Associations Between Sleep Health and Amygdala Reactivity to Negative Facial Expressions in the UK Biobank Cohort (*N* = 25,758)

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Abstract

Background: Sleep health (SH) is considered a key determinant of physiological and psychological human well-being. In line with this, previous studies have found that poor sleep is associated with various psychiatric disorders, in particular with anxiety and depression. Although little is known about the neural mechanisms underlying these associations, recent findings suggest that essential dimensions of SH are associated with altered amygdala reactivity (AR), but evidence to date is inconsistent and reliant on small sample sizes.

Methods: Addressing this problem, the current pre-registered study investigated associations between SH and AR to negative facial expressions in the UK Biobank cohort (25,758 participants). Drawing on a large sample size and consistent data acquisition, five dimensions of SH (insomnia symptoms, sleep duration, daytime sleepiness, chronotype, and sleep medication) were examined.

Results: Exploratory analyses revealed that short sleep duration was associated with decreased AR while neither any of the remaining SH dimensions nor a composite measure of all SH dimensions were associated with AR.

Conclusions: To our knowledge, this is the largest study to test associations between SH and AR. Habitual short sleep duration may be associated with decreased AR, possibly indicating compensation for impaired prefrontal processes and hampered emotion regulation.

Introduction

Sleep has been linked to emotional outcomes in experimental as well as observational studies (e.g., 1). In particular, there is evidence of bidirectional relationships between poor sleep and both depressive and anxiety symptoms (2; 3; 4; 5; 6; 7). Although neural mechanisms underlying these associations have not been reliably identified, a crucial role is ascribed to the amygdala. For example, sleep deprivation studies in healthy participants (8; 9), as well as studies in participants with insomnia / sleep disturbances (10; 11) and depression (12) have proposed that altered processing of emotional stimuli and dysregulated amygdala function play a key role in linking sleep disturbance with emotional outcomes. However, conclusions drawn from previous studies are limited by small sample sizes and variability in study design and methodology (e.g., sleep deprivation vs. case-control studies, task-related vs. resting-state neuroimaging). Furthermore, sleep health, a broader concept combining multiple dimensions of sleep, has not yet been studied in relation to amygdala function.

Sleep Health and Emotional Outcomes

While it is difficult to formulate a clear-cut definition of sleep health (SH), there is a rather consistent pool of heterogeneous variables that have been considered as relevant (e.g., 13; 14; 15). These were first suggested by Buysse in 2014 and include sleep duration, sleep continuity, timing of sleep, daytime sleepiness and sleep satisfaction / quality. This selection rests principally on theoretical considerations deduced from existing definitions of health in general, as well as on previous research examining associations between different sleep measures and health outcomes (16).

Previous studies in large samples have found a range of associations between SH dimensions and health outcomes. For example, both short and long sleep duration were shown to be associated with impaired cognitive performance (17), higher risks of

cardiovascular morbidity (18) and all-cause mortality (19). Difficulties in initiating or maintaining sleep were found to be associated with cardiovascular morbidity and mortality (20; 21), to be a predictor of depression and anxiety disorders (3; 2), and confer risk for suicidal thoughts and behaviors (22). Excessive daytime sleepiness was shown to indicate cardiovascular mortality in elderly subjects (23) and to be a risk factor for depressive symptoms (24). Late chronotype is associated with an increased risk of arterial hypertension (25) and more severe depressive symptoms (26). Beside these mostly epidemiological findings, there are many more research results from well-controlled laboratory studies underlining the importance of SH (for a tabular overview, see 16).

In particular, SH seems to be closely linked to cardiovascular and emotional outcomes. With respect to the latter, Bouwmans et al. (27) found that changes in sleep quality predicted changes in affect as measured by items from the Positive and Negative Affect Schedule (PANAS). Sin et al. (28) observed long sleep duration to predict PANAS scores and Chiang et al. (29) showed poor sleep efficiency to strengthen the association between stress and depressive symptoms. Moreover, a strong link between insomnia and emotional outcomes has been suggested in neuroimaging studies of brain morphometry, activation and connectivity patterns (for a review, see 30; for a broader conceptual embedding, see 31). This apparently close relationship, which is additionally backed by an extensive epidemiological study on genetics in the UK Biobank cohort (32), leads to the question about the specific mechanisms of action underlying the association between SH and emotional outcomes.

The Role of Amygdala Reactivity to Emotional Stimuli

AR can be defined as amygdala activity associated with the presentation of an emotional or otherwise salient stimulus as compared to control stimuli (33). Increased AR is commonly interpreted as amplified emotional response (34). In the following, according

to this interpretation, AR and the term emotional reactivity are referred to as neurobiological and psychological description of the same concept, respectively.

AR has been shown to be associated with at least some aspects of SH in previous studies, for example Prather et al. (35) found bilateral AR towards fearful facial expressions to predict depressive symptoms and higher perceived stress in subjects with poor sleep quality. Baglioni et al. (10) found AR towards insomnia-related stimuli to be increased in patients with insomnia compared to healthy good sleepers. However, this effect was not observed for negative non-sleep-related stimuli. Focusing on AR in the context of overnight system consolidation, Wassing et al. (11) found that restless REM sleep is associated with impaired AR adaptation (no attenuation of AR overnight). Moreover, AR is assumed to be consistently increased in patients with either post-traumatic stress disorder, social anxiety disorder or specific phobia as demonstrated in a meta-analysis by Etkin and Wager (36).

While the link between AR and emotional outcomes has long been documented (37), the link between AR and SH dimensions rests on fewer studies, often focusing on concepts beyond mere emotional reactivity (e.g., 11; 34) and drawing on relatively small sample sizes (e.g., 10; 11). In light of recent criticism of low replicability, insufficient statistical power, and heterogeneity of data acquisition and image processing in neuroimaging studies (38; 39; 40), it must be stated that the association between AR and SH needs further, well-powered investigation.

The UK Biobank: An Epidemiological Approach

The UK Biobank (UKBB) offers a unique opportunity for epidemiological research by providing a very large sample size, consistent data acquisition and state-of-the-art image processing (41; 42; 43). AR has been recorded in the UK Biobank project since functional magnetic resonance imaging (fMRI) was introduced in 2014. The current analysis

examined the independent associations between several SH variables and AR in 25.758 individuals in the UKBB.

Our aims were to assess a) whether SH is associated with AR and b) if distinct SH dimensions differ in their relationships with AR. Our hypothesis was that poor SH is associated with increased AR measured as fMRI responses to negative facial expressions.

Material and Methods

Preregistration

The detailed analysis plan of the current study was officially preregistered at Open Science Framework (https://osf.io/gnrpv?mode=&view_only) on the 14th of May in 2020 at 07:00 AM. The preregistration was verifiably initiated on the 11th of May in 2020 at 02:44 PM and not modified afterwards. Hence, all analysis steps had been specified before the UKBB dataset used in this study was downloaded on the 12th of May in 2020 at 02:33 PM. As a consequence, the current analysis is confirmatory in nature and based on original, a-priori formulated hypotheses.

Participants

The UKBB is a prospective epidemiological study, which enrolled over 500,000 adults aged 37 to 73 years between 2006 and 2010 (41). Multimodal MRI scanning of a subgroup of 100,000 individuals began in 2014 and is set to be completed by 2022. The present study included data from the 2020 data release of functional imaging data (Instance 2: Imaging visit, 2014+), which included 32,915 participants. For the purposes of the present study, participants were excluded if they self-reported a neurological condition (*n* = 843; see Table S1 for a list of conditions) or sleep apnea syndrome (*n* = 133). Furthermore, participants were excluded if they had missing data at Instance 2 for sleep duration (*n* = 254), insomnia symptoms (*n* = 15), daytime sleepiness (*n* = 30), chronotype

(*n* = 2770), socioeconomic status (*n* = 23), Body Mass Index (BMI; *n* = 825), level of education (*n* = 1746) or depressive symptoms (*n* = 518) leaving a sample of 25,758 participants. All UKBB research procedures have been approved by the NHS National Research Ethics Service (Ref. 11 / NW / 0382) and all participants gave written informed consent. Ethical procedures are constantly controlled by a dedicated Ethics Advisory Committee (http://www.ukbiobank.ac.uk/ethics), which has developed a UKBB-specific Ethics and Governance Framework (given in full at https://www.ukbiobank.ac.uk/media/0xsbmfmw/egf.pdf).

Sleep-Related Variables

The aim of the current operationalization of SH was to select available variables in the UKBB (Instance 2) which: a) represent central aspects of SH (see 16), b) provide a high consistency with previous SH studies – in particular with our recent study on sleep health and neurocognitive function (17), and c) exhibit a certain degree of heterogeneity (e.g. nighttime- and daytime-related, quantitative and qualitative information) and therefore draw a multifaceted picture of SH. On that basis, the chosen variables were sleep duration, insomnia symptoms (following the SH dimensions sleep continuity and – to a limited extent – sleep satisfaction / quality), excessive daytime sleepiness, chronotype (following the SH dimension timing of sleep) and sleep medication use.

Sleep duration was assessed by means of the question “About how many hours sleep do you get in every 24 hours? (please include naps)”. Taking account of the U-shaped relation between sleep duration and health outcomes (44), participants were categorized as short sleepers (< 7 hours), normal sleepers (7 – 9 hours) and long sleepers (> 9 hours) based on recent guidelines (45). Insomnia symptoms were assessed by means of the question “Do you have trouble falling asleep at night or do you wake up in the middle of the night?” with responses “never/rarely”, “sometimes” and “usually”.

Participants were categorized as subjects with insomnia symptoms if they answered “usually”, otherwise they were categorized as control subjects without insomnia symptoms. Daytime sleepiness was assessed by the means of the question "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving)" with responses “never/rarely”, “sometimes”, “often” and “all of the time”. Participants were categorized as sleepy if they answered “sometimes” or “often”, they were categorized as non-sleepy if they answered “never/rarely”. No person answered “all of the time”. Insomnia symptoms and daytime sleepiness were dichotomized because the primary aim was to compare participants with and without clinically relevant symptoms. Chronotype was assessed by means of the question “Do you consider yourself to be definitely a ‘morning’ person / more a ‘morning’ than an ‘evening’ person / more an ‘evening’ than a ‘morning’ person / definitely an ‘evening’ person?”. The two middle responses were collapsed into an intermediate chronotype category, permitting comparisons with the early (‘definitely morning’) and late (‘definitely evening’) chronotype category. Sleep medication use (sedatives and hypnotics as specified in Dashti et al., 46; see Table S2 for a complete list) was self-reported to a research nurse and dichotomized into sleep medication use vs. no sleep medication use.

Magnetic Resonance Imaging

Full details of the MRI acquisition protocols, image processing pipeline and image data files for the brain imaging component of the UKBB project have been described previously (42). An official in-depth documentation is available online (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367 and http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977). In the current analysis, fMRI data based upon the Hariri faces / shapes “emotion” task (33; 47) – ‘median blood oxygenation level dependent (BOLD) effect in group-defined (amygdala activation) mask for faces-

shapes contrast' – served as dependent variable. The Hariri task is a widely used paradigm to assess AR to negative facial expressions (e.g., in the Human Connectome Project; 48).

The Hariri faces / shapes "emotion" task was implemented with the psychology software tool E-Prime (49) and comprised two different block types (see Figure 1): In the experimental block type, participants had to match one of two simultaneously presented images of negative emotional stimuli (angry and fearful facial expressions) with an identical target image. In the control block type, participants had to complete a sensorimotor control task (matching geometric shapes). Block types were shown alternately. Procedure details are described in Barch et al. (47). Additionally, the E-Prime script used in the UKBB project can be viewed and downloaded at https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=1462.

FIGURE 1

Covariates

Socioeconomic status was measured by the Townsend index of material deprivation, which was log-transformed due to skewed distribution using an 'ln (x+7)' equation (minimum of non-transformed index: -6.26). Level of education was assessed by means of the question "Which of the following qualifications do you have? (You can select more than one)" with the possibility to specify "College or University degree", "A levels / AS levels or equivalent", "O levels / GCSEs or equivalent", "CSEs or equivalent", "NVQ or HND or HNC or equivalent" and / or "Other professional qualifications, eg: nursing, teaching". The variable was dichotomized into academic training vs. no academic training ("College or University degree" was vs. was not among the given responses). Depressive

symptoms were assessed by means of the question “Over the past two weeks, how often have you felt down, depressed or hopeless?” with responses “not at all”, “several days”, “more than half the days” or “nearly every day”. Participants were categorized as subjects with depressive symptoms if they answered “several days”, “more than half the days” or “nearly every day”, otherwise they were categorized as control subjects without depressive symptoms. Intracranial brain volume (ICV = volume of gray matter + volume of white matter + volume of ventricular cerebrospinal fluid), BMI (continuous), sex (male vs. female) and age (continuous) as well as psychotropic medication use (mood stabilizers, antidepressants, and antipsychotics; see Table S3) were also included as covariates in the analyses. All measures were taken from Instance 2.

Statistical Analysis

The response options “do not know” and “prefer not to answer” were handled as missing values. Mean values and standard deviations were used for descriptive data presentation. The association between SH variables and AR was analyzed using a linear regression model (LM) with sleep duration (3 factor levels with ‘normal sleep duration’ as the reference category), insomnia symptoms (2 factor levels), excessive daytime sleepiness (2 factor levels), chronotype (3 factor levels with the ‘intermediate type’ as the reference category) and sleep medication use (2 factor levels) as predictor variables and the ‘median BOLD effect in group-defined (amygdala activation) mask for faces-shapes contrast’ as dependent variable.

