Supplementary Information

Sleep Health at the Genomic Level: Six Distinct Factors and Their Relationships With Psychopathology

Genome-wide association study (GWAS) phenotypes

Sleep health. All GWAS summary statistics are described in more depth in the below referenced papers. All sleep health GWAS summary statistics were downloaded from https://sleep.hugeamp.org/downloads.html. Subjective sleep health phenotypes, ascertained via self-reported data, were chronotype (1), daytime sleepiness (2), self-report sleep duration (3), napping (4) and insomnia (5). Objective sleep health phenotypes, collected by actigraphy, were sleep midpoint (mid), least active 5 hours (L5), most active 10 hours (M10), efficiency, episodes, diurnal inactivity, actigraphy sleep duration, and standard deviation of actigraphy sleep duration, and are described briefly in the main text (6).

We used the rank-normalized effect size, standard deviation. and p value (from the public summary statistics) for the actigraphy data. Sleep midpoint, M10, L5, episodes, daytime sleepiness, napping, diurnal inactivity, insomnia, and standard deviation of sleep duration were reverse-coded so findings could be interpreted in the context of "health." For example, once munged, the insomnia z-statistic in the summary statistic file was multiplied by –1. We then referred to it as "non insomnia," so that non-insomnia would, on average, associated positively with better health. We recognize that napping could be considered beneficial in certain circumstances (i.e. shorter naps especially in sleep deprived populations (4) but the long-term effects of perpetual napping on health remains unknown. Further, the raw napping summary

statistics positively correlated with the raw diurnal and daytime sleepiness summary statistics, indicated it should be reversed to load on the Alertness factor in the same direction as the other indicators.

Psychopathology. All GWAS summary statistics are described in the referenced GWASs. We briefly describe ascertainment and description of phenotypes here. The anxiety (Anx) summary statistics included 25,453 cases and 51,113 controls (7). Cases were defined as having at least one of the following: diagnoses from anxiety, nerves, social phobia, other phobias, or panic attacks/disorders. Cases did not have comorbid schizophrenia, bipolar disorder, anorexia, bulimia, autism, attention-deficit/hyperactivity disorder (ADHD), or any other type of psychosis-based illness. Controls were defined as having no lifetime diagnosis of mental health disorder, no UK Biobank history of psychotropic medication and no substance use or abuse disorders. Summary statistics were downloaded from https://docs.google.com/document/d/160qjZrACuLbJcYz9VFtHw4ZkImBEPE4WjQkhLnXJfzI/edit.

The major depressive disorder (MDD) summary statistics included 170,756 cases and 329,443 controls (8). Cases were based on self-reported answers to "Have you ever seen a general practitioner or psychiatrist for nerves, anxiety, tension or depression?" in the UK Biobank and Psychiatric Genetics Consortium (PGC). Cases did not have comorbid bipolar disorder, schizophrenia, personality disorders or any prescriptions for anti-psychotic medications. Summary statistics were downloaded from https://www.med.unc.edu/pgc/download-results/.

The post-traumatic stress disorder (PTSD) summary statistics included 23,212 cases and 151,447 controls (9). Cases met criteria for lifetime or current PTSD diagnosis based on various

versions of the Diagnostic Statistical Manual (DSM). Controls did not meet criteria for PTSD diagnosis. Summary statistics were downloaded from https://www.med.unc.edu/pgc/download-results/.

The problematic alcohol use (Alc) summary statistics included 121,604 participants who completed the Alcohol Use Disorders Identification Test (AUDIT) (10). The phenotype was taken from the AUDIT-P (problematic alcohol use) that consists of items 4-10. Summary statistics were downloaded from https://www.med.unc.edu/pgc/download-results/.

The cigarettes per day summary statistics included 337,334 participants (11). They were asked on average how many cigarettes they smoked per day and the phenotype was treated as quasi-continuous. Bins were: 1-5, 6-15, 16-25, 26-35 and 36+. Summary statistics were downloaded from https://genome.psych.umn.edu/index.php/GSCAN.

The cannabis use disorder (CUD) summary statistics included 21,041 cases and 363,884 controls (12). Cases were defined as having met a lifetime diagnosis of cannabis abuse or dependence as defined by the DSM-IV, DSM-III-R or International Classification of Diseases (ICD)-10. Controls were taken from the general population regardless of cannabis exposure across the lifetime. Summary statistics were downloaded from: https://www.med.unc.edu/pgc/download-results/.

