SLEEPJ, 2021, 1–13

doi: 10.1093/sleep/zsaa154
Advance Access Publication Date: 17 August 2020
Original Article

ORIGINAL ARTICLE

Inference of causal relationships between sleep-related traits and 1,527 phenotypes using genetic data

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Abstract

Study Objective: Sleep is essential for both physical and mental health, and there is a growing interest in understanding how different factors shape individual variation in sleep duration, quality and patterns, or confer risk for sleep disorders. The present study aimed to identify novel inferred causal relationships between sleep-related traits and other phenotypes, using a genetics-driven hypothesis-free approach not requiring longitudinal data.

Methods: We used summary-level statistics from genome-wide association studies and the latent causal variable (LCV) method to screen the phenome and infer causal relationships between seven sleep-related traits (insomnia, daytime dozing, easiness of getting up in the morning, snoring, sleep duration, napping, and morningness) and 1,527 other phenotypes.

Results: We identify 84 inferred causal relationships. Among other findings, connective tissue disorders increase insomnia risk and reduce sleep duration; depression-related traits increase insomnia and daytime dozing; insomnia, napping, and snoring are affected by obesity and cardiometabolic traits and diseases; and working with asbestos, thinner, or glues may increase insomnia risk, possibly through an increased risk of respiratory disease or socio-economic related factors.

Conclusion: Overall, our results indicate that changes in sleep variables are predominantly the consequence, rather than the cause, of other underlying phenotypes and diseases. These insights could inform the design of future epidemiological and interventional studies in sleep medicine and research.

Statement of Significance

Individual differences in sleep quality, duration, and patterns have been correlated with variables such as sex, age, genetics, body size, occupation, mental and physical illness status, and cultural and environmental factors. Investigating causation among pairs of correlated variables by traditional observational methods is challenging. This study leverages a recently developed method that relies on genetic data to infer causal relationships between pairs of variables, and describe inferred causal relationships between seven sleep-related traits and a set of 1,527 other phenotypes.

Key words: sleep; genetics; causal inference; epidemiology; complex-traits; insomnia; snoring; daytime dozing

Submitted: 7 May, 2020; **Revised:** 30 July, 2020

Introduction

Sleep is a complex neurological and physiological state that is essential for various biological processes and systems, ranging from homeostasis and restoration of energy levels to memory consolidation [1]. Individual differences in sleep quality, duration, and patterns have been associated with numerous variables, including sex, age, genetics, body size, occupation, mental and physical illness status, and cultural and environmental factors [2]. Furthermore, growing evidence suggests that inadequate sleep and sleep disorders are associated with several cardiometabolic, psychiatric, and neurodegenerative disorders [3–5].

To date, most large-scale epidemiological studies of sleep have focused on a few measurable traits, such as sleep duration, snoring, chronotype, or daytime dozing, and diseases such as insomnia and sleep apnea [6, 7]. Twin and family studies have demonstrated that genetic factors partly explain individual variation in sleep-related traits, with heritability estimates ranging from 0.30 for insomnia and 0.34 for daytime dozing [8], to 0.42 for morningness [9] and 0.52 for snoring [10, 11].

More recently, genome-wide association studies (GWAS) have achieved considerable success in the characterization of the genetic architecture of sleep-related traits [12–15]. GWAS have identified 351 genomic risk loci associated with chronotype [13], 41 genomic loci associated with snoring [15], and 202 genomic loci associated with insomnia [16]. Furthermore, significant genetic overlap with other conditions has been uncovered. For instance, genetic correlations (r_G) were found between insomnia and depressive symptoms, major depression, anxiety disorder, higher neuroticism scores, and lower subjective well-being scores [16]. While snoring was genetically correlated with sleep apnea, excessive daytime sleepiness, body mass index (BMI), daytime dozing, schizophrenia, anorexia nervosa, and neuroticism score, among others [15].