Socioeconomic status, level of education, depressive symptoms, ICV, BMI, sex, age and psychotropic medication use were implemented as covariates. By doing so, all variables were used as described in our preregistration, referring to our previous study on sleep health and neurocognitive function (17). The significance level was set at $\alpha = 0.05$.

Accounting for the principle of parsimony for statistical models, covariates were added gradually starting with a strictly reduced model (insomnia symptoms only), continuing with two moderately adjusted models (first adding basic demographic variables as covariates, then adding all remaining covariates) and ending with a fully adjusted model including all described variables (adding all remaining SH variables, see Table S4). Hereby, the prioritization of insomnia symptoms as sleep-related variable arises from the assumption that subjective difficulties in initiating / maintaining sleep cover multiple aspects of SH, such as sleep satisfaction and – to a limited extent – sleep continuity or efficiency and subjective short sleep duration. The significance of improvement between models was evaluated by partial *F*-tests.

In addition to our pre-registered analysis plan the following sensitivity and exploratory analyses were conducted: a) We cleaned the fMRI data (median BOLD effect for faces-shapes contrast) from zeros, which occurred in an unexpectedly high number (discernible in Figure 3) and may indicate drop out in this specific region of interest (personal communication with UKBB imaging analysis team). b) Accounting for weaknesses arising from the pre-registered, theory-driven analysis plan (coarseness, multicollinearity), a data-driven, stepwise model comparison by the Akaike Information Criterion (AIC) was implemented. For this purpose, the fully adjusted model was chosen as starting point and variables were dropped one by one depending on the explanatory power they add to the model according to the AIC.

Furthermore, we examined c) whether including anxiety as an additional covariate changes the current results, d) whether a composite measure of SH is associated with AR, e) whether operationalizing insomnia symptoms and excessive daytime sleepiness with multiple factor levels (instead of dichotomizing these variables) leads to a different outcome, and f) whether associations between SH and AR are altered when considering

SH stability over years (by using SH data from Instance 0: Initial assessment visit, 2006-2010).

Results

Sample Characteristics

The sample consisted of 13,993 (54.3%) women and 11,765 (45.7%) men with a mean age of 62.9 ± 7.4 years. Further characteristics are presented in Table 1. An overview of mean AR differences between subsamples (depending on factor level constellations of sleep-related variables) is depicted in Figure 2b.

TABLE 1

Main analysis

Once basic demographic variables were added (LM 2), the inclusion of further variables (LM 3 and 4) did not result in a significant increase of explained variance (see Table S5; for an overview of all estimates and p-values, see Table S6). Standardized effect sizes (Cohen's d) and *p*-values for the effects of all independent variables of LM 2 on AR are presented in Figure 2a. According to our analysis, large ICV ($\beta = 5.32 \times 10^{-08}$, $d = 0.04$, $p < 0.001$), high BMI ($\beta = 3.79 \times 10^{-04}$, $d = 0.01$, $p = 0.021$), and low socioeconomic status ($\beta = 2.59 \times 10^{-03}$, $d = 0.01$, $p = 0.050$) were associated with increased AR. High level of education ($\beta = -6.76 \times 10^{-03}$, $d = -0.03$, $p < 0.001$) and old age ($\beta = -1.05 \times 10^{-03}$, $d = -0.07$, $p < 0.001$) were associated with decreased AR. Neither sex ($\beta = 1.94 \times 10^{-03}$, $d = 0.01$, $p = 0.267$) nor insomnia symptoms ($\beta = 3.01 \times 10^{-04}$, $d = 0.00$, $p = 0.843$) were related to AR.

FIGURE 2

FIGURE 3

Sensitivity and Exploratory Analyses

a) Removing zeros from the fMRI data did not change the results of the main or exploratory analyses considerably, while reducing the sample size by 156 participants (see Table S7). b) Testing each variable's individual contribution by the Akaike Information Criterion (AIC) in a stepwise algorithm (50), a new model was obtained (LM 5) – consisting exclusively of variables with a ~~significant~~ relevant increment value~~-~~, as identified by the AIC (see Table S8). Significant associations as reported in LM 2 remained unaffected in LM 5. Short sleep duration was the only SH variable to survive stepwise model comparison. All results of LM 5 are depicted in Table S9. Differences in AR between short sleepers vs. normal sleepers and between participants with vs. without insomnia symptoms are depicted in Figures 3a and b. c) When expanding a LM comprising all sleep-related variables and all covariates by the variable "Worrier / anxious feelings" (UKBB Data-Field 1980: *https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=1980*, Instance 2), effect sizes were slightly altered. However, significant results as reported above remained unchanged (see Table S10). d*)* When replacing all sleep-related variables in the same model by a single composite measure of SH (oriented towards previous research, e.g. 15), no significant association was found (see Table S11). Details on how the composite measure was obtained are provided in Figure S1. e) When assigning multiple factor levels to previously dichotomized SH variables, significant results as reported above remained unchanged. Additionally, we found that participants who answered "often" in the daytime sleepiness item had a decreased AR (β = -1.07 × 10^{-2}, d = -0.01, p = 0.029, see Table S12). f) When assigning time-dependent factor levels to SH variables in the same model,

significant associations were found between stable short sleep duration and decreased AR (β = -5.72 × 10^{-3}, d = -0.02, p = 0.013) as well as between instable long sleep duration and increased AR (β = 7.09 × 10^{-2}, d = 0.01, p = 0.048). All results are depicted in Table S13.

Discussion

The goal of the current analysis was to investigate associations between SH and AR to negative facial expressions in the UKBB cohort (N = 25,758). In the pre-registered analysis, indicators of SH were not associated with AR. Against our hypothesis, exploratory analyses suggested that short sleep duration (compared to normal sleep duration) ~~was~~ may be associated with *decreased* AR.

Sleep Health Variables

Previous research has shown associations between sleep-related variables and amygdala function but sample characteristics, study designs (experimental manipulation vs. case-control studies), and specific methods for data collection and processing have varied considerably in these studies (8; 9; 10; 11; 12; 34). The current study adds to this literature by showing that trait-like individual differences in SH are not associated with AR to negative facial expressions on the epidemiological level. With respect to insomnia symptoms, this finding sheds doubt on theoretical considerations that sleep disruption is associated with amplified emotional reactivity to stimuli of negative valence (1). However, the absence of an association between insomnia and AR to general negative stimuli is in line with some previous case-control studies investigating AR (10; 51).

Testing each variable's individual contribution by the AIC in an exploratory stepwise model comparison yielded that self-reported short sleep duration was associated with decreased AR. To our knowledge, this is a new finding. Experimental sleep deprivation, in

contrast, has been shown to result in *increased* AR (8; 9). Likewise, most studies suggest that experimental sleep deprivation (beyond a therapeutic context) leads to increased emotional reactivity on the behavioral level (52). In addition, acute and chronic sleep loss have been shown to be associated with sustained attention towards negative stimuli (53), reduced capacity for cognitive reappraisal strategies (54), and with impaired prefrontal brain functions related to emotion regulation (55; 56; 57). In particular, brain connectivity within and between prefrontal and subcortical areas cease to function properly under REM sleep loss (57; 34). In light of these findings, the association between *habitual* short sleep duration and decreased AR may protect the short sleeper against emotional overwhelming. This hypothesis is further supported by our exploratory analysis revealing that only stable short sleep duration (over years) is associated with decreased AR.

Covariates

The observed associations between the covariates and AR are mostly in line with previous empirical research and theoretical assumptions. Low socioeconomic status, which includes a low level of education, has been shown before to be associated with increased AR to negative stimuli (58). The association between older age and decreased AR to negative stimuli is also in line with previous evidence (59) and adds to literature reporting that the impact of negative information on attention and memory processes decreases during adulthood (60). To our knowledge, associations between BMI and AR have not been systematically investigated so far. However, negative emotions have been shown to play an important role in the development of obesity (61). The lack of association between depressive symptoms and AR is surprising and, thus, presented in detail in Tamm et al. (62).

Limitations

The following limitations need to be addressed: a) All SH variables were assessed by means of a single question. This circumstance might bring with it an increased degree of imprecision in operationalization. However, for example, single items on insomnia symptoms have a high accuracy of discriminating insomnia cases from controls (63). Moreover, due to the large sample size provided by the UKBB cohort, statistical power to detect even small effect sizes was still guaranteed in heavily contaminated group comparisons (e.g. healthy controls falsely classified as patients with insomnia). b) Since the current analysis is an epidemiological approach, subsample sizes were not adjusted. Consequently, subsamples defined by a characteristic of low prevalence were smaller, thus resulting in a higher uncertainty of statistical estimates. c) The sample consisted predominantly of older adults, which reduces the generalizability of the results. d) The UKBB does not provide data on performance in the Hariri task (e.g., reaction times, percentage of correct responses). Hence, it cannot be ruled out that different levels of vigilance or attention both between- and within-subjects had an impact on the current results.

Outlook and Conclusions

The current analysis and previous evidence clearly demonstrate that it is important to differentiate between habitual short sleep duration, acute sleep loss and insomnia when investigating AR. For future research, it might be of particular interest to examine longitudinally if AR decreases over time under persisting short sleep duration. Additionally, it may be worthwhile to investigate higher order, non-linear associations between SH dimensions and AR as well as more complex associations using latent class or machine learning approaches. It may also be of interest to investigate associations between SH and cortical structures involved in the regulation of emotional reactivity. In particular, further research on functional and structural connectivity between the prefrontal cortex and the

limbic system might help to integrate the current findings on SH and AR into established neurobiological models (64).

Concluding, our results (based on a large sample size, consistent methods, and a pre-registered analysis plan) suggest that a) short sleep duration may be associated with decreased AR, possibly indicating compensation for impaired prefrontal processes and hampered emotion regulation, and b) other SH dimensions are not associated with AR.

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References

1 Baglioni C, Spiegelhalder K, Lombardo C, Riemann D (2010): Sleep and emotions: a focus on insomnia. *Sleep Medicine Reviews* 14: 227-238.

2 Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, *et al.* (2011): Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders* 135: 10-19.

3 Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A, *et al.* (2019): Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Medicine Reviews* 43: 96-105.

4 Pigeon WR, Hegel M, Unützer J, Fan MY, Sateia MJ, Lyness JM, *et al.* (2008): Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort?. *Sleep* 31: 481-488.

5 Lustberg L, Reynolds III CF (2000): Depression and insomnia: questions of cause and effect. *Sleep Medicine Reviews* 4: 253-262.

6 Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, *et al.* (2016): Sleep and mental disorders: a meta-analysis of polysomnographic research. *Psychological Bulletin* 142: 969.

7 Riemann D, Krone LB, Wulff K, Nissen C (2020): Sleep, insomnia, and depression. *Neuropsychopharmacology* 45: 74-89.

8 Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP (2007): The human emotional brain without sleep – a prefrontal amygdala disconnect. *Current Biology* 17: R877-R878.

9 Motomura Y, Kitamura S, Oba K, Terasawa Y, Enomoto M, Katayose Y, *et al.* (2013): Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PloS One* 8: e56578.

10 Baglioni C, Spiegelhalder K, Regen W, Feige B, Nissen C, Lombardo C, *et al.* (2014): Insomnia disorder is associated with increased amygdala reactivity to insomnia-related stimuli. *Sleep* 37: 1907-1917.

11 Wassing R, Lakbila-Kamal O, Ramautar JR, Stoffers D, Schalkwijk F, Van Someren EJ (2019): Restless REM sleep impedes overnight amygdala adaptation. *Current Biology* 29: 2351-2358.

12 Klumpp H, Hosseini B, Phan KL (2018): Self-reported sleep quality modulates amygdala resting-state functional connectivity in anxiety and depression. *Frontiers in Psychiatry* 9: 220.

13 Furihata R, Hall MH, Stone KL, Ancoli-Israel S, Smagula SF, Cauley JA, *et al.* (2017): An aggregate measure of sleep health is associated with prevalent and incident clinically significant depression symptoms among community-dwelling older women. *Sleep* 40: zsw075.

14 Brindle RC, Cribbet MR, Samuelsson LB, Gao C, Frank E, Krafty RT, *et al.* (2018): The relationship between childhood trauma and poor sleep health in adulthood. *Psychosomatic Medicine* 80: 200.

15 Dong L, Martinez AJ, Buysse DJ, Harvey AG (2019): A composite measure of sleep health predicts concurrent mental and physical health outcomes in adolescents prone to eveningness. *Sleep Health* 5: 166-174.

16 Buysse DJ (2014): Sleep health: can we define it? Does it matter?. *Sleep* 37: 9-17.

17 Kyle SD, Sexton CE, Feige B, Luik AI, Lane J, Saxena R, *et al.* (2017): Sleep and cognitive performance: cross-sectional associations in the UK Biobank. *Sleep Medicine* 38: 85-91.

18 Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA (2011): Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *European Heart Journal* 32: 1484-1492.

19 Liu TZ, Xu C, Rota M, Cai H, Zhang C, Shi MJ, *et al.* (2017): Sleep duration and risk of all-cause mortality: a flexible, non-linear, meta-regression of 40 prospective cohort studies. *Sleep Medicine Reviews* 32: 28-36.