The ADHD summary statistics included 20,183 cases and 35,191 controls (13). Cases were defined based on the ICD-10 and did not have any severe-moderate mental illness, but other comorbid diagnoses were allowed. Controls did not meet criteria for ADHD or have severe-moderate mental illness, but other comorbid diagnoses were allowed. Summary statistics were downloaded from: https://www.med.unc.edu/pgc/download-results/.

The schizophrenia (Scz) summary statistics included 34,241 cases and 45,604 controls (14). Cases were defined based on the DSM-IV and ICD-10. Summary statistics were downloaded from https://www.med.unc.edu/pgc/download-results/.

The bipolar disorder (BP) summary statistics included 41,917 cases and 371,549 controls (15). Cases met criteria for lifetime diagnosis of bipolar disorder by DSM-IV or ICD-10. Controls were obtained from the general public and were not screened for other specific mental illnesses. Summary statistics were downloaded from https://www.med.unc.edu/pgc/download-results/.

The anorexia (AN) summary statistics included 16,992 cases and 55,525 controls (16). Cases in most cohorts met diagnostic criteria for DSM-III-R, DSM-IV, ICD-8, ICD-9 or ICD-10 lifetime eating disorder. Cases in the UK Biobank cohort were based on self-reported eating disorder disclosure. Some, but not all, controls were screened for other mental illnesses. Summary statistics were downloaded from: https://www.med.unc.edu/pgc/download-results/.

The obsessive-compulsive disorder (OCD) summary statistics included 2,688 cases and 7,037 controls (17). Cases met criteria for DSM-IV OCD. Controls were not screened. Summary statistics were downloaded from https://www.med.unc.edu/pgc/download-results/.

Sleep health model modifications

The major aim of this paper was to create a sleep-health factor model at the genomic level. We used prior sleep health literature to inform the factor structure of this model. First, we examined the genetic covariance matrix of 15 publicly available sleep related GWAS summary statistics and considered which sleep health factors they could be assigned to, in conjunction with the sleep expert co-authors. These experts suggested incorporating regularity of sleep, so we

added a GWAS of the standard deviation of actigraphy sleep duration to the list of candidate indicators.

There were some methodological issues that limited our ability to include all the sleep measures in the same model. In particular, including variables that are linear combinations of other variables or derived from other variables that are also in the model can result in model estimation problems due to non-positive definite covariance matrices (18), or, if the models can be estimated, poor fit due to the need for residual correlations. In this case, there were two sets of variables that were derived from the same measures: short and long sleep were created from self-reported sleep duration, and actigraphy sleep duration was the numerator of the efficiency variable. Thus, both sets of variables showed very large correlations, and models that did not exclude some of these variables showed poor fit. Although we considered some model modifications to try to rectify this poor fit, we ultimately realized that it was not good SEM practice to include variables that were transformations of other variables. Thus, we focused on a model that used efficiency but not actigraphy duration, and self-reported sleep duration but not short and long sleep.

The exclusion of short and long sleep is discussed in more detail in the *Alternative to a linear duration* section. The exclusion of actigraphy duration means that our Duration factor reflects only self-reported duration. While actigraphy sleep duration and self-report sleep duration relate similarly to other sleep phenotypes, there are several psychopathology phenotypes to which they relate divergently (MDD, PTSD, alcohol use, schizophrenia, bipolar disorder and anorexia). This divergence is not entirely surprising given previous findings that objective and subjective sleep phenotypes do not always relate consistently to psychopathology (19).

Alertness is a commonly studied sleep health domain, so theoretically daytime sleepiness, diurnal inactivity, and napping aligned with that construct. However, those indicators were reverse coded to reflect *alertness* as opposed to sleepiness. Similarly, efficiency is a commonly studied sleep health domain, so sleep efficiency and number of sleep episodes aligned with that construct. The final domain of sleep health we attempted to incorporate was satisfaction of sleep. Short sleep duration, daytime sleepiness, and insomnia were all potential indicators of satisfaction, but daytime sleepiness and short sleep only correlated at .15. At this point, we opted to not try to replicate satisfaction of sleep but instead to create an insomnia factor. Insomnia is frequently comorbid with many psychopathologies. As the second aim of this paper was to see how sleep health relates to psychopathology at the genetic level, we felt it would be informative to see how insomnia performs on its own, especially as opposed to omitting it from the analysis fully. The insomnia indicator was reverse coded to reflect *non-insomnia*.

