scores.

Glycoprotein acetyls, an inflammation-related metabolic marker, and 3-hydroxybutyrate were also positively associated with both sleep variability and anxiety symptoms. Overall, all 13 shared metabolic measures showed directionally concordant associations with the two outcomes, identifying a common metabolic pattern spanning fatty acid composition, lipoprotein metabolism, inflammation, and ketone metabolism.

Sensitivity analyses

The main findings were robust across sensitivity analyses. Associations of BMI, waist-to-hip ratio, and body fat percentage with sleep variability were similar in the full analytical cohort and in the primary cohort restricted to participants with accelerometer-derived mean daily sleep time between 4 and 14 h/day (Supplementary Table S2). The association between sleep variability and GAD-7 score was likewise consistent across these analytical populations.

Excluding participants with an ever-recorded hospital diagnosis of obstructive sleep apnea produced little change in the associations of adiposity with sleep variability or in the associations of objective sleep characteristics with anxiety

symptoms (Supplementary Table S3). Associations were also generally consistent across progressively adjusted covariate models (Supplementary Table S1).

Discussion

Principal findings

In this large population-based study integrating baseline adiposity, subsequent accelerometer-derived sleep characteristics, later anxiety symptoms, and baseline NMR metabolic profiling, we identified several interrelated findings. First, higher BMI, waist-to-hip ratio, and body fat percentage were consistently associated with greater day-to-day sleep variability, with evidence of nonlinear dose–response relationships. Second, greater sleep variability was associated with higher subsequent anxiety symptom scores, whereas mean daily sleep time exhibited a nonlinear association with anxiety symptoms. Third, sleep variability statistically accounted for a small proportion of the associations between adiposity and anxiety symptoms, with estimated indirect proportions ranging from approximately 2% to 5%. Finally, we identified 13 baseline NMR metabolic measures associated with both sleep variability and anxiety symptoms after adjustment for BMI and multiple testing. These shared metabolic signatures predominantly involved fatty acid composition and lipoprotein-related measures, together with inflammation-related and ketone body metabolites. Collectively, these findings suggest that sleep variability and metabolic characteristics may provide complementary perspectives on the relationship between adiposity and anxiety symptoms.

Adiposity and day-to-day sleep variability

Our findings extend previous research on obesity and sleep by highlighting day-to-day variability in objectively estimated sleep time as a potentially relevant sleep characteristic. Although the relationships between obesity, short sleep duration, and sleep-disordered breathing have been extensively investigated, comparatively less attention has been given to the consistency of sleep duration across successive days [11]. In the present study, all three adiposity measures were positively associated with sleep variability, suggesting that the observed relationship was not limited to a single measure of body size or fat distribution. The associations with waist-to-hip ratio and body fat percentage further suggest that both central and overall adiposity may be relevant to variations in daily sleep patterns.

Several pathways could plausibly contribute to these associations. Excess adiposity is associated with metabolic dysregulation, low-grade systemic inflammation, and increased risk of sleep-disordered breathing, each of which may influence sleep continuity and daily sleep patterns [12, 13]. Behavioral factors, including irregular schedules, physical inactivity, and dietary habits, may also contribute to both adiposity and sleep variability [14]. However, these pathways were not directly evaluated in the present study, and the observed associations should not be interpreted as evidence that adiposity causes irregular sleep.

The nonlinear associations observed in restricted cubic spline analyses provide additional insight into the relationship between adiposity and sleep variability. Although greater adiposity was generally associated with greater sleep variability, the shape and magnitude of these associations differed across BMI, waist-to-hip ratio, and body fat percentage. These findings suggest that linear models may not fully capture the relationship across the entire adiposity distribution. Nevertheless, the spline results should be interpreted cautiously at the extremes of the exposure distributions, where fewer observations may contribute to wider confidence intervals.

Objective sleep characteristics and anxiety symptoms

The association between greater sleep variability and higher subsequent anxiety symptom scores is consistent with emerging evidence emphasizing the importance of sleep regularity for mental health. Previous studies have

increasingly demonstrated that variability in sleep timing and duration may convey health-related information beyond average sleep duration [15]. In a large UK Biobank cohort, Windred and colleagues reported that objectively measured sleep regularity was strongly associated with mortality risk [3]. More recently, a prospective UK Biobank study found that greater accelerometer-derived sleep regularity was associated with a lower risk of incident anxiety and depression, including among individuals with recommended sleep durations [4]. Our findings complement these observations by demonstrating an association between day-to-day variability in estimated sleep time and subsequent anxiety symptom severity.