20 Li M, Zhang XW, Hou WS, Tang ZY (2014): Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. *International Journal of Cardiology* 176: 1044-1047.

21 Meng L, Zheng Y, Hui R (2013): The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertension Research* 36: 985-995.

22 Pigeon WR, Pinquart M, Conner K (2012): Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *The Journal of Clinical Psychiatry* 73: 1160-1167.

23 Empana JP, Dauvilliers Y, Dartigues JF, Ritchie K, Gariepy J, Jouven X, *et al.* (2009): Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the three city study. *Stroke* 40: 1219-1224.

24 Jaussent I, Bouyer J, Ancelin ML, Akbaraly T, Peres K, Ritchie K, *et al.* (2011): Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep* 34: 1103-1110.

25 Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, *et al.* (2013): Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiology International* 30: 470-477.

26 Au J, Reece J (2017): The relationship between chronotype and depressive symptoms: a meta-analysis. *Journal of Affective Disorders* 218: 93-104.

27 Bouwmans ME, Bos EH, Hoenders HR, Oldehinkel AJ, de Jonge P (2017): Sleep quality predicts positive and negative affect but not vice versa. An electronic diary study in depressed and healthy individuals. *Journal of Affective Disorders* 207: 260-267.

28 Sin NL, Almeida DM, Crain TL, Kossek EE, Berkman LF, Buxton OM (2017): Bidirectional, temporal associations of sleep with positive events, affect, and stressors in daily life across a week. *Annals of Behavioral Medicine* 51: 402-415.

29 Chiang JJ, Kim JJ, Almeida DM, Bower JE, Dahl RE, Irwin MR, *et al.* (2017): Sleep efficiency modulates associations between family stress and adolescent depressive symptoms and negative affect. *Journal of Adolescent Health* 61: 501-507.

30 Schiel JE, Holub F, Petri R, Leerssen J, Tamm S, Tahmasian M, *et al.* (2020): Affect and arousal in insomnia: through a lens of neuroimaging studies. *Current Psychiatry Reports* 22: 1-8.

31 Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, Nissen C (2010): The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Medicine Reviews* 14: 19-31.

32 Lane JM, Jones SE, Dashti HS, Wood AR, Aragam KG, van Hees VT, *et al.* (2019): Biological and clinical insights from genetics of insomnia symptoms. *Nature Genetics* 51: 387-393.

33 Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR (2002): The amygdala response to emotional stimuli: a comparison of faces and scenes. *NeuroImage* 17: 317-323.

34 Van Der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP (2011): REM sleep depotentiates amygdala activity to previous emotional experiences. *Current Biology* 21: 2029-2032.

35 Prather AA, Bogdan R, Hariri AR (2013): Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. *Psychosomatic Medicine* 75: 350.

36 Etkin A, Wager TD (2007): Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* 164: 1476-1488.

37 Zald DH (2003): The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews* 41: 88-123.

38 Spiegelhalder K, Regen W, Baglioni C, Nissen C, Riemann D, Kyle SD (2015): Neuroimaging insights into insomnia. *Current Neurology and Neuroscience Reports* 15: 9.

39 Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafò MR (2013): Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience* 14: 365-376.

40 Nord CL, Valton V, Wood J, Roiser JP (2017): Power-up: a reanalysis of 'power failure' in neuroscience using mixture modeling. *Journal of Neuroscience* 37: 8051-8061.

41 Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, *et al.* (2015): UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *Plos Med* 12: e1001779.

42 Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, *et al.* (2016): Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neuroscience* 19: 1523-1536.

43 Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JL, Griffanti L, Douaud G, *et al.* (2018): Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *NeuroImage* 166: 400-424.

44 Alvarez GG, Ayas NT (2004): The impact of daily sleep duration on health: a review of the literature. *Progress in Cardiovascular Nursing* 19: 56-59.

45 Consensus Conference Panel, Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, *et al.* (2015): Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Journal of Clinical Sleep Medicine* 11: 591-592.

46 Dashti HS, Jones SE, Wood AR, Lane JM, Van Hees VT, Wang H, *et al.* (2019): Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nature Communications* 10: 1-12.

47 Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, *et al.* (2013): Function in the human connectome: task-fMRI and individual differences in behavior. *NeuroImage* 80: 169-189.

48 Elam JS, Glasser MF, Harms MP, Sotiropoulos SN, Andersson JL, Burgess GC, *et al.* (2021): The Human Connectome Project: A retrospective. *NeuroImage* 244: 118543.

49 Taylor PJ, Marsh JE (2017): E-Prime (Software). *The International Encyclopedia of Communication Research Methods* 1-3.

50 Hu S (2007): Akaike information criterion. *Center for Research in Scientific Computation* 93.

51 Wassing R, Schalkwijk F, Lakbila-Kamal O, Ramautar JR, Stoffers D, Mutsaerts HJ, *et al.* (2019): Haunted by the past: old emotions remain salient in insomnia disorder. *Brain* 142: 1783-1796.

52 Beattie L, Kyle SD, Espie CA, Biello SM (2015): Social interactions, emotion and sleep: A systematic review and research agenda. *Sleep Medicine Reviews* 24: 83-100.

53 Cote K, Jancsar C, Hunt B (2015): Event-related neural response to emotional picture stimuli following sleep deprivation. *Psychology & Neuroscience* 8: 102.

54 Mauss IB, Troy AS, LeBourgeois MK (2013): Poorer sleep quality is associated with lower emotion-regulation ability in a laboratory paradigm. *Cognition & Emotion* 27: 567-576.

55 Palmer CA, Alfano CA (2017): Sleep and emotion regulation: an organizing, integrative review. *Sleep Medicine Reviews* 31, 6-16.

56 Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, *et al.* (2000): Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research* 9: 335-352.

57 Verweij IM, Romeijn N, Smit DJ, Piantoni G, Van Someren EJ, van der Werf YD (2014): Sleep deprivation leads to a loss of functional connectivity in frontal brain regions. *BMC Neuroscience* 15: 1-10.

58 Farah MJ (2017): The neuroscience of socioeconomic status: Correlates, causes, and consequences. *Neuron* 96: 56-71.

59 Leclerc CM, Kensinger EA (2011): Neural processing of emotional pictures and words: A comparison of young and older adults. *Developmental Neuropsychology* 36: 519-538.

60 Mather M (2016): The affective neuroscience of aging. *Annual Review of Psychology* 67: 213-238.

61 Leehr EJ, Krohmer K, Schag K, Dresler T, Zipfel S, Giel KE (2015): Emotion regulation model in binge eating disorder and obesity-a systematic review. *Neuroscience & Biobehavioral Reviews* 49: 125-134.

62 Tamm S, Harmer CJ, Schiel JE, Holub F, Rutter MK, Spiegelhalder K, *et al.* (in press): Amygdala responses to negative faces are not associated with depressive symptoms: cross-sectional data from 28 638 individuals in the UK Biobank cohort. *American Journal of Psychiatry*.

63 Hammerschlag AR, Stringer S, De Leeuw CA, Sniekers S, Taskesen E, Watanabe K, *et al.* (2017): Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nature Genetics* 49: 1584-1592.

64 Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U (2014): Neural network of cognitive emotion regulation – an ALE meta-analysis and MACM analysis. *NeuroImage* 87: 345-355.

Appendix

TABLE S1 – S13

FIGURE S1

Tables / Legends for Figures

Figure 1. Setup of the Hariri faces / shapes “emotion” task as used in the UKBB project. Top left: Exemplary trial (experimental block) depicting male, fearful facial expressions. Top right: Exemplary trial (experimental block) depicting female, angry facial expressions. Bottom left: Exemplary trial (control block) depicting neutral figures. Bottom right: Illustration of how participants had to give their responses (right hand; index finger = left option, middle finger = right option).

Table 1
Sample Characteristics

	Short, *n* (%)	Normal, *n* (%)	Long, *n* (%)
Sleep duration	6,114 (23.7)	19,367 (75.2)	277 (1.1)
	Early, *n* (%)	Intermediate, *n* (%)	Late, *n* (%)
Chronotype	7,190 (27.9)	16,141 (62.7)	2,427 (9.4)
	Yes, *n* (%)	No, *n* (%)	
Insomnia symptoms	8,061 (31.3)	17,697 (68.7)	
Excessive daytime sleepiness	5,672 (22.0)	20,086 (78.0)	
Sleep medication use	144 (0.6)	25,614 (99.4)	
Psych. medication use	2210 (8.6)	23,548 (91.4)	
Depressive symptoms	4,544 (17.6)	21,214 (82.4)	

Figure 2. **A** Overview of all results from LM 2, depicted as standardized effect sizes (Cohen’s *d*: vertical, colored labels) and *p*-values (-log10, y-axis). Complete results from LM 1-4 are depicted in Table S6. Blue color indicates a negative effect size, red color indicates a positive effect size, gray color indicates an effect size close to zero ($-0.01 > d > 0.01$). The horizontal, gray dotted line visualizes the significance level $\alpha = 0.05$ (-log10) set for this analysis. **B** Illustration of mean AR increase / decrease in subsamples (vs. control samples) depending on factor level constellations of sleep-related variables (mean AR subsample minus mean AR control sample). SDS = sleep duration (short), SDL = sleep duration (long),

INS = insomnia symptoms, EDS = excessive daytime sleepiness, CE = chronotype (early), CL = chronotype (late), SM = sleep medication.

Figure 3. Boxplots (medians, quartiles, 5% and 95% quantiles) of the sleep-related variables **A** sleep duration (normal vs. short; $t(10249) = 2.0$, $p = 0.045$) on the left and **B** insomnia symptoms (no vs. yes; $t(15618) = 0.7$, $p = 0.491$) on the right. The violet point clouds in the background depict individual measured values, providing a more differentiated visualization of the underlying distribution.

Associations Between Sleep Health and Amygdala Reactivity to Negative Facial Expressions in the UK Biobank Cohort (*N* = 25,758)

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SLEEP HEALTH, AMYGDALA REACTIVITY, UK BIOBANK,
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Abstract

Background: Sleep health (SH) is considered a key determinant of physiological and psychological human well-being. In line with this, previous studies have found that poor sleep is associated with various psychiatric disorders, in particular with anxiety and depression. Although little is known about the neural mechanisms underlying these associations, recent findings suggest that essential dimensions of SH are associated with altered amygdala reactivity (AR), but evidence to date is inconsistent and reliant on small sample sizes.

Methods: Addressing this problem, the current pre-registered study investigated associations between SH and AR to negative facial expressions in the UK Biobank cohort (25,758 participants). Drawing on a large sample size and consistent data acquisition, five dimensions of SH (insomnia symptoms, sleep duration, daytime sleepiness, chronotype, and sleep medication) were examined.

Results: Exploratory analyses revealed that short sleep duration was associated with decreased AR while neither any of the remaining SH dimensions nor a composite measure of all SH dimensions were associated with AR.

Conclusions: To our knowledge, this is the largest study to test associations between SH and AR. Habitual short sleep duration may be associated with decreased AR, possibly indicating compensation for impaired prefrontal processes and hampered emotion regulation.

Introduction

Sleep has been linked to emotional outcomes in experimental as well as observational studies (e.g., 1). In particular, there is evidence of bidirectional relationships between poor sleep and both depressive and anxiety symptoms (2; 3; 4; 5; 6; 7). Although neural mechanisms underlying these associations have not been reliably identified, a crucial role is ascribed to the amygdala. For example, sleep deprivation studies in healthy participants (8; 9), as well as studies in participants with insomnia / sleep disturbances (10; 11) and depression (12) have proposed that altered processing of emotional stimuli and dysregulated amygdala function play a key role in linking sleep disturbance with emotional outcomes. However, conclusions drawn from previous studies are limited by small sample sizes and variability in study design and methodology (e.g., sleep deprivation vs. case-control studies, task-related vs. resting-state neuroimaging). Furthermore, sleep health, a broader concept combining multiple dimensions of sleep, has not yet been studied in relation to amygdala function.

Sleep Health and Emotional Outcomes

While it is difficult to formulate a clear-cut definition of sleep health (SH), there is a rather consistent pool of heterogeneous variables that have been considered as relevant (e.g., 13; 14; 15). These were first suggested by Buysse in 2014 and include sleep duration, sleep continuity, timing of sleep, daytime sleepiness and sleep satisfaction / quality. This selection rests principally on theoretical considerations deduced from existing definitions of health in general, as well as on previous research examining associations between different sleep measures and health outcomes (16).

Previous studies in large samples have found a range of associations between SH dimensions and health outcomes. For example, both short and long sleep duration were shown to be associated with impaired cognitive performance (17), higher risks of

cardiovascular morbidity (18) and all-cause mortality (19). Difficulties in initiating or maintaining sleep were found to be associated with cardiovascular morbidity and mortality (20; 21), to be a predictor of depression and anxiety disorders (3; 2), and confer risk for suicidal thoughts and behaviors (22). Excessive daytime sleepiness was shown to indicate cardiovascular mortality in elderly subjects (23) and to be a risk factor for depressive symptoms (24). Late chronotype is associated with an increased risk of arterial hypertension (25) and more severe depressive symptoms (26). Beside these mostly epidemiological findings, there are many more research results from well-controlled laboratory studies underlining the importance of SH (for a tabular overview, see 16).