Alternative to linear duration

Because short and long sleep have both been associated with some negative health outcomes, a linear conceptualization of sleep duration may not be appropriate. Ideally, we would be able to model sleep duration with linear and quadradic variables to best assess how it relates to psychopathology, but we cannot directly manipulate the previously published GWAS of sleep duration to represent a quadratic curve in Genomic SEM. Therefore, we also examined long- and short-sleep categorical variables created by Dashti et al (2019) (3): They used the self-report sleep duration phenotype to perform separate GWASs on those who reported sleeping <7 hours/night (short sleep) and those who reported sleeping >9 hours/night (long sleep) compared to those who reported sleeping 7-8 hours/night (controls). As shown in Supplemental Figure S3, both short and long sleep genetically relate positively to most psychopathology measures (*r*Gs=

–0.19 - 0.48; short or long sleep genetic liability is associated with increased psychopathology liability).

We could not include self-reported sleep duration, short sleep, and long sleep measures in the same model, because the inclusion of multiple variables derived from the same measure would create problems in model estimation/fit, particularly in light of the following pattern: Short sleep relates negatively and very strongly to full-scale sleep duration (rG= –0.89), while long sleep relates positively and moderately to full-scale sleep duration rG= 0.69), but short and long sleep both relate positively to most psychopathologies (indicating they both are associated with shared genetic liability to psychopathology). Figure S3 details the correlations between short sleep, long sleep, sleep duration and psychopathology.

We decided to omit short and long sleep in favor of including self-reported full-scale sleep duration, because duration is an important sleep health domain and sleep duration problems such as short sleep are already captured in the model with other indicators, particularly non-insomnia ($r\text{G}_{\text{shortsleep-non-insomnia}}$= –0.65; the insomnia indicator was reverse coded for this project, so this negative correlation indicates short sleep and insomnia liability are genetically associated in a positive manner). We kept Non-Insomnia as a separate factor as it is a sleep trait that is frequently studied on its own and highly related to health outcomes and was a close proxy to the sleep satisfaction domain of sleep health. A multiple regression analysis of non-insomnia and short sleep duration predicting all psychopathology factors shows that after controlling for the correlation between insomnia and short sleep (rG= –0.65, p<.001), non-insomnia seems to capture most of the associations with Internalizing ($\beta_{\text{non-insomnia}}$ = –0.43, p<.001; $\beta_{\text{shortsleep}}$= 0.08, p=0.055) but not Externalizing ($\beta_{\text{non-insomnia}}$= –0.21, p<.001; $\beta_{\text{shortsleep}}$= 0.28, p<.001), while non-insomnia and short sleep both show small relations to the Compulsive Thought Disorder factor

($\beta_{non\text{-}insomnia}$= –0.06, p=0.409; $\beta_{shortsleep}$= –0.05, p=0.508), and the Psychosis Thought Disorder factor ($\beta_{non\text{-}insomnia}$= –0.14, p<.001; $\beta_{shortsleep}$= –0.14, p<.001).

Because we ran the above model to evaluate our decision to exclude short sleep from the final sleep health model, we also ran a model where we allowed long sleep and self-reported duration to correlate and predict all psychopathology factors to assess whether the long sleep summary statistics are being captured by Duration. We would not necessarily assume long sleep would be captured by linear, self-reported sleep duration because often long sleep relates negatively to health while sleep duration relates positively to health (20). Controlling for the correlation between long sleep and self-reported duration (rG= 0.69, p<.001), long sleep was associated with psychopathology more significantly than self-reported duration in all cases except for the Compulsive Thought Disorder factor ($\beta_{longsleep}$= 0.07, p=0.014; $\beta_{selfduration}$= 0.25, p=0.358). For Internalizing, Externalizing and the Psychosis Thought Disorder factor both long sleep and self-reported duration were negatively predictive. These findings imply long sleep is genetically associated with more psychopathology liability, whereas self-reported (linear) sleep duration is genetically associated with less psychopathology liability.