A genetic correlation between two polygenic traits may be due to horizontal pleiotropic effects, and therefore is not necessarily indicative of a causal relationship [17]. Horizontal pleiotropy poses challenges to statistical methods designed to infer causal relationships between environmental exposures and health outcomes using genetic data, such as Mendelian randomization (MR). Besides pleiotropy, MR can also become limited by weakly powered discovery GWAS studies, which increase the likelihood of false-positive findings, and by the need of requiring independent samples to avoid genetic overlap [17, 18]. Given the limitations of MR, alternative methods such as latent causal variable (LCV) have been developed where the need for independent samples and genome-wide significant single nucleotide polymorphisms (SNPs) is lessened [17]. LCV mediates the genetic correlation between two traits through a latent variable that has a causal effect on each trait. The LCV method distinguishes between genetic correlation due to horizontal pleiotropy and full or partial genetic causation by estimating the genetic causality proportion (GCP), a parameter that can range from 0 (no genetic causality) to 1 (full genetic causality of trait A on trait B) or –1 (full genetic causality of trait B on trait A) [17].

Due to the importance of sleep in human health, there is growing interest in understanding the determinants of sleep-related traits and their relationships with other health conditions. Previous studies have reported associations between tobacco smoking, alcohol consumption, and body mass index with an increased risk of snoring [15]; insomnia and an increased risk of depression, diabetes, and cardiovascular disease [16]; longer sleep duration with an increased risk of breast cancer in women [19]; and shorter sleep duration with a higher risk for myocardial infarction [20]. Nonetheless, most of these studies lack the design principles to perform causal inferences. In fact, many interventional studies on sleep would be considered unethical.

In the present study, we sought to explore the potential causal relationships of sleep-related traits with a broad spectrum of variables, using new statistical methods to infer causation which rely on SNP data from well-powered GWAS for pairs of traits measured on the same, or different samples. We leverage the extensive collection (n = 1,527) of GWAS summary statistics in the complex traits genetics virtual lab (CTG-VL) to conduct a hypothesis-free phenome-wide screening of variables causally associated with seven sleep-related phenotypes: insomnia, daytime dozing, easiness to get up, snoring, sleep duration, napping, and morningness. Our results confirm some of the causal associations hypothesized through observational studies, and provide new insights into the relationships between sleep, lifestyle, and health.

Methods

Sleep-related traits datasets

The present study used summary statistics from GWAS for the seven sleep phenotypes under investigation. The summary statistics resulting from a genome-wide scan summarize relevant parameters including allele frequency, effect size, standard error, and the p-value of each genetic variant tested on the trait of interest. Most published GWAS have made their summary statistics available to the scientific community, which enables researchers to leverage previous findings to advance knowledge in distinct fields. The GWAS summary statistics used here were obtained from samples with European ancestry and correspond to studies of seven self-reported sleep-related traits including snoring, insomnia, daytime dozing, getting up, sleep duration, napping, and morningness (information for each study is listed in Table 1). Datasets were obtained from the repositories reported in their corresponding publications [15, 16], where genetic signals are demonstrated to be driven by polygenicity rather than population stratification given that the LD score regression intercept for each sleep-related trait was between 0.99 and 1.10 suggesting genuine association effects due to polygenicity [15, 16]. In addition, these datasets exclude participants whose answers were “I do not know” or “Prefer not to answer” [15, 16]. Snoring GWAS summary statistics were adjusted for age, sex, genotyping array and the first 20 genetic principal components [15], whereas GWAS summary statistics for insomnia, daytime dozing, getting up, sleep duration, napping, and morningness were adjusted for age, sex, genotyping array and 10 genetic principal components [16]. No age cutoffs were applied [15, 16].