In particular, SH seems to be closely linked to cardiovascular and emotional outcomes. With respect to the latter, Bouwmans et al. (27) found that changes in sleep quality predicted changes in affect as measured by items from the Positive and Negative Affect Schedule (PANAS). Sin et al. (28) observed long sleep duration to predict PANAS scores and Chiang et al. (29) showed poor sleep efficiency to strengthen the association between stress and depressive symptoms. Moreover, a strong link between insomnia and emotional outcomes has been suggested in neuroimaging studies of brain morphometry, activation and connectivity patterns (for a review, see 30; for a broader conceptual embedding, see 31). This apparently close relationship, which is additionally backed by an extensive epidemiological study on genetics in the UK Biobank cohort (32), leads to the question about the specific mechanisms of action underlying the association between SH and emotional outcomes.

The Role of Amygdala Reactivity to Emotional Stimuli

AR can be defined as amygdala activity associated with the presentation of an emotional or otherwise salient stimulus as compared to control stimuli (33). Increased AR is commonly interpreted as amplified emotional response (34). In the following, according

to this interpretation, AR and the term emotional reactivity are referred to as neurobiological and psychological description of the same concept, respectively.

AR has been shown to be associated with at least some aspects of SH in previous studies, for example Prather et al. (35) found bilateral AR towards fearful facial expressions to predict depressive symptoms and higher perceived stress in subjects with poor sleep quality. Baglioni et al. (10) found AR towards insomnia-related stimuli to be increased in patients with insomnia compared to healthy good sleepers. However, this effect was not observed for negative non-sleep-related stimuli. Focusing on AR in the context of overnight system consolidation, Wassing et al. (11) found that restless REM sleep is associated with impaired AR adaptation (no attenuation of AR overnight). Moreover, AR is assumed to be consistently increased in patients with either post-traumatic stress disorder, social anxiety disorder or specific phobia as demonstrated in a meta-analysis by Etkin and Wager (36).

While the link between AR and emotional outcomes has long been documented (37), the link between AR and SH dimensions rests on fewer studies, often focusing on concepts beyond mere emotional reactivity (e.g., 11; 34) and drawing on relatively small sample sizes (e.g., 10; 11). In light of recent criticism of low replicability, insufficient statistical power, and heterogeneity of data acquisition and image processing in neuroimaging studies (38; 39; 40), it must be stated that the association between AR and SH needs further, well-powered investigation.

The UK Biobank: An Epidemiological Approach

The UK Biobank (UKBB) offers a unique opportunity for epidemiological research by providing a very large sample size, consistent data acquisition and state-of-the-art image processing (41; 42; 43). AR has been recorded in the UK Biobank project since functional magnetic resonance imaging (fMRI) was introduced in 2014. The current analysis

examined the independent associations between several SH variables and AR in 25.758 individuals in the UKBB.

Our aims were to assess a) whether SH is associated with AR and b) if distinct SH dimensions differ in their relationships with AR. Our hypothesis was that poor SH is associated with increased AR measured as fMRI responses to negative facial expressions.

Material and Methods

Preregistration

The detailed analysis plan of the current study was officially preregistered at Open Science Framework (https://osf.io/gnrpv?mode=&view_only) on the 14th of May in 2020 at 07:00 AM. The preregistration was verifiably initiated on the 11th of May in 2020 at 02:44 PM and not modified afterwards. Hence, all analysis steps had been specified before the UKBB dataset used in this study was downloaded on the 12th of May in 2020 at 02:33 PM. As a consequence, the current analysis is confirmatory in nature and based on original, a-priori formulated hypotheses.

Participants

The UKBB is a prospective epidemiological study, which enrolled over 500,000 adults aged 37 to 73 years between 2006 and 2010 (41). Multimodal MRI scanning of a subgroup of 100,000 individuals began in 2014 and is set to be completed by 2022. The present study included data from the 2020 data release of functional imaging data (Instance 2: Imaging visit, 2014+), which included 32,915 participants. For the purposes of the present study, participants were excluded if they self-reported a neurological condition (n = 843; see Table S1 for a list of conditions) or sleep apnea syndrome (n = 133). Furthermore, participants were excluded if they had missing data at Instance 2 for sleep duration (n = 254), insomnia symptoms (n = 15), daytime sleepiness (n = 30), chronotype

(*n* = 2770), socioeconomic status (*n* = 23), Body Mass Index (BMI; *n* = 825), level of education (*n* = 1746) or depressive symptoms (*n* = 518) leaving a sample of 25,758 participants. All UKBB research procedures have been approved by the NHS National Research Ethics Service (Ref. 11 / NW / 0382) and all participants gave written informed consent. Ethical procedures are constantly controlled by a dedicated Ethics Advisory Committee (http://www.ukbiobank.ac.uk/ethics), which has developed a UKBB-specific Ethics and Governance Framework (given in full at https://www.ukbiobank.ac.uk/media/0xsbmfmw/egf.pdf).

Sleep-Related Variables

The aim of the current operationalization of SH was to select available variables in the UKBB (Instance 2) which: a) represent central aspects of SH (see 16), b) provide a high consistency with previous SH studies – in particular with our recent study on sleep health and neurocognitive function (17), and c) exhibit a certain degree of heterogeneity (e.g. nighttime- and daytime-related, quantitative and qualitative information) and therefore draw a multifaceted picture of SH. On that basis, the chosen variables were sleep duration, insomnia symptoms (following the SH dimensions sleep continuity and – to a limited extent – sleep satisfaction / quality), excessive daytime sleepiness, chronotype (following the SH dimension timing of sleep) and sleep medication use.

Sleep duration was assessed by means of the question “About how many hours sleep do you get in every 24 hours? (please include naps)”. Taking account of the U-shaped relation between sleep duration and health outcomes (44), participants were categorized as short sleepers (< 7 hours), normal sleepers (7 – 9 hours) and long sleepers (> 9 hours) based on recent guidelines (45). Insomnia symptoms were assessed by means of the question “Do you have trouble falling asleep at night or do you wake up in the middle of the night?” with responses “never/rarely”, “sometimes” and “usually”.

Participants were categorized as subjects with insomnia symptoms if they answered “usually”, otherwise they were categorized as control subjects without insomnia symptoms. Daytime sleepiness was assessed by the means of the question "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving)" with responses “never/rarely”, “sometimes”, “often” and “all of the time”. Participants were categorized as sleepy if they answered “sometimes” or “often”, they were categorized as non-sleepy if they answered “never/rarely”. No person answered “all of the time”. Insomnia symptoms and daytime sleepiness were dichotomized because the primary aim was to compare participants with and without clinically relevant symptoms. Chronotype was assessed by means of the question “Do you consider yourself to be definitely a ‘morning’ person / more a ‘morning’ than an ‘evening’ person / more an ‘evening’ than a ‘morning’ person / definitely an ‘evening’ person?”. The two middle responses were collapsed into an intermediate chronotype category, permitting comparisons with the early (‘definitely morning’) and late (‘definitely evening’) chronotype category. Sleep medication use (sedatives and hypnotics as specified in Dashti et al., 46; see Table S2 for a complete list) was self-reported to a research nurse and dichotomized into sleep medication use vs. no sleep medication use.

Magnetic Resonance Imaging

Full details of the MRI acquisition protocols, image processing pipeline and image data files for the brain imaging component of the UKBB project have been described previously (42). An official in-depth documentation is available online (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367 and http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977). In the current analysis, fMRI data based upon the Hariri faces / shapes “emotion” task (33; 47) – ‘median blood oxygenation level dependent (BOLD) effect in group-defined (amygdala activation) mask for faces-

shapes contrast' – served as dependent variable. The Hariri task is a widely used paradigm to assess AR to negative facial expressions (e.g., in the Human Connectome Project; 48).

The Hariri faces / shapes "emotion" task was implemented with the psychology software tool E-Prime (49) and comprised two different block types (see Figure 1): In the experimental block type, participants had to match one of two simultaneously presented images of negative emotional stimuli (angry and fearful facial expressions) with an identical target image. In the control block type, participants had to complete a sensorimotor control task (matching geometric shapes). Block types were shown alternately. Procedure details are described in Barch et al. (47). Additionally, the E-Prime script used in the UKBB project can be viewed and downloaded at https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=1462.

FIGURE 1

Covariates

Socioeconomic status was measured by the Townsend index of material deprivation, which was log-transformed due to skewed distribution using an 'ln (x+7)' equation (minimum of non-transformed index: -6.26). Level of education was assessed by means of the question "Which of the following qualifications do you have? (You can select more than one)" with the possibility to specify "College or University degree", "A levels / AS levels or equivalent", "O levels / GCSEs or equivalent", "CSEs or equivalent", "NVQ or HND or HNC or equivalent" and / or "Other professional qualifications, eg: nursing, teaching". The variable was dichotomized into academic training vs. no academic training ("College or University degree" was vs. was not among the given responses). Depressive

symptoms were assessed by means of the question “Over the past two weeks, how often have you felt down, depressed or hopeless?” with responses “not at all”, “several days”, “more than half the days” or “nearly every day”. Participants were categorized as subjects with depressive symptoms if they answered “several days”, “more than half the days” or “nearly every day”, otherwise they were categorized as control subjects without depressive symptoms. Intracranial brain volume (ICV = volume of gray matter + volume of white matter + volume of ventricular cerebrospinal fluid), BMI (continuous), sex (male vs. female) and age (continuous) as well as psychotropic medication use (mood stabilizers, antidepressants, and antipsychotics; see Table S3) were also included as covariates in the analyses. All measures were taken from Instance 2.

Statistical Analysis

The response options “do not know” and “prefer not to answer” were handled as missing values. Mean values and standard deviations were used for descriptive data presentation. The association between SH variables and AR was analyzed using a linear regression model (LM) with sleep duration (3 factor levels with ‘normal sleep duration’ as the reference category), insomnia symptoms (2 factor levels), excessive daytime sleepiness (2 factor levels), chronotype (3 factor levels with the ‘intermediate type’ as the reference category) and sleep medication use (2 factor levels) as predictor variables and the ‘median BOLD effect in group-defined (amygdala activation) mask for faces-shapes contrast’ as dependent variable.

Socioeconomic status, level of education, depressive symptoms, ICV, BMI, sex, age and psychotropic medication use were implemented as covariates. By doing so, all variables were used as described in our preregistration, referring to our previous study on sleep health and neurocognitive function (17). The significance level was set at $\alpha = 0.05$.

Accounting for the principle of parsimony for statistical models, covariates were added gradually starting with a strictly reduced model (insomnia symptoms only), continuing with two moderately adjusted models (first adding basic demographic variables as covariates, then adding all remaining covariates) and ending with a fully adjusted model including all described variables (adding all remaining SH variables, see Table S4). Hereby, the prioritization of insomnia symptoms as sleep-related variable arises from the assumption that subjective difficulties in initiating / maintaining sleep cover multiple aspects of SH, such as sleep satisfaction and – to a limited extent – sleep continuity or efficiency and subjective short sleep duration. The significance of improvement between models was evaluated by partial *F*-tests.

In addition to our pre-registered analysis plan the following sensitivity and exploratory analyses were conducted: a) We cleaned the fMRI data (median BOLD effect for faces-shapes contrast) from zeros, which occurred in an unexpectedly high number (discernible in Figure 3) and may indicate drop out in this specific region of interest (personal communication with UKBB imaging analysis team). b) Accounting for weaknesses arising from the pre-registered, theory-driven analysis plan (coarseness, multicollinearity), a data-driven, stepwise model comparison by the Akaike Information Criterion (AIC) was implemented. For this purpose, the fully adjusted model was chosen as starting point and variables were dropped one by one depending on the explanatory power they add to the model according to the AIC.

Furthermore, we examined c) whether including anxiety as an additional covariate changes the current results, d) whether a composite measure of SH is associated with AR, e) whether operationalizing insomnia symptoms and excessive daytime sleepiness with multiple factor levels (instead of dichotomizing these variables) leads to a different outcome, and f) whether associations between SH and AR are altered when considering

SH stability over years (by using SH data from Instance 0: Initial assessment visit, 2006-2010).

Results

Sample Characteristics

The sample consisted of 13,993 (54.3%) women and 11,765 (45.7%) men with a mean age of 62.9 ± 7.4 years. Further characteristics are presented in Table 1. An overview of mean AR differences between subsamples (depending on factor level constellations of sleep-related variables) is depicted in Figure 2b.

TABLE 1

Main analysis

Once basic demographic variables were added (LM 2), the inclusion of further variables (LM 3 and 4) did not result in a significant increase of explained variance (see Table S5; for an overview of all estimates and p-values, see Table S6). Standardized effect sizes (Cohen's d) and *p*-values for the effects of all independent variables of LM 2 on AR are presented in Figure 2a. According to our analysis, large ICV ($\beta = 5.32 \times 10^{-08}$, $d = 0.04$, $p < 0.001$), high BMI ($\beta = 3.79 \times 10^{-04}$, $d = 0.01$, $p = 0.021$), and low socioeconomic status ($\beta = 2.59 \times 10^{-03}$, $d = 0.01$, $p = 0.050$) were associated with increased AR. High level of education ($\beta = -6.76 \times 10^{-03}$, $d = -0.03$, $p < 0.001$) and old age ($\beta = -1.05 \times 10^{-03}$, $d = -0.07$, $p < 0.001$) were associated with decreased AR. Neither sex ($\beta = 1.94 \times 10^{-03}$, $d = 0.01$, $p = 0.267$) nor insomnia symptoms ($\beta = 3.01 \times 10^{-04}$, $d = 0.00$, $p = 0.843$) were related to AR.