An important methodological distinction is that our study quantified sleep variability using the standard deviation of seven daily sleep estimates, whereas previous investigations frequently used the Sleep Regularity Index, which incorporates the consistency of sleep–wake states across consecutive days. These measures capture related but nonidentical dimensions of sleep regularity. Accordingly, our findings should be interpreted as evidence concerning variability in daily sleep time rather than as a direct replication of studies using the Sleep Regularity Index.

We also observed distinct dose–response patterns for mean daily sleep time and sleep variability. Mean daily sleep time exhibited a nonlinear association with anxiety symptoms, with higher GAD-7 scores at both shorter and longer estimated sleep durations. By contrast, sleep variability showed an approximately linear positive association with anxiety symptom scores. These findings suggest that average sleep time and day-to-day variability may represent different dimensions of sleep behavior, each potentially relevant to emotional health.

Several mechanisms may help explain the relationship between variable sleep patterns and anxiety symptoms [16, 17]. Irregular sleep may be accompanied by fluctuations in circadian timing, impaired sleep continuity, and changes in emotional regulation. Experimental evidence also suggests that insufficient or disturbed sleep can increase emotional reactivity and reduce the effectiveness of prefrontal regulatory processes [18]. Conversely, anxiety-related hyperarousal may contribute to unstable sleep patterns, raising the possibility of bidirectional relationships [19]. Although the temporal ordering of measurements in our study reduces some concerns about simultaneity, it does not exclude pre-existing anxiety symptoms or reverse causation [20].

Indirect associations through sleep variability

A notable finding was that sleep variability statistically accounted for a small but consistent proportion of the associations between adiposity and subsequent anxiety symptoms. The estimated indirect proportions were approximately 4.2% for BMI, 2.1% for waist-to-hip ratio, and 4.7% for body fat percentage. Although these proportions were modest, their consistency across different adiposity measures suggests that day-to-day sleep variability may represent one component of the broader relationship between adiposity and psychological health.

The relatively small indirect proportions are also biologically plausible. Associations between adiposity and anxiety symptoms are likely to involve multiple interacting pathways, including metabolic disturbances, systemic inflammation, physical health burden, body image concerns, psychosocial stress, and sleep-related processes [21–23]. Variability in daily sleep time captures only one aspect of sleep behavior and therefore would not be expected to account for the entire association [24].

Importantly, the indirect association analysis was intended to characterize statistical relationships within a temporally ordered observational framework rather than to establish causal mediation. Although adiposity preceded accelerometer assessment and anxiety symptom measurement, unmeasured confounding, pre-existing psychological symptoms, and bidirectional relationships may still influence the estimated pathways. The findings therefore support

the relevance of sleep variability as an intermediate correlate but do not establish that modifying sleep variability would necessarily reduce anxiety symptoms among individuals with greater adiposity.

Shared metabolic signatures of sleep variability and anxiety symptoms

An additional contribution of this study was the identification of shared baseline metabolic signatures associated with both sleep variability and anxiety symptoms. Among 251 NMR metabolic measures, 39 were associated with sleep variability and 97 with anxiety symptom scores after adjustment for BMI and correction for multiple testing. Thirteen measures were associated with both outcomes and exhibited concordant directions of association. These findings suggest that variability in daily sleep time and anxiety symptom severity may be linked to partially overlapping metabolic profiles, although the observed associations do not establish shared causal mechanisms.

Fatty acid composition was particularly prominent among the shared metabolic measures. Higher proportions of linoleic acid, polyunsaturated fatty acids (PUFAs), and omega-6 fatty acids relative to total fatty acids, as well as a higher PUFA-to-monounsaturated fatty acid ratio, were associated with lower sleep variability and lower anxiety symptom scores. Conversely, higher concentrations of saturated fatty acids, monounsaturated fatty acids, and total fatty acids were associated with less favorable profiles for both outcomes. These findings suggest that the relative composition of circulating fatty acids may provide information beyond their absolute concentrations.

The potential relevance of fatty acid composition is supported by previous research linking lipid metabolism to cardiometabolic and psychiatric health. In a large UK Biobank NMR biomarker atlas, Julkunen and colleagues identified widespread associations of circulating metabolic measures, including fatty acid ratios, with diverse disease outcomes [7].