Complex traits genomics virtual lab panel datasets

A collection of 1,527 GWAS is publicly available in the CTG-VL (https://genoma.io/) web-based platform [21]. Sources of each of these GWAS are described directly in CTG-VL; however, the

Table 1. LCV method summary results for each sleep-related trait

Trait	Average sample size	Number of sig. genetic correlations	Number of potential causal relationships	Number of traits that influence the sleep trait/influenced by the sleep trait
Insomnia	384,891	608	48	48/0
Dozing	383,691	147	9	7/2
Getting up	384,310	192	11	10/1
Snoring	408,317	299	10	10/0
Sleep Duration	382,685	202	5	5/0
Napping	384,935	35	1	1/0
Morningness	344,084	84	0	0/0

The number of genetic correlations and the number of potential causal relationships correspond to those results with FDR < 5%. Traits were tested against a panel of 1,527 potentially heritable traits in the CTG-VL catalogue.

majority of these correspond to the second wave of GWAS results released by the Neale Lab (www.nealelab.is/uk-biobank/) [22]. The inclusion criteria for GWAS in CTG-VL includes having a nominally significant heritability derived from LD-score regression [21] to ensure that analyses such as LCV and genetic correlations can be performed. All GWAS summary statistics were from European ancestry, including for the UK Biobank phenotypes, and they were adjusted for age, age-squared, inferred_sex, age * inferred_sex, age-squared* inferred_sex, and 20 genetic ancestry principal components [22]. The phenotypes are used as reported by the UK Biobank including both self-reports and objective laboratory measurements [22].

Causal architecture analysis pipeline

Summary statistics from GWAS for seven sleep-related traits were collected from previous studies [15, 16]. Then, they were formatted using in-house scripts and uploaded onto the CTG-VL (https://genoma.io/) web-based platform. Subsequently, the *MASSIVE* analysis pipeline, which includes bivariate LD-score regression and LCV analysis was implemented for each sleep-related trait of interest. Finally, causal architecture plots were used to depict the LCV results (Figure 1).

Genetic correlations

A genetic correlation between two traits describes the relationship of genetic effects sizes at mutual genetic variants across two different phenotypes [23]. The LCV method estimates a genetic correlation between traits A and B through a modified linkage disequilibrium score regression [24]. If the genetic correlation is nominally significant, then a latent variable *L* is introduced into the model to assess causality between trait A and trait B, assuming that L is the causal component that mediates the genetic correlation between both traits (see further section) [17, 18]. We corrected for multiple testing using Benjamini–Hochberg's false discovery rate (FDR < 5%).

Genetic causal proportion

LCV is a method that uses summary statistics from GWAS to estimate the GCP parameter, by mediating the genetic correlation between Trait A and Trait B with a latent variable *L*. A GCP of 0 indicates no genetic causality. A GCP of 1 or –1 is indicative of full genetic causality, of Trait A on Trait B, or Trait B on Trait A, respectively. Values between 0 and 1 or 0 and –1 would indicate partial genetic causality [17, 18]. Although causality is often thought of as a binary characteristic, the idea of partial genetic causality is consistent with both a causal relationship between two complex traits and the notion of distinct genetic components underlying complex traits (e.g. a disease could be caused by both, direct genetic effects, and genetic predisposition to one or more environmental exposures).

The major advantage of the LCV method over other methods such as MR is that it differentiates horizontal from vertical pleiotropy. The model assumes that given a directed effect of trait A on trait B, the effects of genetic variants underlying trait A are expected to have proportional effects on trait B, but not vice versa. Thus, by mediating the genetic correlation between trait A and trait B through the *L* parameter, one can estimate the GCP (see [17] for more details). A GCP value close to 0 suggests that horizontal pleiotropy mediates the genetic correlation between traits A and B, and thus any intervention targeting trait A should not affect trait B [17]. In addition, the most attractive features of the LCV method include it is unconfounded by horizontal pleiotropy [18], the mitigation of sample overlap [18], and the use of genetic information aggregated throughout the genome, which increases statistical power and thus, allows phenotypes that would be considered "underpowered" for other statistical methods to be tested in LCV [18].