FIGURE 2

FIGURE 3

Sensitivity and Exploratory Analyses

a) Removing zeros from the fMRI data did not change the results of the main or exploratory analyses considerably, while reducing the sample size by 156 participants (see Table S7). b) Testing each variable's individual contribution by the Akaike Information Criterion (AIC) in a stepwise algorithm (50), a new model was obtained (LM 5) – consisting exclusively of variables with a relevant increment value, as identified by the AIC (see Table S8). Significant associations as reported in LM 2 remained unaffected in LM 5. Short sleep duration was the only SH variable to survive stepwise model comparison. All results of LM 5 are depicted in Table S9. Differences in AR between short sleepers vs. normal sleepers and between participants with vs. without insomnia symptoms are depicted in Figures 3a and b. c) When expanding a LM comprising all sleep-related variables and all covariates by the variable "Worrier / anxious feelings" (UKBB Data-Field 1980: *https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=1980*, Instance 2), effect sizes were slightly altered. However, significant results as reported above remained unchanged (see Table S10). d*)* When replacing all sleep-related variables in the same model by a single composite measure of SH (oriented towards previous research, e.g. 15), no significant association was found (see Table S11). Details on how the composite measure was obtained are provided in Figure S1. e) When assigning multiple factor levels to previously dichotomized SH variables, significant results as reported above remained unchanged. Additionally, we found that participants who answered "often" in the daytime sleepiness item had a decreased AR (β = -1.07 × 10^{-2}, d = -0.01, p = 0.029, see Table S12). f) When assigning time-dependent factor levels to SH variables in the same model, significant

associations were found between stable short sleep duration and decreased AR (β = -5.72 × 10^{-3}, d = -0.02, p = 0.013) as well as between instable long sleep duration and increased AR (β = 7.09 × 10^{-2}, d = 0.01, p = 0.048). All results are depicted in Table S13.

Discussion

The goal of the current analysis was to investigate associations between SH and AR to negative facial expressions in the UKBB cohort (N = 25,758). In the pre-registered analysis, indicators of SH were not associated with AR. Against our hypothesis, exploratory analyses suggested that short sleep duration (compared to normal sleep duration) may be associated with *decreased* AR.

Sleep Health Variables

Previous research has shown associations between sleep-related variables and amygdala function but sample characteristics, study designs (experimental manipulation vs. case-control studies), and specific methods for data collection and processing have varied considerably in these studies (8; 9; 10; 11; 12; 34). The current study adds to this literature by showing that trait-like individual differences in SH are not associated with AR to negative facial expressions on the epidemiological level. With respect to insomnia symptoms, this finding sheds doubt on theoretical considerations that sleep disruption is associated with amplified emotional reactivity to stimuli of negative valence (1). However, the absence of an association between insomnia and AR to general negative stimuli is in line with some previous case-control studies investigating AR (10; 51).

Testing each variable's individual contribution by the AIC in an exploratory stepwise model comparison yielded that self-reported short sleep duration was associated with decreased AR. To our knowledge, this is a new finding. Experimental sleep deprivation, in contrast, has been shown to result in *increased* AR (8; 9). Likewise, most studies suggest

that experimental sleep deprivation (beyond a therapeutic context) leads to increased emotional reactivity on the behavioral level (52). In addition, acute and chronic sleep loss have been shown to be associated with sustained attention towards negative stimuli (53), reduced capacity for cognitive reappraisal strategies (54), and with impaired prefrontal brain functions related to emotion regulation (55; 56; 57). In particular, brain connectivity within and between prefrontal and subcortical areas cease to function properly under REM sleep loss (57; 34). In light of these findings, the association between *habitual* short sleep duration and decreased AR may protect the short sleeper against emotional overwhelming. This hypothesis is further supported by our exploratory analysis revealing that only stable short sleep duration (over years) is associated with decreased AR.

Covariates

The observed associations between the covariates and AR are mostly in line with previous empirical research and theoretical assumptions. Low socioeconomic status, which includes a low level of education, has been shown before to be associated with increased AR to negative stimuli (58). The association between older age and decreased AR to negative stimuli is also in line with previous evidence (59) and adds to literature reporting that the impact of negative information on attention and memory processes decreases during adulthood (60). To our knowledge, associations between BMI and AR have not been systematically investigated so far. However, negative emotions have been shown to play an important role in the development of obesity (61). The lack of association between depressive symptoms and AR is surprising and, thus, presented in detail in Tamm et al. (62).

Limitations

The following limitations need to be addressed: a) All SH variables were assessed by means of a single question. This circumstance might bring with it an increased degree

of imprecision in operationalization. However, for example, single items on insomnia symptoms have a high accuracy of discriminating insomnia cases from controls (63). Moreover, due to the large sample size provided by the UKBB cohort, statistical power to detect even small effect sizes was still guaranteed in heavily contaminated group comparisons (e.g. healthy controls falsely classified as patients with insomnia). b) Since the current analysis is an epidemiological approach, subsample sizes were not adjusted. Consequently, subsamples defined by a characteristic of low prevalence were smaller, thus resulting in a higher uncertainty of statistical estimates. c) The sample consisted predominantly of older adults, which reduces the generalizability of the results. d) The UKBB does not provide data on performance in the Hariri task (e.g., reaction times, percentage of correct responses). Hence, it cannot be ruled out that different levels of vigilance or attention both between- and within-subjects had an impact on the current results.

Outlook and Conclusions

The current analysis and previous evidence clearly demonstrate that it is important to differentiate between habitual short sleep duration, acute sleep loss and insomnia when investigating AR. For future research, it might be of particular interest to examine longitudinally if AR decreases over time under persisting short sleep duration. Additionally, it may be worthwhile to investigate higher order, non-linear associations between SH dimensions and AR as well as more complex associations using latent class or machine learning approaches. It may also be of interest to investigate associations between SH and cortical structures involved in the regulation of emotional reactivity. In particular, further research on functional and structural connectivity between the prefrontal cortex and the limbic system might help to integrate the current findings on SH and AR into established neurobiological models (64).

Concluding, our results (based on a large sample size, consistent methods, and a pre-registered analysis plan) suggest that a) short sleep duration may be associated with decreased AR, possibly indicating compensation for impaired prefrontal processes and hampered emotion regulation, and b) other SH dimensions are not associated with AR.

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References

1 Baglioni C, Spiegelhalder K, Lombardo C, Riemann D (2010): Sleep and emotions: a focus on insomnia. *Sleep Medicine Reviews* 14: 227-238.

2 Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, *et al.* (2011): Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders* 135: 10-19.

3 Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A, *et al.* (2019): Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Medicine Reviews* 43: 96-105.

4 Pigeon WR, Hegel M, Unützer J, Fan MY, Sateia MJ, Lyness JM, *et al.* (2008): Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort?. *Sleep* 31: 481-488.

5 Lustberg L, Reynolds III CF (2000): Depression and insomnia: questions of cause and effect. *Sleep Medicine Reviews* 4: 253-262.

6 Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, *et al.* (2016): Sleep and mental disorders: a meta-analysis of polysomnographic research. *Psychological Bulletin* 142: 969.

7 Riemann D, Krone LB, Wulff K, Nissen C (2020): Sleep, insomnia, and depression. *Neuropsychopharmacology* 45: 74-89.

8 Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP (2007): The human emotional brain without sleep – a prefrontal amygdala disconnect. *Current Biology* 17: R877-R878.

9 Motomura Y, Kitamura S, Oba K, Terasawa Y, Enomoto M, Katayose Y, *et al.* (2013): Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PloS One* 8: e56578.

10 Baglioni C, Spiegelhalder K, Regen W, Feige B, Nissen C, Lombardo C, *et al.* (2014): Insomnia disorder is associated with increased amygdala reactivity to insomnia-related stimuli. *Sleep* 37: 1907-1917.

11 Wassing R, Lakbila-Kamal O, Ramautar JR, Stoffers D, Schalkwijk F, Van Someren EJ (2019): Restless REM sleep impedes overnight amygdala adaptation. *Current Biology* 29: 2351-2358.

12 Klumpp H, Hosseini B, Phan KL (2018): Self-reported sleep quality modulates amygdala resting-state functional connectivity in anxiety and depression. *Frontiers in Psychiatry* 9: 220.

13 Furihata R, Hall MH, Stone KL, Ancoli-Israel S, Smagula SF, Cauley JA, *et al.* (2017): An aggregate measure of sleep health is associated with prevalent and incident clinically significant depression symptoms among community-dwelling older women. *Sleep* 40: zsw075.

14 Brindle RC, Cribbet MR, Samuelsson LB, Gao C, Frank E, Krafty RT, *et al.* (2018): The relationship between childhood trauma and poor sleep health in adulthood. *Psychosomatic Medicine* 80: 200.

15 Dong L, Martinez AJ, Buysse DJ, Harvey AG (2019): A composite measure of sleep health predicts concurrent mental and physical health outcomes in adolescents prone to eveningness. *Sleep Health* 5: 166-174.

16 Buysse DJ (2014): Sleep health: can we define it? Does it matter?. *Sleep* 37: 9-17.

17 Kyle SD, Sexton CE, Feige B, Luik AI, Lane J, Saxena R, *et al.* (2017): Sleep and cognitive performance: cross-sectional associations in the UK Biobank. *Sleep Medicine* 38: 85-91.

18 Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA (2011): Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *European Heart Journal* 32: 1484-1492.

19 Liu TZ, Xu C, Rota M, Cai H, Zhang C, Shi MJ, *et al.* (2017): Sleep duration and risk of all-cause mortality: a flexible, non-linear, meta-regression of 40 prospective cohort studies. *Sleep Medicine Reviews* 32: 28-36.

20 Li M, Zhang XW, Hou WS, Tang ZY (2014): Insomnia and risk of cardiovascular disease: a meta-analysis of cohort studies. *International Journal of Cardiology* 176: 1044-1047.

21 Meng L, Zheng Y, Hui R (2013): The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertension Research* 36: 985-995.

22 Pigeon WR, Pinquart M, Conner K (2012): Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *The Journal of Clinical Psychiatry* 73: 1160-1167.

23 Empana JP, Dauvilliers Y, Dartigues JF, Ritchie K, Gariepy J, Jouven X, *et al.* (2009): Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the three city study. *Stroke* 40: 1219-1224.

24 Jaussent I, Bouyer J, Ancelin ML, Akbaraly T, Peres K, Ritchie K, *et al.* (2011): Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep* 34: 1103-1110.

25 Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, *et al.* (2013): Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiology International* 30: 470-477.

26 Au J, Reece J (2017): The relationship between chronotype and depressive symptoms: a meta-analysis. *Journal of Affective Disorders* 218: 93-104.

27 Bouwmans ME, Bos EH, Hoenders HR, Oldehinkel AJ, de Jonge P (2017): Sleep quality predicts positive and negative affect but not vice versa. An electronic diary study in depressed and healthy individuals. *Journal of Affective Disorders* 207: 260-267.

28 Sin NL, Almeida DM, Crain TL, Kossek EE, Berkman LF, Buxton OM (2017): Bidirectional, temporal associations of sleep with positive events, affect, and stressors in daily life across a week. *Annals of Behavioral Medicine* 51: 402-415.

29 Chiang JJ, Kim JJ, Almeida DM, Bower JE, Dahl RE, Irwin MR, *et al.* (2017): Sleep efficiency modulates associations between family stress and adolescent depressive symptoms and negative affect. *Journal of Adolescent Health* 61: 501-507.

30 Schiel JE, Holub F, Petri R, Leerssen J, Tamm S, Tahmasian M, *et al.* (2020): Affect and arousal in insomnia: through a lens of neuroimaging studies. *Current Psychiatry Reports* 22: 1-8.

31 Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, Nissen C (2010): The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Medicine Reviews* 14: 19-31.

32 Lane JM, Jones SE, Dashti HS, Wood AR, Aragam KG, van Hees VT, *et al.* (2019): Biological and clinical insights from genetics of insomnia symptoms. *Nature Genetics* 51: 387-393.

33 Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR (2002): The amygdala response to emotional stimuli: a comparison of faces and scenes. *NeuroImage* 17: 317-323.

34 Van Der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP (2011): REM sleep depotentiates amygdala activity to previous emotional experiences. *Current Biology* 21: 2029-2032.

35 Prather AA, Bogdan R, Hariri AR (2013): Impact of sleep quality on amygdala reactivity, negative affect, and perceived stress. *Psychosomatic Medicine* 75: 350.

36 Etkin A, Wager TD (2007): Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* 164: 1476-1488.

37 Zald DH (2003): The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews* 41: 88-123.

38 Spiegelhalder K, Regen W, Baglioni C, Nissen C, Riemann D, Kyle SD (2015): Neuroimaging insights into insomnia. *Current Neurology and Neuroscience Reports* 15: 9.

39 Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafò MR (2013): Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience* 14: 365-376.

40 Nord CL, Valton V, Wood J, Roiser JP (2017): Power-up: a reanalysis of 'power failure' in neuroscience using mixture modeling. *Journal of Neuroscience* 37: 8051-8061.