Nevertheless, the present findings should not be interpreted as evidence that particular fatty acids directly protect against or contribute to anxiety symptoms. Circulating fatty acid profiles reflect multiple influences, including diet, endogenous metabolism, adiposity, and other physiological processes [25]. Moreover, the inverse associations observed for omega-6 fatty acid proportions do not necessarily contradict the potential involvement of inflammatory pathways, as individual fatty acid classes and their relative proportions may have different biological implications [26].

Lipoprotein-related measures constituted another major component of the shared metabolic signatures. Higher triglyceride concentrations in LDL and large LDL particles, phospholipids in small HDL, and the proportion of phospholipids within large HDL were associated with both greater sleep variability and higher anxiety symptom scores. These findings indicate that lipoprotein composition, rather than conventional lipid concentrations alone, may be relevant to the metabolic profiles associated with sleep and psychological symptoms [27]. However, the physiological interpretation of individual lipoprotein subclasses remains complex, and their associations may reflect broader metabolic processes rather than independent effects of specific lipid fractions [28].

We additionally identified positive associations involving glycoprotein acetyls (GlycA), an NMR-derived marker of systemic inflammation, and 3-hydroxybutyrate, a circulating ketone body. GlycA reflects signals from circulating glycosylated acute-phase proteins and has been associated with a broad range of adverse health outcomes in population-based metabolomic studies.

Its positive association with both sleep variability and anxiety symptoms is compatible with the possibility that low-grade systemic inflammation contributes to their shared metabolic context. Similarly, the association involving 3-hydroxybutyrate may reflect differences in energy substrate utilization or metabolic adaptation. However, neither inflammatory activity nor ketone metabolism was directly established as a mechanistic pathway in this study.

Importantly, these associations persisted after adjustment for BMI, suggesting that the shared metabolic signatures were not fully explained by differences in overall adiposity. Nevertheless, BMI adjustment does not eliminate confounding by body fat distribution, diet, medication use, or underlying metabolic conditions. In addition, the NMR measures were obtained at baseline, before the accelerometer and anxiety assessments. Consequently, they are more appropriately interpreted as baseline metabolic correlates of later sleep variability and anxiety symptoms rather than metabolic consequences of irregular sleep or mediators of the adiposity–sleep–anxiety association.

Limitations

Several limitations should also be acknowledged. First, the observational design precludes causal inference. Although measurements were temporally ordered, residual confounding, reverse causation, and pre-existing anxiety symptoms could not be excluded. The indirect association estimates should therefore not be interpreted as causal mediation effects. Second, sleep characteristics were derived from seven days of accelerometer-classified daily sleep proportions. These estimates may not correspond directly to conventional nocturnal sleep duration, and the standard deviation of daily sleep time does not capture all dimensions of sleep regularity, including sleep onset timing, wake timing, and fragmentation. The relatively short monitoring period may also limit the representation of habitual long-term sleep patterns. Third, anxiety symptoms were assessed using the GAD-7 questionnaire rather than a structured clinical diagnostic interview. Although the GAD-7 is a validated measure of anxiety symptom severity, it does not establish a clinical diagnosis of an anxiety disorder. Furthermore, the absence of repeated anxiety assessments limited our ability to distinguish newly developed symptoms from persistent or pre-existing symptoms. Fourth, adiposity and NMR metabolic measures were assessed at baseline, whereas sleep and anxiety were measured at later time points. Changes in body composition, metabolic profiles, and other health-related factors during the intervening periods were not captured in the present analysis. Fifth, although multiple covariates were considered, unmeasured factors such as shift work, sleep apnea severity, medication use, dietary patterns, and changes in physical or mental health may have influenced the observed associations. Excluding participants with hospital-recorded sleep apnea cannot fully address undiagnosed or less severe sleep-disordered breathing. Finally, UK Biobank participants are not fully representative of the general population, and the NMR analyses were restricted to participants with available metabolic measurements. Selection bias and limited generalizability should therefore be considered when interpreting the findings.

Conclusions

In this large, temporally ordered observational study, greater adiposity was associated with increased day-to-day variability in accelerometer-derived sleep time, which was in turn associated with higher subsequent anxiety symptom scores. Sleep variability statistically accounted for a small proportion of the adiposity–anxiety association. We further identified 13 baseline NMR metabolic measures shared by sleep variability and anxiety symptoms, predominantly involving fatty acid composition, lipoprotein metabolism, inflammation-related markers, and ketone metabolism. These findings highlight the potential relevance of considering sleep variability alongside average sleep duration when investigating the relationships between adiposity and psychological health. Further longitudinal and interventional studies are needed to determine whether these associations reflect modifiable pathways and to clarify the biological significance of the identified metabolic signatures.