Notably, the LCV method assumes no bidirectional causality and no confounding by environmental correlates of genotypes. Therefore, care is required when these assumptions are not met [18]. Multiple testing in GCP was corrected for using Benjamini–Hochberg's FDR < 5%.

Sensitivity analyses

MR methods are a commonly used approach used to investigate causal relationships between risk factors and health outcomes [25]. MR methods assume that an unconfounded genetic variant is only associated with the outcome through the exposure [26, 27]. Further, MR methods are strictly tied to the statistical power of the samples and phenotypes of interest, as they are required to show several genome-wide significant SNPs [28]. Also, they require independent samples with no overlap in participants [29].

We performed additional sensitivity analyses for the 84 inferred causal relationships that were initially identified. With traditional two-sample MR methods, we were able to test 11 bivariate relationships with MR methods including GSMR, inverse variance weighted (IVW), MR Egger, weighted median, and simple mode. Multiple testing in MR methods was corrected for using Bonferroni *p*-value correction.

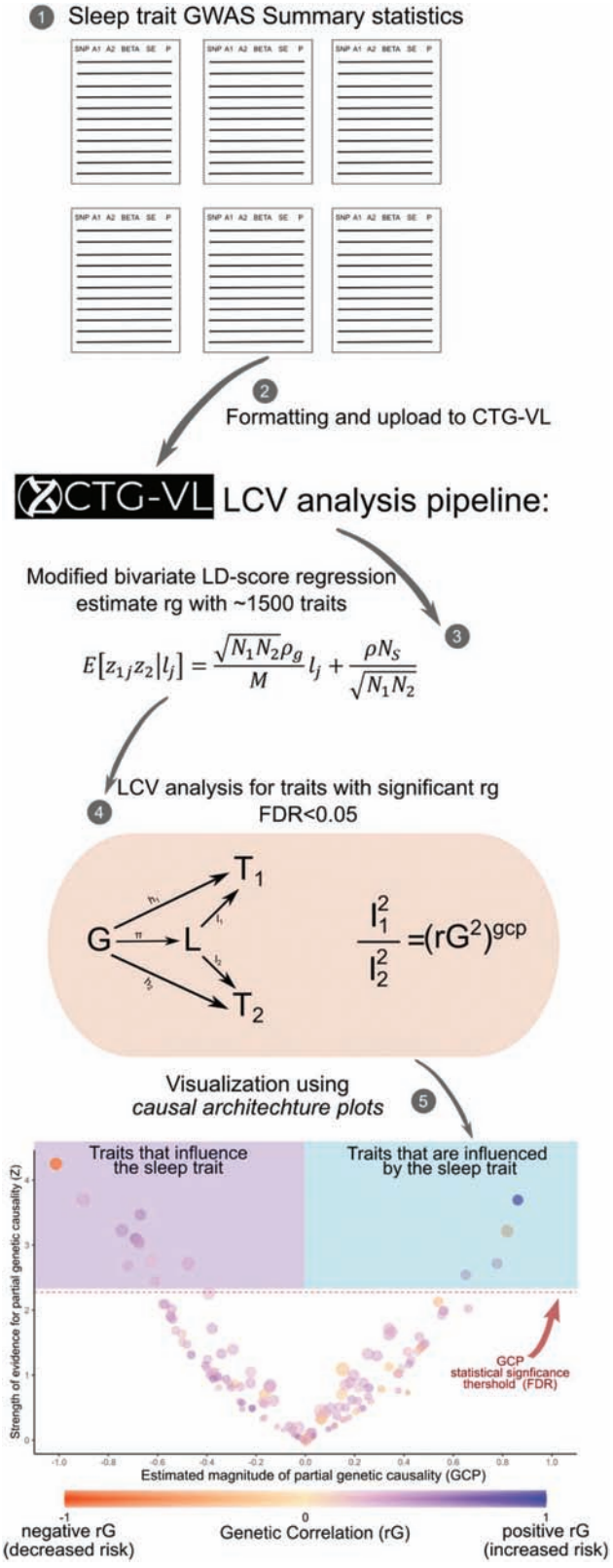

Figure 1. Overview of the causal architecture analysis pipeline. (1) Summary statistics from GWAS for seven sleep-related traits were obtained from previously published studies. (2) Formatting and loading of data to the CTG-VL. (3) Implementation of the *MASSIVE* analysis pipeline, including bivariate LD-score regression and (4) LCV. (5) Causal architecture plots were used to describe the LCV results. Each dot represents a trait with a significant genetic correlation. The x-axis shows the estimated GCP from a LCV. Traits with a positive GCP are influenced by the sleep-related trait studied, whereas traits with a negative GCP are influencing the sleep-related trait of interest. The position on the y-axis represents the strength of the association and a red dashed line shows the statistical significance threshold accounting for multiple testing (FDR < 5%). The LCV diagram of step 4 is based on a diagram from the original LCV publication [17].