41 Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, *et al.* (2015): UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *Plos Med* 12: e1001779.

42 Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, *et al.* (2016): Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neuroscience* 19: 1523-1536.

43 Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JL, Griffanti L, Douaud G, *et al.* (2018): Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *NeuroImage* 166: 400-424.

44 Alvarez GG, Ayas NT (2004): The impact of daily sleep duration on health: a review of the literature. *Progress in Cardiovascular Nursing* 19: 56-59.

45 Consensus Conference Panel, Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, *et al.* (2015): Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Journal of Clinical Sleep Medicine* 11: 591-592.

46 Dashti HS, Jones SE, Wood AR, Lane JM, Van Hees VT, Wang H, *et al.* (2019): Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nature Communications* 10: 1-12.

47 Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, *et al.* (2013): Function in the human connectome: task-fMRI and individual differences in behavior. *NeuroImage* 80: 169-189.

48 Elam JS, Glasser MF, Harms MP, Sotiropoulos SN, Andersson JL, Burgess GC, *et al.* (2021): The Human Connectome Project: A retrospective. *NeuroImage* 244: 118543.

49 Taylor PJ, Marsh JE (2017): E-Prime (Software). *The International Encyclopedia of Communication Research Methods* 1-3.

50 Hu S (2007): Akaike information criterion. *Center for Research in Scientific Computation* 93.

51 Wassing R, Schalkwijk F, Lakbila-Kamal O, Ramautar JR, Stoffers D, Mutsaerts HJ, *et al.* (2019): Haunted by the past: old emotions remain salient in insomnia disorder. *Brain* 142: 1783-1796.

52 Beattie L, Kyle SD, Espie CA, Biello SM (2015): Social interactions, emotion and sleep: A systematic review and research agenda. *Sleep Medicine Reviews* 24: 83-100.

53 Cote K, Jancsar C, Hunt B (2015): Event-related neural response to emotional picture stimuli following sleep deprivation. *Psychology & Neuroscience* 8: 102.

54 Mauss IB, Troy AS, LeBourgeois MK (2013): Poorer sleep quality is associated with lower emotion-regulation ability in a laboratory paradigm. *Cognition & Emotion* 27: 567-576.

55 Palmer CA, Alfano CA (2017): Sleep and emotion regulation: an organizing, integrative review. *Sleep Medicine Reviews* 31, 6-16.

56 Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, *et al.* (2000): Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research* 9: 335-352.

57 Verweij IM, Romeijn N, Smit DJ, Piantoni G, Van Someren EJ, van der Werf YD (2014): Sleep deprivation leads to a loss of functional connectivity in frontal brain regions. *BMC Neuroscience* 15: 1-10.

58 Farah MJ (2017): The neuroscience of socioeconomic status: Correlates, causes, and consequences. *Neuron* 96: 56-71.

59 Leclerc CM, Kensinger EA (2011): Neural processing of emotional pictures and words: A comparison of young and older adults. *Developmental Neuropsychology* 36: 519-538.

60 Mather M (2016): The affective neuroscience of aging. *Annual Review of Psychology* 67: 213-238.

61 Leehr EJ, Krohmer K, Schag K, Dresler T, Zipfel S, Giel KE (2015): Emotion regulation model in binge eating disorder and obesity-a systematic review. *Neuroscience & Biobehavioral Reviews* 49: 125-134.

62 Tamm S, Harmer CJ, Schiel JE, Holub F, Rutter MK, Spiegelhalder K, *et al.* (in press): Amygdala responses to negative faces are not associated with depressive symptoms: cross-sectional data from 28 638 individuals in the UK Biobank cohort. *American Journal of Psychiatry*.

63 Hammerschlag AR, Stringer S, De Leeuw CA, Sniekers S, Taskesen E, Watanabe K, *et al.* (2017): Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. *Nature Genetics* 49: 1584-1592.

64 Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U (2014): Neural network of cognitive emotion regulation – an ALE meta-analysis and MACM analysis. *NeuroImage* 87: 345-355.

Appendix

TABLE S1 – S13

FIGURE S1

Tables / Legends for Figures

Figure 1. Setup of the Hariri faces / shapes “emotion” task as used in the UKBB project. Top left: Exemplary trial (experimental block) depicting male, fearful facial expressions. Top right: Exemplary trial (experimental block) depicting female, angry facial expressions. Bottom left: Exemplary trial (control block) depicting neutral figures. Bottom right: Illustration of how participants had to give their responses (right hand; index finger = left option, middle finger = right option).

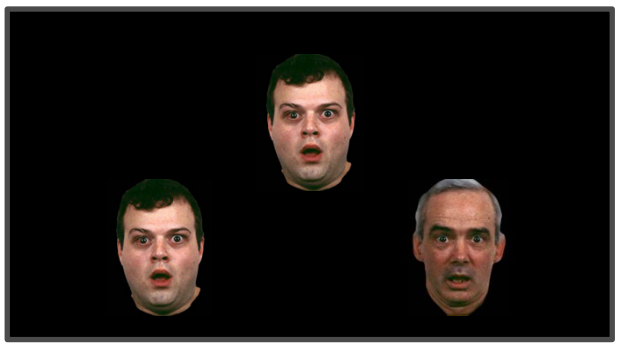
Table 1
Sample Characteristics

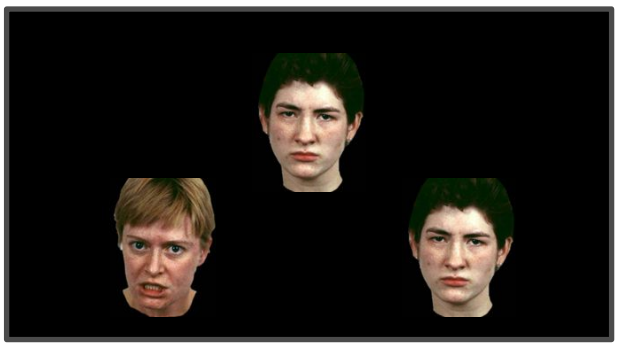
	Short, *n* (%)	Normal, *n* (%)	Long, *n* (%)
Sleep duration	6,114 (23.7)	19,367 (75.2)	277 (1.1)
	Early, *n* (%)	Intermediate, *n* (%)	Late, *n* (%)
Chronotype	7,190 (27.9)	16,141 (62.7)	2,427 (9.4)
	Yes, *n* (%)	No, *n* (%)	
Insomnia symptoms	8,061 (31.3)	17,697 (68.7)	
Excessive daytime sleepiness	5,672 (22.0)	20,086 (78.0)	
Sleep medication use	144 (0.6)	25,614 (99.4)	
Psych. medication use	2210 (8.6)	23,548 (91.4)	
Depressive symptoms	4,544 (17.6)	21,214 (82.4)	

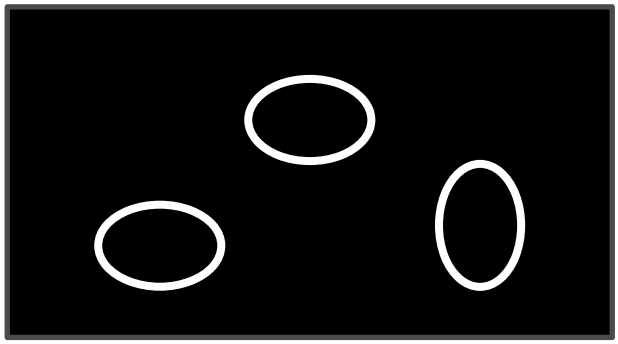
Figure 2. **A** Overview of all results from LM 2, depicted as standardized effect sizes (Cohen’s *d*: vertical, colored labels) and *p*-values (-log10, y-axis). Complete results from LM 1-4 are depicted in Table S6. Blue color indicates a negative effect size, red color indicates a positive effect size, gray color indicates an effect size close to zero ($-0.01 > d > 0.01$). The horizontal, gray dotted line visualizes the significance level $\alpha = 0.05$ (-log10) set for this analysis. **B** Illustration of mean AR increase / decrease in subsamples (vs. control samples) depending on factor level constellations of sleep-related variables (mean AR subsample minus mean AR control sample). SDS = sleep duration (short), SDL = sleep duration (long), INS = insomnia symptoms, EDS = excessive daytime sleepiness, CE = chronotype (early), CL = chronotype (late), SM = sleep medication.

Figure 3. Boxplots (medians, quartiles, 5% and 95% quantiles) of the sleep-related variables **A** sleep duration (normal vs. short; $t(10249) = 2.0$, $p = 0.045$) on the left and **B** insomnia symptoms (no vs. yes; $t(15618) = 0.7$, $p = 0.491$) on the right. The violet point clouds in the background depict individual measured values, providing a more differentiated visualization of the underlying distribution.

Figure 1







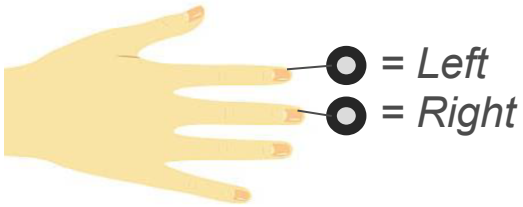


Figure 2

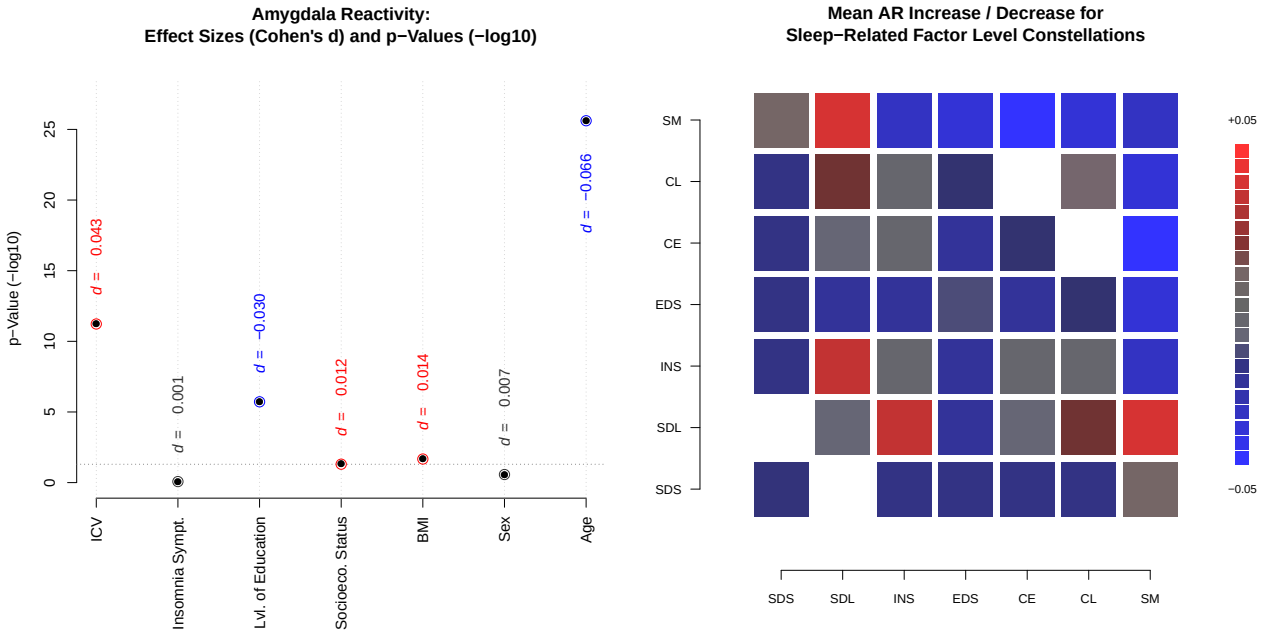

Amygdala Reactivity:
Effect Sizes (Cohen's d) and p−Values (−log10)
p−Value (−log10)
0
5
10
15
20
25
d = 0.043
d = 0.001
d = −0.030
d = 0.012
d = 0.014
d = 0.007
d = −0.066
ICV
Insomnia Sympt.
Lvl. of Education
Socioeco. Status
BMI
Sex
Age
Mean AR Increase / Decrease for
Sleep−Related Factor Level Constellations
SM
CL
CE
EDS
INS
SDL
SDS
+0.05
−0.05