However, because we already decided to exclude long sleep from the model, as it is derived from another measure in the model, we ran one final analysis to see how long sleep is associated with psychopathology above and beyond all other sleep health domains given the finding that it is associated with psychopathology above and beyond Duration. The model fit well: $\chi^2(201)$= 6,566.06, CFI=0.945 SRMR=0.068. Interestingly, long sleep was significantly associated with Externalizing (β= 0.87, p<.001), Internalizing (β= 0.52, p<.001) and the Psychosis Thought Disorder factor (β= 0.29, p<.001) after controlling for correlations among all

sleep health domains. Moreover, long sleep was significantly correlated with Alertness (rG= –0.39, p<.001) and Duration (rG= 0.68, p<.001), but not the other sleep health factors.

These findings provide some important insight into the inclusion of long sleep in a multi-dimensional sleep health model in that long sleep does appear to have specific genetic liability associated with genetic liability for psychopathology. While it is a limitation that we could not include long sleep in our model, a future direction could be to develop additional genetic phenotypes that are not derived directly from other measures to better parse these relationships.

Alternative sleep health-psychopathology models

A specific relationship between Regularity and OCD

Given the low CFI of the sleep health and psychopathology model, we inspected the model residuals and found the largest psychopathology and sleep indicator residual correlation was between sleep duration SD and OCD (r_{resid}=–0.22). This large residual suggests the association between sleep Regularity and Compulsive Thought Disorders might reflect a specific relationship to OCD. Indeed, a modified model in which the Regularity factor was associated with OCD and anorexia individually (not through the Compulsive Thought Disorder factor), $\chi^2(187)$=4,859.17, CFI=0.921, SRMR=0.065, revealed that OCD was significantly associated with Regularity (β= 0.32, p=0.006) but anorexia was not (β=0.05, p=0.487). Further, this modified model had a significantly better fit to the data: $\Delta\chi(1)$=410.190, p=0.016).

Hierarchical sleep health and psychopathology

Although the hierarchical sleep health model fit did not fit well, we examined a model that correlated the psychopathology factors with the higher-order Sleep Health factor to see how the psychopathology factors relate instead to a single sleep health domain (although Circadian Preference was not related to the higher-order Sleep Health factor). All psychopathology factors

except the Compulsive Thought Disorder factor were significantly correlated with the higher-order Sleep Health factor (*r*Gs=–0.12 to –0.61, *p*s<0.001). However, as expected, this model fit significantly worse than a model in which psychopathology factors were allowed to correlate with the lower order sleep health factors (χ^2(217)=12,187.55, CFI=0.798, SRMR=0.091; Table 2), indicating the correlations between the psychopathology factors and the sleep health sub-factors were not captured with a higher-order factor.

Psychopathology factors independently associated with sleep health factors

Despite a wide body of literature on sleep health and psychopathology, the true nature and directionality of these relationships remains unknown. Because determining causality was beyond the scope of this paper, our multiple regression analysis was intended to assess how sleep health domains are differentially associated with psychopathology when controlling for the correlations among sleep health. However, a multiple regression analysis in the other direction (psychopathology factors associated with sleep health controlling for the correlations among psychopathology) could be informative.

This model fit well (identical to the correlational and multiple regression sleep health and psychopathology models presented in the main text): χ^2(188)= 4,864.96, CFI=0.921 SRMR=0.067. See Supplemental Figure S4 for comparison of sleep health and psychopathology factor correlations vs partial coefficients with psychopathology predicting sleep health. Controlling for the correlations among psychopathology, no psychopathology factors were significantly associated with Efficiency or Regularity. Internalizing and the Psychosis Thought Disorder factors were significantly negatively associated with Alertness (β_{Int}= −0.38, *p*=0.013, $\beta_{Psychosis}$= –0.20, *p*=0.025) while the Compulsive Thought Disorder factor was positively associated with Alertness (β= 0.44, *p*=0.011). The Psychosis Thought Disorder factor was

negatively associated with Circadian Preferences (β= –0.14, p=.037). Internalizing was negatively associated with Non-Insomnia (β= –0.53, p<.001), while the Psychosis Thought Disorder factor was positively associated with Non-Insomnia (β= 0.25, p<001), indicating higher genetic liability to psychosis disorders is related to lower genetic liability to insomnia disorders. Finally, controlling for the correlations among psychopathology, the Psychosis Thought Disorder factor was positively associated with Duration (β= 0.43, p<001). Overall, none of these results are in stark contrast to what we saw in the correlational or sleep health predicting psychopathology models but do provide a unique perspective to the directionality of some of these genetic relationships.