Results

Insomnia

We identified significant genetic correlations between insomnia and 608 traits (FDR < 5%). A total of 48 of those traits showed an inferred causal effect on insomnia risk (negative GCP estimates), and we did not find any significant causal effect of insomnia on another trait (Table 1). The traits with the strongest evidence of causal effect on insomnia were *dyspepsia* (r_G = 0.34, GCP = –0.97, p-value$_{GCP}$ = 2.37 × 10^{-213}), *often worked with materials containing asbestos* (r_G = 0.26, GCP = –0.97, p-value$_{GCP}$ = 7.23 × 10^{-202}), and *chest pain during physical activity* (r_G = 0.57, GCP = –0.96, p-value$_{GCP}$ = 1.33 × 10^{-100}; Table 2). Consistently, *rarely/never worked with materials containing asbestos* was causally associated with reduced insomnia risk (r_G = –0.44, GCP= –0.92, p-value$_{GCP}$ = 2.30 ×10^{-33}; Figure 2 and Supplementary File S1).

Traits related to connective tissue and musculoskeletal health, such as *other specific joint derangements/joint disorders* (r_G = 0.64, GCP = –0.73, p-value$_{GCP}$ = 3.21 × 10^{-04}), *synovitis* and *tenosynovitis (ICD10)* (r_G = 0.28, GCP = –0.50, p-value$_{GCP}$ = 9.65 × 10^{-26}), and *other arthrosis* (r_G = 0.51, GCP = –0.79, p-value$_{GCP}$ = 1.17 × 10^{-07}), also showed inferred causal relationships with insomnia risk. Additionally, respiratory-related traits including *interstitial lung disease (ILD)* (r_G = 0.38, GCP = –0.65, p-value$_{GCP}$ = 0.003) and *chronic obstructive pulmonary disease (COPD)* (r_G = 0.38, GCP = –0.65, p-value$_{GCP}$ = 0.003) showed evidence of increasing the risk for insomnia as did gastrointestinal phenotypes including *other gastritis* (r_G = 0.51, GCP = –0.76, p-value$_{GCP}$ = 2.35 × 10^{-06}). A similar pattern was observed for *stopped smoking due to an illness* (r_G = 0.46, GCP = –0.85, p-value$_{GCP}$ = 1.64 × 10^{-14}) *or due to a doctor's advice* (r_G = 0.40, GCP = –0.75, p-value$_{GCP}$ = 7.20 × 10^{-06}; Figure 2).