Declarations

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Authors' contributions

YZ: Writing – original draft, Writing – review & editing. WH: Writing – original draft, Writing – review & editing. YW: Writing – original draft. GL: Investigation, Writing – original draft, Writing – review & editing.

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Data Availability Statement

Access to data from UK Biobank (https://www.ukbiobank.ac.uk/) is available upon application.

Ethics approval and consent to participate

UK Biobank has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank approval (REC reference: 16/NW/0274), in accordance with the Declaration of Helsinki. All participants gave written informed consent before enrolled in the study.

Consent for publication

Not applicable.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language polishing, grammar correction, and academic phrasing refinement in the English text. The scientific content, study design, data analysis, interpretation of results, and conclusions were entirely generated and reviewed by the authors. All outputs from the AI tool were carefully reviewed and edited by the authors to ensure accuracy and appropriateness. The authors take full responsibility for the content of the submitted manuscript.

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Figures

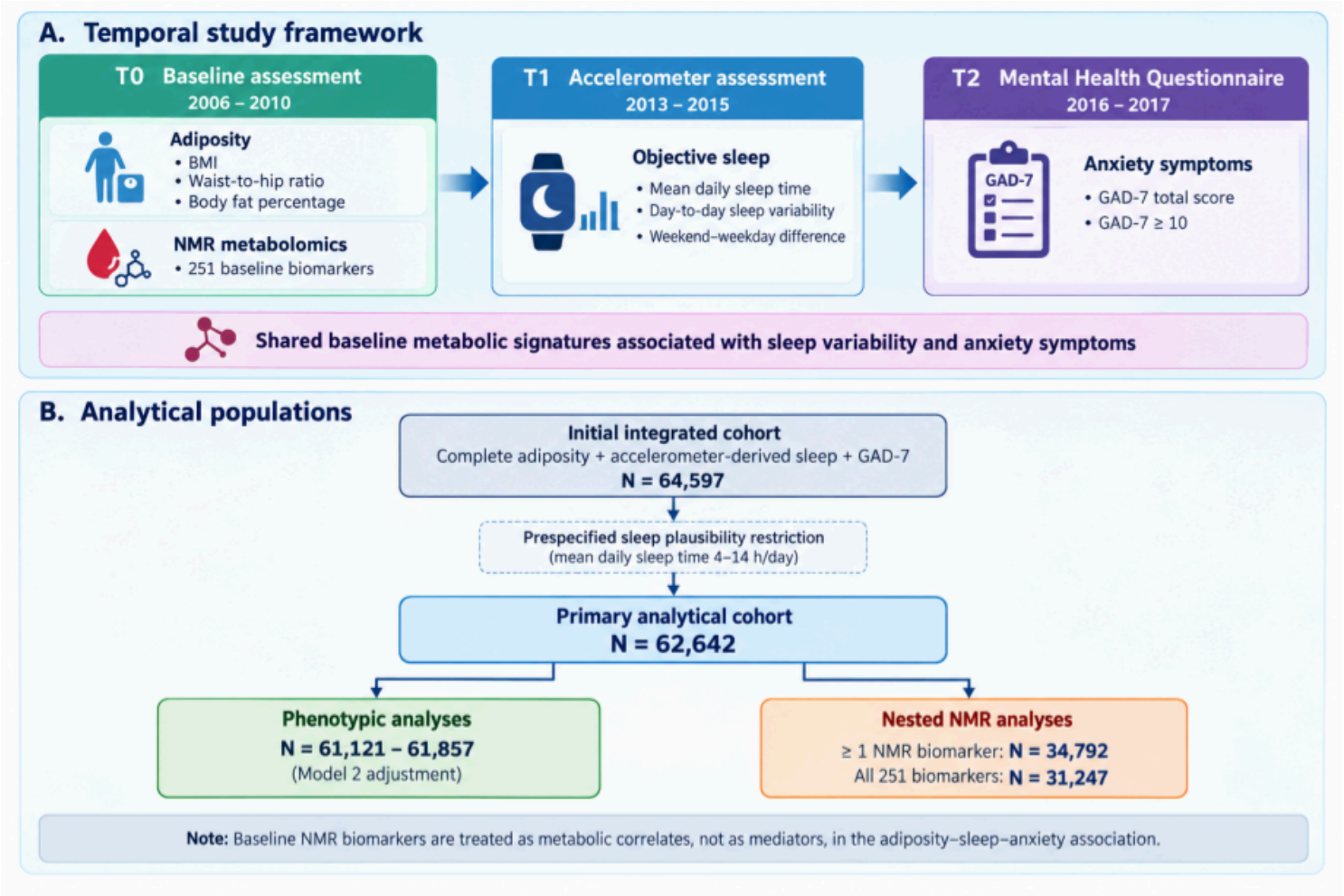


Figure 1

Study design, temporal assessment framework, and analytical populations