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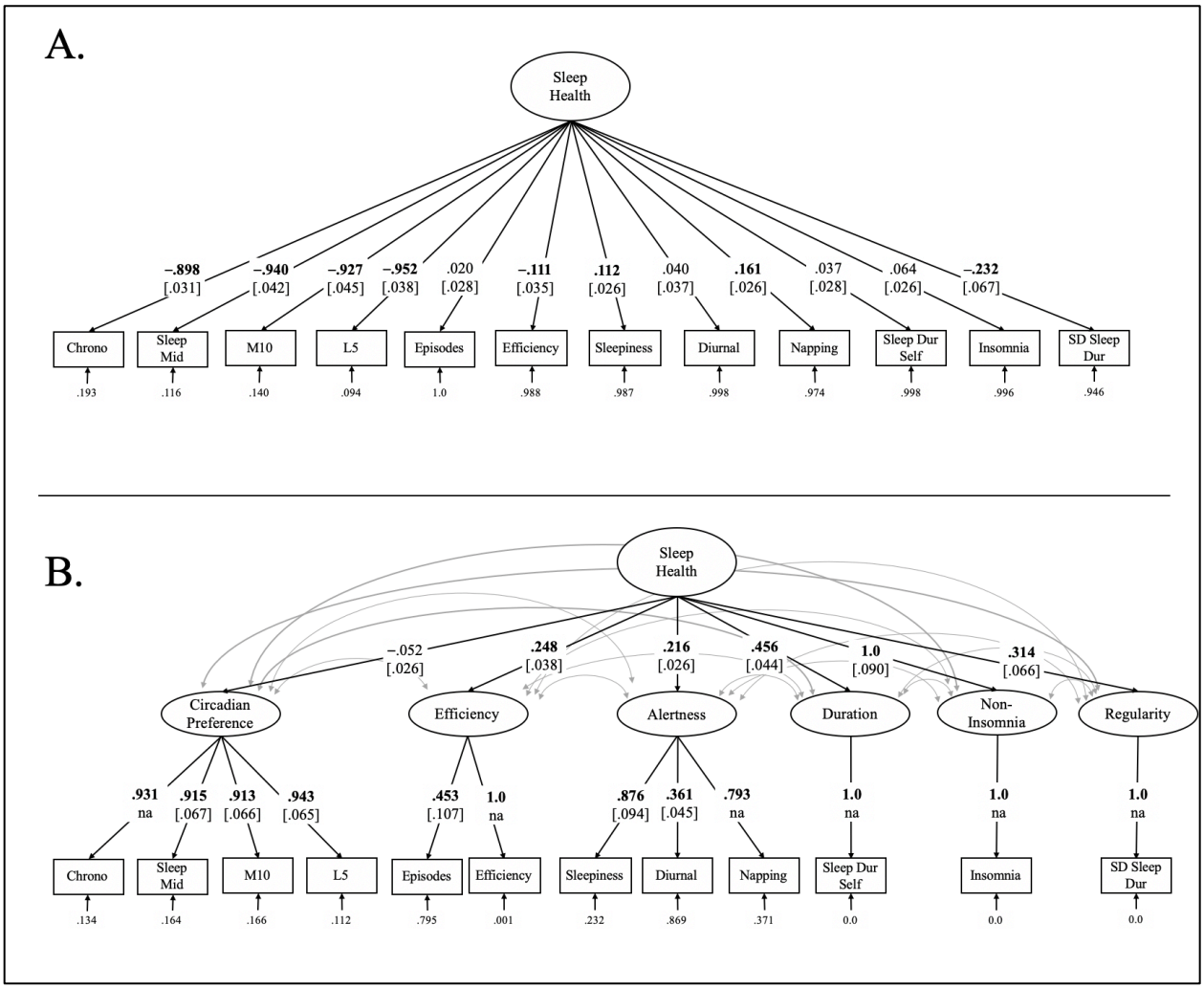