Daytime dozing

We identified 147 traits with a significant genetic correlation with daytime dozing and 9 with evidence for an inferred causal relationship. Of those, seven influence dozing, and two are putative consequences of it (Figure 3, A). Moreover, five out of the nine inferred causal relationships directly involve depression, with the trait *no bipolar disorder or depression* showing the most robust evidence for decreasing the risk for daytime dozing (r_G = –0.32, GCP = –0.68, p-value$_{GCP}$ = 2.13 × 10^{-05}), followed by seeing a doctor (GP) for *nerves, anxiety, tension, or depression*, which increased risk for daytime dozing (r_G = 0.27, GCP = –0.53, p-value$_{GCP}$ = 2.15 × 10^{-04}; Table 3).

Snoring

Snoring was genetically correlated with 299 different traits, 10 of which held a causal effect on snoring (Figure 3, B). The identified inferred causal relationships that increased the risk of snoring included *umbilical hernia* (r_G = 0.25, GCP = –0.42, p-value$_{GCP}$ = 4.55 × 10^{-11}), *angina pectoris* (r_G = 0.26, GCP = –0.80, p-value$_{GCP}$ = 3.90 × 10^{-09}), and *obesity* (r_G = 0.27, GCP = –0.73, p-value$_{GCP}$ = 2.54 × 10^{-05}; Table 3), all of which were ascertained as an International Classification of Diseases (ICD10) diagnosis (see discussion).

Table 2. Traits with a causal effect on insomnia

Trait	GCP	GCP se	GCP pval	r_G	r_G se	r_G pval
Dyspepsia (ICD10)	−0.972	0.031	2.37E−213	0.344	0.116	3.01E−03
Often worked with materials containing asbestos	−0.968	0.031	7.23E−202	0.266	0.1138	1.90E−02
Chest pain felt during physical activity	−0.956	0.044	1.33E−100	0.575	0.1944	3.07E−03
Other disorders of fluid, electrolyte and acid-base balance (ICD10)	−0.910	0.076	5.17E−33	0.378	0.1364	5.59E−03
Difficulty concentrating during worst period of anxiety	−0.870	0.080	1.83E−27	0.313	0.1357	2.09E−02
Self-reported type 2 diabetes	−0.934	0.095	8.66E−23	0.233	0.100	1.98E−02
Self-reported sciatica	−0.701	0.090	6.63E−15	0.412	0.179	2.16E−02
Why stopped smoking: Illness or ill health	−0.856	0.111	1.64E−14	0.455	0.141	1.29E−03
Small vessel stroke (Europeans only)	−0.881	0.122	6.51E−13	0.311	0.120	1.35E−02
Destinations on discharge from hospital: Transfer to other NHS provider: General ward, young physically disabled, A&E	−0.769	0.107	7.69E−13	0.426	0.155	6.71E−03
Endocrine, nutritional and metabolic diseases	−0.810	0.131	6.27E−10	0.401	0.150	9.19E−03
Other arthrosis	−0.793	0.149	1.17E−07	0.513	0.130	1.11E−04
Workplace sometimes very noisy	−0.791	0.149	1.23E−07	0.362	0.120	2.64E−03
Cylindrical power (left)	−0.768	0.147	1.95E−07	0.224	0.097	2.17E−02
Fibroblastic disorders	−0.784	0.153	3.24E−07	0.189	0.061	2.20E−03
Fractured bone site(s): Other bones	−0.758	0.153	8.41E−07	0.264	0.081	2.68E−03
Self-reported cervical spondylosis	−0.767	0.159	1.59E−06	0.392	0.119	1.05E−03
Other gastritis (incl. Duodenitis)	−0.767	0.162	2.35E−06	0.506	0.097	2.20E−07
Fibroblastic disorders (ICD10)	−0.760	0.168	6.36E−06	0.186	0.064	3.49E−03
Why stopped smoking: Doctor's advice	−0.756	0.168	7.20E−06	0.397	0.104	1.44E−04
Mouth/teeth dental problems: Toothache	−0.726	0.166	1.23E−05	0.315	0.071	9.56E−06
Mouth/teeth dental problems: Mouth ulcers	−0.739	0.170	1.51E−05	0.200	0.046	1.86E−05
Primary gonarthrosis (Bilateral)	−0.733	0.171	1.93E−05	0.298	0.117	1.11E−02
Treatment/medication: Diazepam	−0.740	0.174	2.13E−05	0.443	0.170	9.47E−03
Mouth ulcers	−0.723	0.170	2.24E−05	0.193	0.042	5.49E−06
Knee pain for 3+ months	−0.718	0.181	7.46E−05	0.395	0.101	1.04E−04
Diseases of the ear and mastoid process	−0.718	0.183	9.14E−05	0.301	0.116	9.90E−03
Workplace sometimes very dusty	−0.718	0.194	2.13E−04	0.489	0.149	1.07E−03
Other specific joint derangements/joint disorders	−0.728	0.202	3.21E−04	0.647	0.131	7.92E−07
Palmar fascial fibromatosis [Dupuytren]	−0.702	0.206	6.72E−04	0.165	0.059	5.40E−03
Ever heard an un-real voice	−0.677	0.203	8.63E−04	0.265	0.106	1.26E−02
ILD differential diagnosis	−0.648	0.214	2.49E−03	0.37	0.059	2.59E−10
COPD differential diagnosis	−0.648	0.214	2.49E−03	0.37	0.059	2.59E−10