Note: Adiposity measures and NMR metabolic biomarkers were assessed at the UK Biobank baseline assessment (T0; 2006–2010). Objective sleep characteristics were subsequently derived from 7-day accelerometer assessments conducted during 2013–2015 (T1), and anxiety symptoms were assessed using the GAD-7 during the online Mental Health Questionnaire in 2016–2017 (T2). The primary analytical cohort included 62,642 participants after applying the prespecified plausibility restriction for accelerometer-derived mean daily sleep time (4–14 h/day). Sample sizes in individual regression models varied because of missing exposure or covariate data. NMR analyses were conducted as

a nested metabolic analysis. NMR biomarkers were evaluated as baseline metabolic phenotypes rather than as mediators in the adiposity–sleep–anxiety pathway. BMI, body mass index; GAD-7, 7-item Generalized Anxiety Disorder scale; NMR, nuclear magnetic resonance.

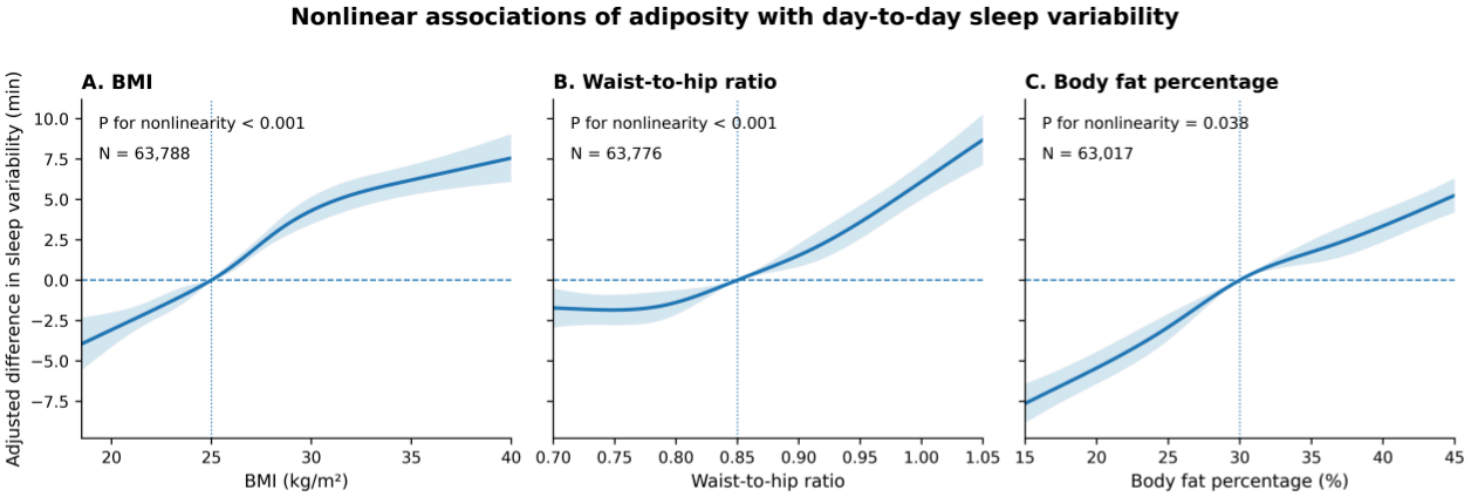


Figure 2

Nonlinear associations of adiposity with day-to-day sleep variability

Note: Restricted cubic spline analyses showing the associations of (A) body mass index, (B) waist-to-hip ratio, and (C) body fat percentage with day-to-day variability in accelerometer-derived daily sleep time. Models were adjusted for age, sex, ethnicity, Townsend deprivation index, and educational attainment. Solid lines represent adjusted differences in sleep variability relative to the prespecified reference values (BMI, 25 kg/m²; waist-to-hip ratio, 0.85; body fat percentage, 30%), and shaded areas indicate 95% confidence intervals. Restricted cubic splines were fitted using five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.