Figure 3

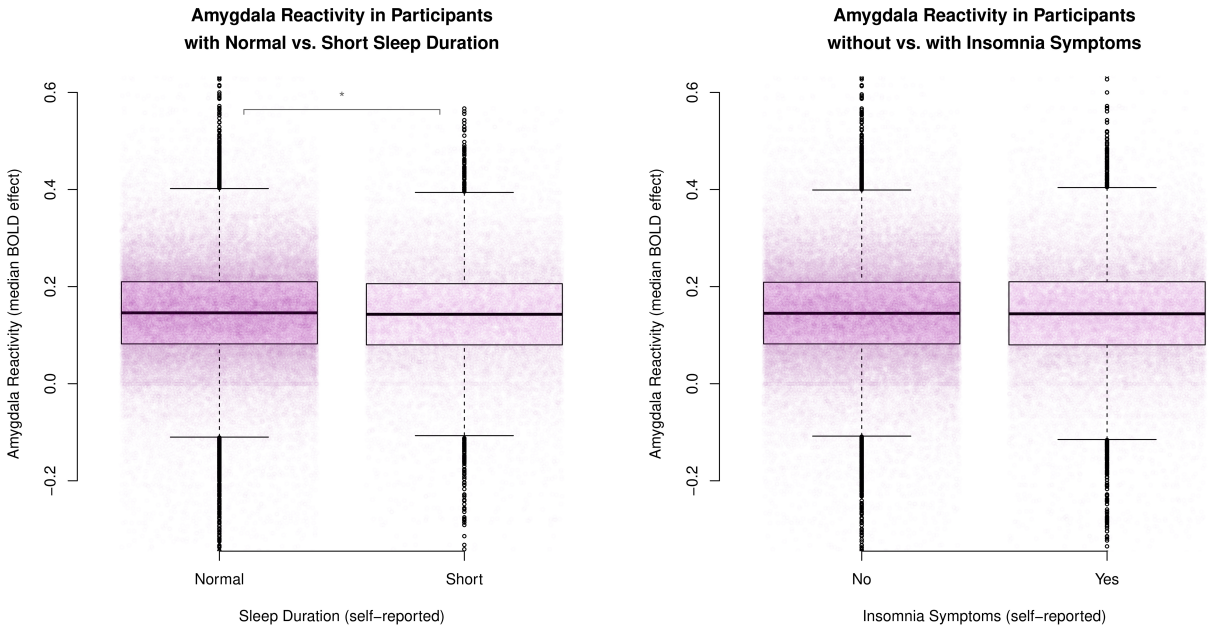

Amygdala Reactivity in Participants
with Normal vs. Short Sleep Duration
Amygdala Reactivity (median BOLD effect)
0.6
0.4
0.2
0.0
−0.2
*
Normal
Short
Sleep Duration (self−reported)
Amygdala Reactivity in Participants
without vs. with Insomnia Symptoms
Amygdala Reactivity (median BOLD effect)
0.6
0.4
0.2
0.0
−0.2
No
Yes
Insomnia Symptoms (self−reported)

Table S1
List of Neurological Conditions

Data Field	Code(s)	Description
6150	3	Stroke
20001	1031	Meningeal cancer / Malignant meningioma
	1032	Brain cancer / Primary malignant brain tumour
20002	1491	Brain haemorrhage
	1245	Brain abscess / Intracranial abscess
	1425	Cerebral aneurysm
	1433	Cerebral palsy
	1258	Chronic / Degenerative neurological problem
	1263	Dementia / Alzheimer's disease / Cognitive impairment
	1246	Encephalitis
	1264	Epilepsy
	1266	Head injury
	1244	Infection of nervous system
	1583	Ischaemic stroke
	1659	Meningioma / Benign meningeal tumour
	1247	Meningitis
	1259	Motor neurone disease
	1261	Multiple Sclerosis
	1240	Neurological injury / trauma
	1683	Benign Neuroma
	1397	Other demyelinating disease (not multiple sclerosis)
	1434	Other neurological problem
	1262	Parkinson's disease
	1524	Spina bifida
	1086	Subarachnoid haemorrhage
	1083	Subdural haemorrhage / Haematoma
	1082	Transient ischaemic attack (TIA)

Table S2

List of Sedatives and Hypnotics (Sleep Medication)

Data Field	Codes	Description (substance / trade name)
20003	1140863152	Diazepam
	1141157496	Diazepam product
	1140863244	Valium 2 mg tablet
	1140863250	Valium 2 mg / 5 ml syrup
	1140855856	Valium 10 mg suppository
	1140863202	Temazepam
	1140863210	Normison 10 mg capsule
	1140863138	Euhypnos 10 mg / 5 ml oral solution
	1140863144	Zopiclone
	1140928004	Zimovane ls 3.75 mg tablet
	1141171404	Zaleplon
	1141171410	Sonata 5 mg capsule
	1140865016	Zolpidem
	1140864916	Stilnoct 5 mg tablet
	1140863182	Nitrazepam
	1140863194	Mogadon 5 mg tablet
	1140855896	Nitrados 5 mg tablet
	1140863196	Remnos 5 mg tablet
	1140855900	Somnite 5 mg tablet
	1140855898	Noctesed 5 mg tablet
	1140855902	Surem 5 mg capsule
	1140855904	Unisomnia 5 mg tablet
	1140863104	Flunitrazepam
	1140863106	Rohypnol 1 mg tablet
	1140855914	Triazolam
	1140855920	Halcion 125 micrograms tablet

Table S3 (1/2)
List of Mood Stabilisers, Antidepressants, and Antipsychotics (Psychotropic Medication)

Data Field	Codes	Description (substance / trade name)
20003	1140867490	Lithium product
	1140867504	Priadel 200 mg m/r tablet
	1140867494	Camcolit 250 tablet
	1140872198	Sodium valproate
	1140872200	Epilim 100 mg crushable tablet
	1141172838	Depakote 250 mg e/c tablet
	1140872214	Valproic acid
	1140872064	Carbamazepine product
	2038459704	Carbamazepine
	1140872072	Tegretol 100 mg tablet
	1141167860	Teril cr 200 mg m/r tablet
	1141185460	Teril retard 200 mg m/r tablet
	1141162898	Timonil retard 200 mg m/r tablet
	1140864452	Epimaz 100 mg tablet
	1140867888	Paroxetine
	1140882236	Seroxat 20 mg tablet
	1140879540	Fluoxetine
	1140867876	Prozac 20 mg capsule
	1140921600	Citalopram
	1141151946	Cipramil 10 mg tablet
	1141180212	Escitalopram
	1141190158	Cipralex 5 mg tablet
	1140867878	Sertraline
	1140867884	Lustral 50 mg tablet
	1140879544	Fluvoxamine
	1141152732	Mirtazapine
	1141152736	Zispin 30 mg tablet
	1141200564	Duloxetine
	1141201834	Cymbalta 30 mg gastro-resistant capsule
	1141200570	Yentreve 20 mg gastro-resistant capsule
	1140916282	Venlafaxine
	1140916288	Efexor 37.5 mg tablet
	1140879616	Amitriptyline
	1140867658	Elavil 10 mg tablet
	1140867668	Tryptizol 10 mg tablet
	1140867662	Lentizol 25 mg m/r capsule
	1140867948	Amitriptyline hydrochloride 10 mg + Perphenazine 2 mg tablet
	1140867934	Triptafen tablet
	1140867938	Amitriptyline 12.5 mg + Chlordiazepoxide 5 mg capsule
	1140856186	Limbitrol 10 mg capsule
	1140867928	Limbitrol 5 mg capsule
	1140867850	Phenelzine
	1140910704	MAOI / Phenelzine
	1140867852	Nardil 15 mg tablet
	1140867920	Moclobemide
	1140867922	Manerix 150 mg tablet
	1140879630	Imipramine
	1140867712	Tofranil 10 mg tablet
	1140867756	Trimipramine
	1140867758	Surmontil 10 mg tablet
	1140879628	Dothiepin
	1140909806	Dosulepin
	1140867624	Prothiaden 25 mg capsule
	1141171824	Thaden 25 mg capsule
	1140879620	Clomipramine

Table S3 (2/2)
List of Mood Stabilisers, Antidepressants, and Antipsychotics (Psychotropic Medication)

Data Field	Codes	Description (substance / trade name)
20003	1140867690	Anafranil 10 mg capsule
	1140867726	Lofepramine
	1140882310	Gamanil 70 mg tablet
	1141146062	Lomont 70 mg / 5 ml s/f suspension
	1140879556	Mianserin
	1140867806	Bolvidon 10 mg tablet
	1140867812	Norval 10 mg tablet
	1140879658	Chlorpromazine
	1140910358	CPZ / Chlorpromazine
	1140863416	Largactil 10 mg tablet
	1140867168	Haloperidol
	1140867184	Haldol 5 mg tablet
	1140867092	Serenace 500 micrograms capsule
	1140867398	Fluphenazine decanoate
	1140882098	Fluphenazine
	1140867456	Modecate 12.5 mg/0.5 ml oily injection
	1140867156	Moditen 1 mg tablet
	1140856004	Moditen enanthate 25 mg/ml injection
	1140909800	Flupentixol
	1140867150	Flupenthixol
	1140867152	Depixol 3 mg tablet
	1140867952	Fluanxol 500 micrograms tablet
	1140882100	Zuclopenthixol
	1140867342	Clopixol 2 mg tablet
	1140867406	Loxapine
	1140867414	Loxapac 10 mg capsule
	1140867084	Droperidol
	1140867086	Droleptan 10 mg tablet
	1140868120	Trifluoperazine
	1140867244	Stelazine 1 mg tablet
	1140879750	Thioridazine
	1140867312	Melleril 10 mg tablet
	1141152848	Quetiapine
	1141152860	Seroquel 25 mg tablet
	1140867444	Risperidone
	1141177762	Risperdal 0.5 mg tablet
	1140928916	Olanzapine
	1141167976	Zyprexa 2.5 mg tablet
	1141195974	Aripiprazole
	1141202024	Abilify 5 mg tablet
	1141153490	Amisulpride
	1141184742	Solian 100 mg/ml s/f oral solution
	1140867420	Clozapine
	1140882320	Clozaril 25 mg tablet

Table S4

Independent Variables Included in Linear Models 1-4

	Linear Model 1	Linear Model 2	Linear Model 3	Linear Model 4
Sleep-related variables	Insomnia symptoms	+ None	+ Sleep medication use	+ Sleep duration, excessive daytime sleepiness, chronotype
Other variables	None	+ Socioeconomic status, level of education, ICV, BMI, sex, age	+ Depressive symptoms, psychotropic medication use	+ None

Note. All models were compared by means of partial *F*-tests (all results listed in Table S5).

Table S5

Results of all Partial F-tests, Comparing Nested Models Regarding their Statistical Explanatory Power

	Res. Df.	RSS	Df.	Sum of Sq.	F	Pr (>F)
LM 1	25756	329.94				
LM 2	25750	326.20	6	3.738	49.179	< 0.001
LM 2	25750	326.20				
LM 3	25747	326.18	3	0.022	0.578	0.630
LM 3	25747	326.18				
LM 4	25742	326.08	5	0.102	1.615	0.152

Table S6
Results of LM 1-4

Variable	LM 1			LM 2			LM 3			LM 4		
	β	*d*	*p*	*β*	*d*	*p*	*β*	*d*	*p*	*β*	*d*	*p*
ICV				0.000	0.043	< 0.001	0.000	0.043	< 0.001	0.000	0.043	< 0.001
Insomnia	-0.001	-0.004	0.491	0.000	0.001	0.843	0.000	0.001	0.811	0.001	0.006	0.361
Short sleep duration										-0.004	-0.015	0.020
Long sleep duration										-0.001	-0.001	0.870
Sleep medication							-0.019	-0.008	0.191	-0.019	-0.008	0.200
Daytime sleepiness										-0.001	-0.004	0.487
Early chronotype										-0.002	-0.008	0.209
Late chronotype										-0.001	-0.001	0.825
Level of education				-0.007	-0.030	< 0.001	-0.007	-0.030	< 0.001	-0.007	-0.029	< 0.001
Socioeconomic status (log-transformed)				0.003	0.012	0.050	0.003	0.012	0.048	0.003	0.013	0.038
Depressive symptoms							0.000	0.000	0.998	0.000	0.001	0.893
Psychotropic medication							-0.000	-0.000	0.956	-0.000	-0.001	0.876
BMI				0.000	0.014	0.021	0.000	0.014	0.021	0.000	0.015	0.017
Sex				0.002	0.007	0.267	0.002	0.007	0.273	0.002	0.007	0.267
Age				-0.001	-0.066	< 0.001	-0.001	-0.066	< 0.001	-0.001	-0.065	< 0.001

Note. All values rounded to three decimal places, *β* = estimate, *d* = Cohen's *d*, *p* = *p*-value.

Table S7

Results of LM 2 and 5 After Exclusion of Zeros (N = 25,602)

Model	Variable	*β*	*d*	*p*-Value
LM 2	ICV	$5.167 * 10^{-8}$	0.042	< 0.001
	Insomnia symptoms	$4.062 * 10^{-4}$	0.002	0.790
	Level of education	$-6.773 * 10^{-3}$	-0.030	< 0.001
	Socioeconomic status (log-transformed)	$2.692 * 10^{-3}$	0.013	0.041
	BMI	$3.378 * 10^{-4}$	0.013	0.041
	Sex	$2.004 * 10^{-3}$	0.007	0.253
	Age	$-1.069 * 10^{-3}$	-0.068	< 0.001
LM 5	ICV	$5.626 * 10^{-8}$	0.056	< 0.001
	Short sleep duration	$-3.857 * 10^{-3}$	-0.015	0.020
	Long sleep duration	$-1.661 * 10^{-3}$	-0.002	0.808
	Level of education	$-6.598 * 10^{-3}$	-0.029	< 0.001
	Socioeconomic status (log-transformed)	$2.784 * 10^{-3}$	0.013	0.035
	BMI	$3.689 * 10^{-4}$	0.014	0.025
	Age	$-1.056 * 10^{-3}$	-0.068	< 0.001

Note. β = estimate, *d* = Cohen's *d*, *p* = *p*-value.