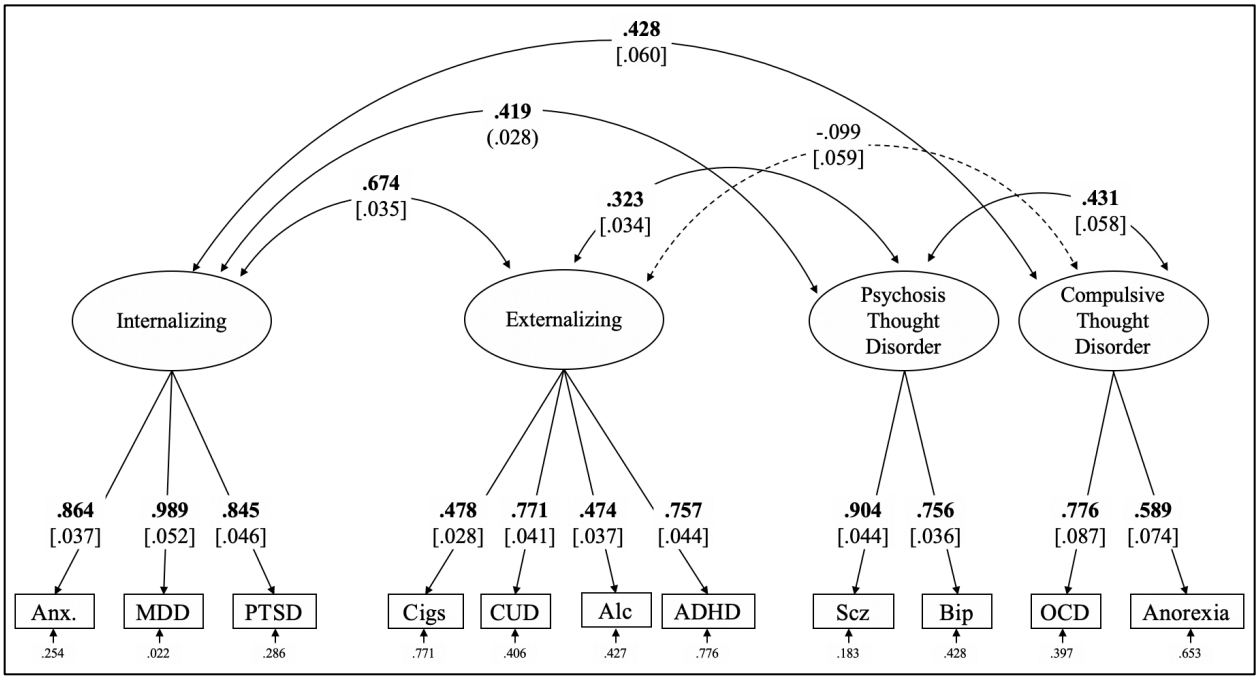
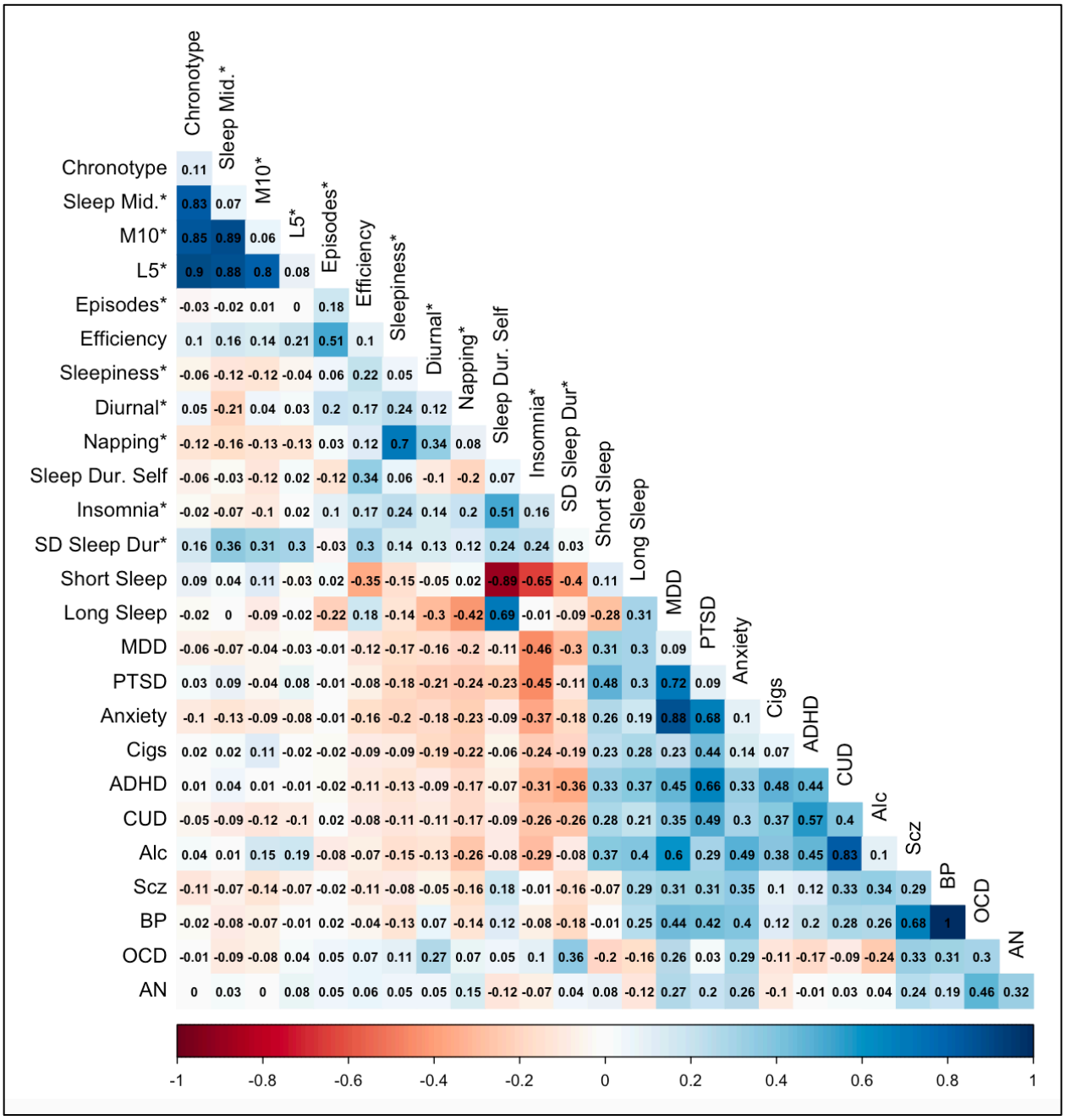