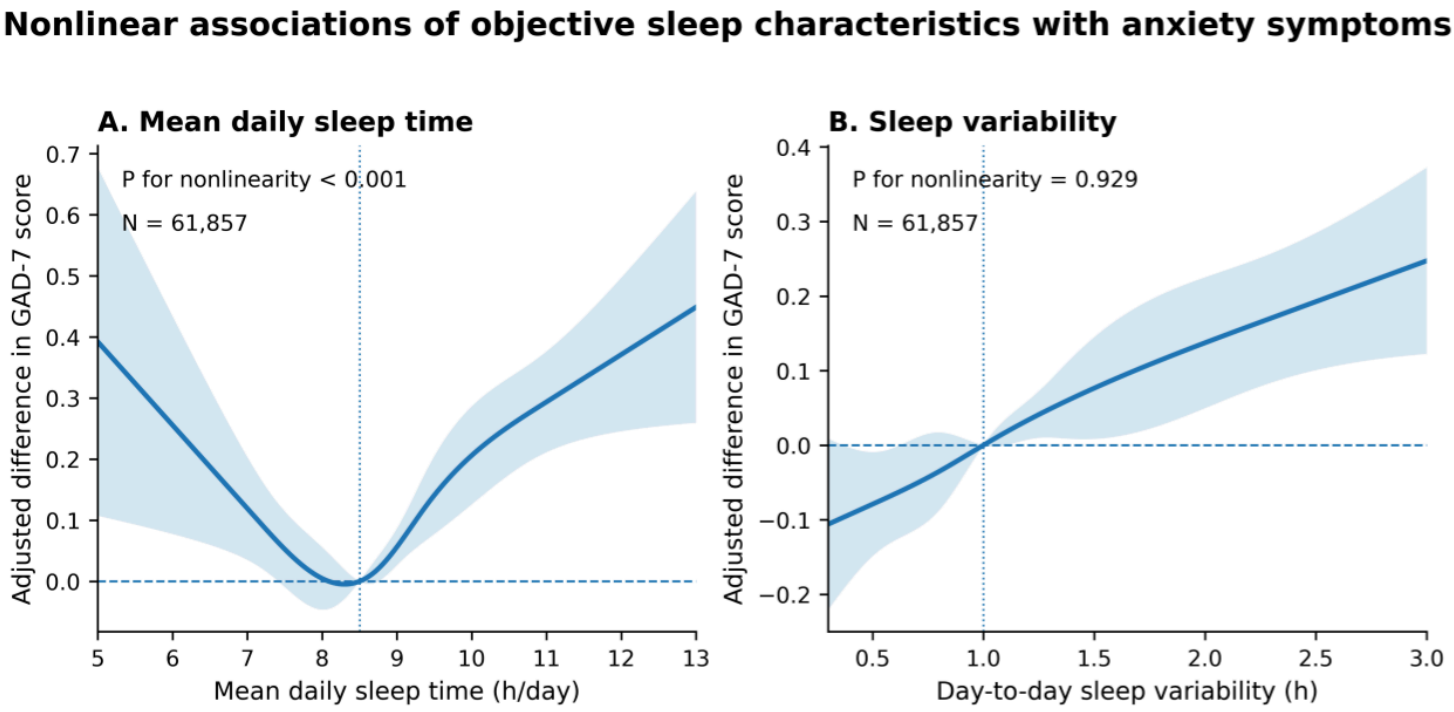


Figure 3

Nonlinear associations of objectively measured sleep characteristics with anxiety symptoms

Note: Restricted cubic spline analyses showing the associations of (A) accelerometer-derived mean daily sleep time and (B) day-to-day sleep variability with GAD-7 score. Models were adjusted for age, sex, ethnicity, Townsend deprivation index, and educational attainment. Solid lines represent adjusted differences in GAD-7 score relative to the reference values of 8.5 h/day for mean daily sleep time and 1.0 h for sleep variability; shaded areas indicate 95% confidence intervals. Restricted cubic splines were fitted using five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.