Table S8

Results of the Stepwise Model Comparison (Last Step with AIC = -112524.6)

Variable	Sum of Squares	RSS	AIC
- none -	-	326.15	-112525
Sleep duration	0.069	326.22	-112523
Socioeconomic status (log-transformed)	0.052	326.20	-112523
BMI	0.078	326.23	-112520
Level of education	0.273	326.42	-112505
ICV	1.066	327.21	-112443
Age	1.465	327.61	-112411

Note. RSS = Residual Sum of Squares, AIC = Akaike Information Criterion. Dropping further variables will not produce a model with higher statistical explanatory power (with lower AIC).

Table S9
Results of LM 5

Variable	*β*	*d*	*p*-Value
ICV	$5.771 * 10^{-8}$	0.057	< 0.001
Sleep duration (short)	$-3.861 * 10^{-3}$	-0.015	0.020
Sleep duration (long)	$-1.379 * 10^{-3}$	-0.001	0.840
Level of education	$-6.590 * 10^{-3}$	-0.029	< 0.001
Socioeconomic status (log-transformed)	$2.678 * 10^{-3}$	0.013	0.042
BMI	$4.092 * 10^{-4}$	0.016	0.013
Age	$-1.035 * 10^{-3}$	-0.067	< 0.001

Note. β = estimate, *d* = Cohen's *d*, *p* = *p*-value.

Table S10
Results of the Fully Adjusted Model, Expanded by the Variable "Worrier / anxious feelings"

Variable	*β*	*d*	*p*-Value
ICV	$5.238 * 10^{-8}$	0.042	< 0.001
Insomnia symptoms	$2.213 * 10^{-3}$	0.009	0.171
Sleep duration (short)	$-3.771 * 10^{-3}$	-0.014	0.031
Sleep duration (long)	$4.814 * 10^{-4}$	0.000	0.944
Sleep medication use	$-1.844 * 10^{-2}$	-0.008	0.213
Excessive daytime sleepiness	$-1.051 * 10^{-3}$	-0.004	0.545
Chronotype (early)	$-1.828 * 10^{-3}$	-0.007	0.257
Chronotype (late)	$-1.215 * 10^{-3}$	-0.003	0.626
Level of education	$-6.957 * 10^{-3}$	-0.031	< 0.001
Socioeconomic status (log-transformed)	$2.348 * 10^{-3}$	0.011	0.078
Depressive symptoms	$1.375 * 10^{-3}$	0.004	0.484
Worrier / anxious feelings	$-4.137 * 10^{-3}$	-0.017	0.006
Psychotropic medication use	$-7.499 * 10^{-4}$	-0.002	0.805
BMI	$3.386 * 10^{-4}$	0.013	0.044
Sex	$1.476 * 10^{-3}$	0.005	0.408
Age	$-1.062 * 10^{-3}$	-0.066	< 0.001

Note. β = estimate, *d* = Cohen's *d*, *p* = *p*-value.

Table S11

Results of the Fully Adjusted Model, Replacing all Sleep-related Variables by a Single Composite Measure of SH

Variable	*β*	*d*	*p*-Value
ICV	$5.293 * 10^{-8}$	0.043	< 0.001
Composite SH measure	$1.121 * 10^{-3}$	0.009	0.152
Level of education	$-6.747 * 10^{-3}$	-0.030	< 0.001
Socioeconomic status (log-transformed)	$2.640 * 10^{-3}$	0.012	0.045
Depressive symptoms	$4.289 * 10^{-4}$	0.001	0.822
Psychotropic medication use	$-3.228 * 10^{-4}$	-0.001	0.914
BMI	$3.980 * 10^{-4}$	0.015	0.016
Sex	$1.884 * 10^{-3}$	0.007	0.283
Age	$-1.042 * 10^{-3}$	-0.065	< 0.001

Note. β = estimate, *d* = Cohen's *d*, *p* = *p*-value.

Table S12

Results of the Fully Adjusted Model with Multiple Factor Levels for Insomnia and Daytime Sleepiness

Variable	*β*	*d*	*p*-Value
ICV	$5.299 * 10^{-8}$	0.043	< 0.001
Insomnia symptoms (sometimes)	$-1.429 * 10^{-3}$	-0.005	0.434
Insomnia symptoms (usually)	$5.816 * 10^{-4}$	0.002	0.776
Sleep duration (short)	$-3.965 * 10^{-3}$	-0.014	0.022
Sleep duration (long)	$-6.748 * 10^{-4}$	-0.001	0.922
Sleep medication use	$-1.855 * 10^{-2}$	-0.008	0.212
Excessive daytime sleepiness (sometimes)	$-1.732 * 10^{-4}$	-0.001	0.923
Excessive daytime sleepiness (often)	$-1.065 * 10^{-2}$	-0.014	0.029
Chronotype (early)	$-1.987 * 10^{-3}$	-0.008	0.189
Chronotype (late)	$-5.552 * 10^{-4}$	-0.001	0.822
Level of education	$-6.583 * 10^{-3}$	-0.029	< 0.001
Socioeconomic status (log-transformed)	$2.758 * 10^{-3}$	0.013	0.037
Depressive symptoms	$4.692 * 10^{-4}$	0.002	0.806
Psychotropic medication use	$-4.450 * 10^{-4}$	-0.001	0.883
BMI	$3.978 * 10^{-4}$	0.015	0.017
Sex	$1.824 * 10^{-3}$	0.006	0.303
Age	$-1.045 * 10^{-3}$	-0.065	< 0.001

Note. β = estimate, *d* = Cohen's *d*, *p* = *p*-value.

Table S13

Results of the Fully Adjusted Model with Time-dependent Factor Levels for all SH Variables

Variable	Inst. 0	Inst. 2	*β*	*d*	*p*-Value
ICV			$5.225 * 10^{-8}$	0.042	< 0.001
Insomnia symptoms	Yes	No	$-1.373 * 10^{-3}$	-0.003	0.605
	No	Yes	$1.916 * 10^{-3}$	0.006	0.349
	Yes	Yes	$6.681 * 10^{-4}$	0.002	0.752
Sleep duration	Short	Normal	$4.909 * 10^{-4}$	0.001	0.849
	Long	Normal	$-3.626 * 10^{-3}$	-0.002	0.712
	Normal	Short	$-1.918 * 10^{-3}$	-0.005	0.407
	Short	Short	$-5.718 * 10^{-3}$	-0.016	0.013
	Long	Short	$7.029 * 10^{-3}$	0.001	0.836
	Normal	Long	$-8.502 * 10^{-3}$	-0.007	0.272
	Short	Long	$7.091 * 10^{-2}$	0.012	0.048
	Long	Long	$1.693 * 10^{-2}$	0.007	0.286
Sleep medication use	Yes	No	$-1.400 * 10^{-2}$	-0.007	0.274
	No	Yes	$-1.888 * 10^{-2}$	-0.005	0.394
	Yes	Yes	$-1.985 * 10^{-2}$	-0.006	0.321
Excessive daytime sleepiness	Yes	No	$-1.469 * 10^{-3}$	-0.004	0.571
	No	Yes	$-1.457 * 10^{-3}$	-0.004	0.525
	Yes	Yes	$-1.348 * 10^{-3}$	-0.004	0.560
Chronotype	Early	Interm.	$-1.578 * 10^{-3}$	-0.003	0.602
	Late	Interm.	$-3.570 * 10^{-3}$	-0.006	0.364
	Interm.	Early	$-2.122 * 10^{-3}$	-0.005	0.390
	Early	Early	$-1.803 * 10^{-3}$	-0.006	0.356
	Late	Early	$-5.473 * 10^{-3}$	-0.001	0.812
	Interm.	Late	$-4.779 * 10^{-3}$	-0.008	0.210
	Early	Late	$-2.373 * 10^{-2}$	-0.006	0.373
	Late	Late	$2.314 * 10^{-3}$	0.005	0.464
Level of education			$-6.594 * 10^{-3}$	-0.029	< 0.001
Socioeconomic status (log-transformed)			$2.787 * 10^{-3}$	0.013	0.035
Depressive symptoms			$3.621 * 10^{-4}$	0.001	0.850
Psychotropic medication use			$-3.307 * 10^{-4}$	-0.001	0.913
BMI			$4.113 * 10^{-4}$	0.015	0.014
Sex			$2.083 * 10^{-3}$	0.007	0.239
Age			$-1.037 * 10^{-3}$	-0.064	< 0.001

Note. *β* = estimate, *d* = Cohen's *d*, *p* = *p*-value.

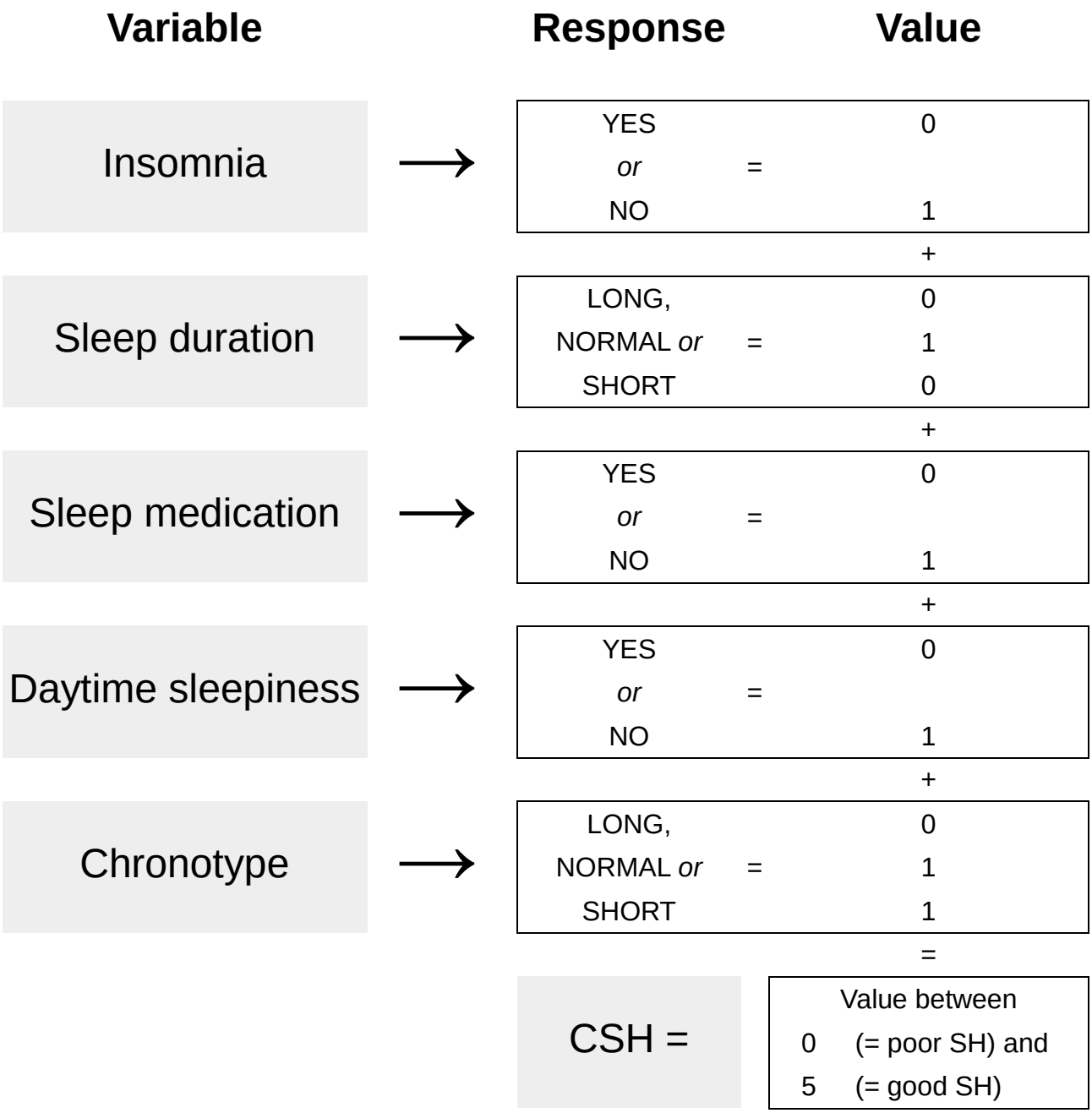


Figure S1. Details on how the composite measure was obtained.

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.
Antibody		
Bacterial or Viral Strain		
Biological Sample		
Cell Line		
Chemical Compound or Drug		
Commercial Assay Or Kit		
Deposited Data; Public Database	The sample consisted of 13,993 (54.3%) women and 11,7	The UK Biobank - UKBB (Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, et al. (2016): Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nature Neuroscience 19: 1523-1536.)
Genetic Reagent		
Organism/Strain		
Peptide, Recombinant Protein		
Recombinant DNA		
Sequence-Based Reagent		
Software; Algorithm		
Transfected Construct		
Other		

Identifiers	Additional Information
Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Application number: 6818.	https://www.ukbiobank.ac.uk/

Key Resource Table

In This Issue

Sleep health (SH) is considered a key determinant of physiological and psychological human well-being. To better understand neural mechanisms underlying the association between poor SH and psychiatric disorders, the current study investigated amygdala reactivity (AR) to negative facial expressions in the UK Biobank cohort (*N* = 25,758 participants). Exploratory analyses revealed that short sleep duration was associated with decreased AR, possibly indicating compensation for impaired prefrontal processes and hampered emotion regulation.