Supplemental Figure S1. Alternative Genomic SEM sleep health factor structures tested. Panel A shows the single factor model (Model 2, $\chi^2(54)$= 14,519.13, CFI=0.210, SRMR=0.176). Panel B shows the hierarchical Sleep Health factor model (Model 3, $\chi^2(49)$= 1,647.39, CFI=0.913, SRMR=0.105). Bold font indicates p<.05, 'na' indicates the loading was specified to ensure model identification and therefore Genomic SEM did not estimate a standard error. Chrono= chronotype, sleep mid= sleep midpoint, M10= most active 10 hours of the day, L5= least active 5 hours of the day, sleep dur self= self-reported sleep duration, SD sleep dur= standard deviation of the actigraphic sleep duration.



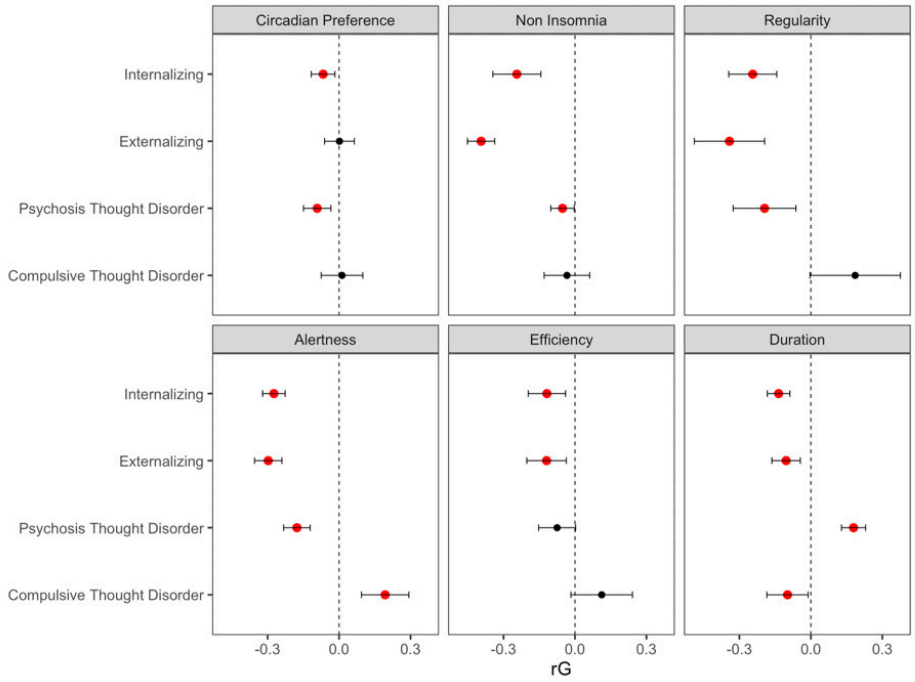
Supplemental Figure S2. Psychopathology factor structure. Model fit was good: $\chi^2(38)=$ 153.24, CFI= 0.960, SRMR= 0.076. Anx= anxiety, MDD= major depressive disorder; PTSD= post-traumatic stress disorder, cigs= cigarettes per day, CUD= cannabis use disorder, alc= problematic alcohol use, ADHD= attention deficit/ hyperactivity disorder, scz= schizophrenia, Bip= bipolar disorder, OCD= obsessive compulsive disorder. Bold font and solid lines indicate $p<.05$.