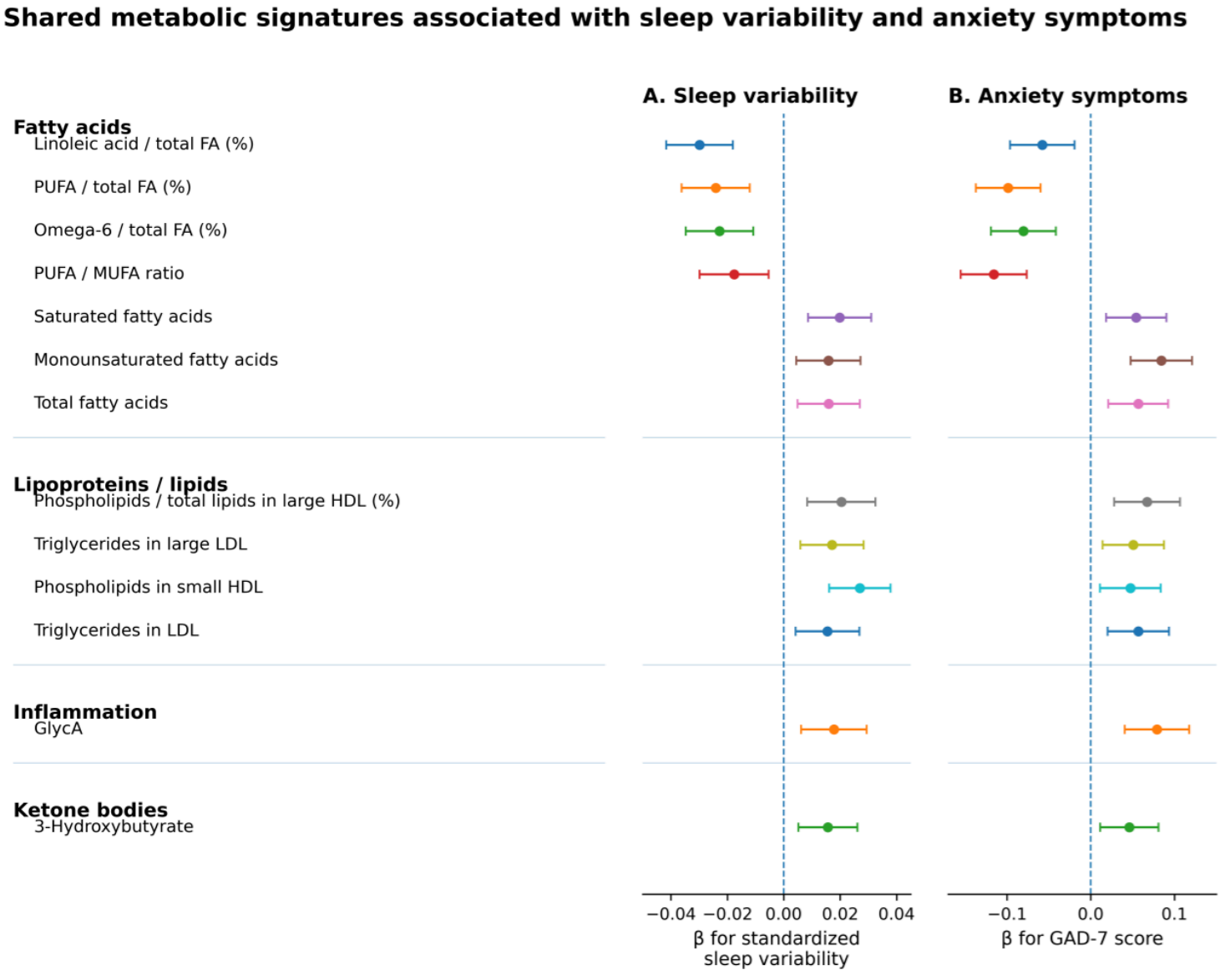


Figure 4

Shared metabolic signatures associated with sleep variability and anxiety symptoms

Note: Forest plots show 13 baseline NMR biomarkers that were significantly associated with both day-to-day sleep variability and GAD-7 score after false-discovery-rate correction in BMI-adjusted models. Models were adjusted for age, sex, ethnicity, Townsend deprivation index, educational attainment, and BMI. In panel A, β coefficients represent differences in standardized sleep variability per 1-SD higher NMR biomarker. In panel B, β coefficients represent

differences in GAD-7 score per 1-SD higher NMR biomarker. Points indicate β coefficients and horizontal bars indicate 95% confidence intervals. All 13 shared biomarkers showed concordant directions of association across the two outcomes.

Supplementary Files

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