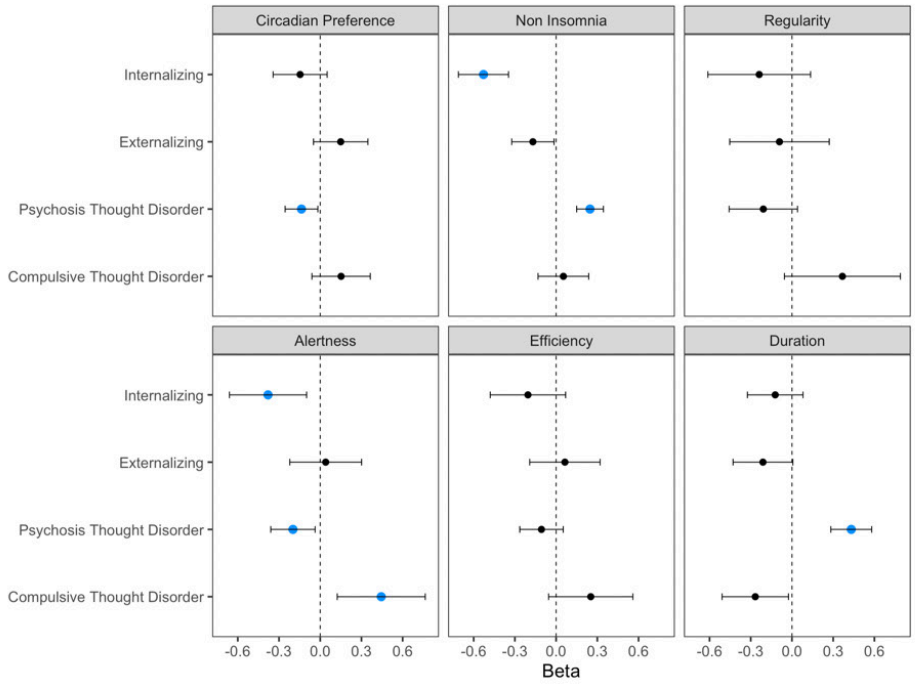
Supplemental Figure S3. Genetic correlations from LDSC with heritabilities on the diagonal of all sleep and psychopathology traits in final model. Sleep mid= sleep midpoint, M10= most active 10 hours of the day, L5= least active 5 hours of the day, sleep dur acti= actigraphic sleep duration, sleep dur self= self-reported sleep duration, SD sleep dur= standard deviation of the

actigraphic sleep duration, anx= anxiety, MDD= major depressive disorder; PTSD= post-traumatic stress disorder, cigs= cigarettes per day, CUD= cannabis use disorder, alc= problematic alcohol use, ADHD= attention deficit/ hyperactivity disorder, scz= schizophrenia, Bip= bipolar disorder, OCD= obsessive compulsive disorder. * indicates summary statistics were reverse coded to reflect health.

A. Genetic correlations between sleep health and psychopathology latent factors



B. Partial regression coefficients of psychopathology latent factors predicting sleep health latent factors



Supplemental Figure S4. Genetic correlations and partial regression coefficients of sleep health factors and psychopathology factors. Panel A shows latent correlations between sleep health and psychopathology factors. Panel B shows regression coefficients of psychopathology factors predicting sleep health factors (i.e., statistically controlling for covariances among psychopathology factors). Error bars are 95% confidence intervals and red coloring (panel A) or blue coloring (panel B) indicates statistical significance after FDR correction.