This table shows all traits with a significant (FDR < 5%) GCP for insomnia with a positive genetic correlation ($r_G > 0$) and a strong GCP estimate (GCP < −0.60). Results for all nominally significant genetic correlations for insomnia are reported in Supplementary File S1.

Sleep duration

Two hundred and two traits were genetically correlated with sleep duration. Five of them were found to causally influence sleep duration. Similar to insomnia, traits related to connective tissue and musculoskeletal health showed evidence of an inferred causal association, including *disorders of synovium and tendon + bursophaties* (r_G = −0.33, GCP = −0.83, p-value$_{GCP}$ = 2.39 × 10^{-16}) and *primary gonarthrosis (bilateral)* (r_G = −0.35, GCP = −0.79, p-value$_{GCP}$ = 9.34 × 10^{-08}), both decreasing sleep duration (Figure 4, A and Table 3).

Getting up

The *ease of getting up in the morning* was genetically correlated with 192 traits. We found 10 traits with an inferred causal relationship with getting up, and one being causally influenced by it. The *age at the first episode of depression* was the only trait associated with being easier for an individual to get up in the morning (r_G = 0.44, GCP = −0.79, p-value$_{GCP}$ = 1.51 × 10^{-07}). In contrast, the only trait that was influenced by getting up was *ever had prolonged feelings of sadness or depression* (r_G = −0.37, GCP = 0.68, p-value$_{GCP}$ = 0.002). Out of the 11 inferred causal relationships that were identified, 6 of them directly involve either depression, anxiety or panic attacks (Figure 4, B and Table 3).

Napping and morningness

Out of the 35 traits genetically correlated with napping, only *triglyceride levels* held a significant inferred causal effect that increased the risk for napping (r_G = 0.16, GCP = −0.83, p-value$_{GCP}$ = 1.30 × 10^{-14}; Table 3; Supplementary Figure S1, A). For morningness, genetic correlations with 84 traits were identified. However, none of them supported a potential causal relationship independent of pleiotropy (Supplementary Figure S1, B and Supplementary File S1).

Sensitivity analyses

As a sensitivity analysis, we attempted to perform traditional MR methods such as GSMR, IVW, MR Egger, weighted median, and simple mode for the 84 inferred causal relationships identified through the LCV method. Traditional MR methods rely on the availability of sufficient instruments (i.e. genome-wide significant loci). However, the majority of the 84 phenotypes showed too few genome-wide significant loci each, thus lacking sufficient statistical power for traditional MR methods (Supplementary File S2). Out of the 11 bivariate relationships that we were able to test with MR methods, the inferred causal relationship in which *triglycerides* increased napping was

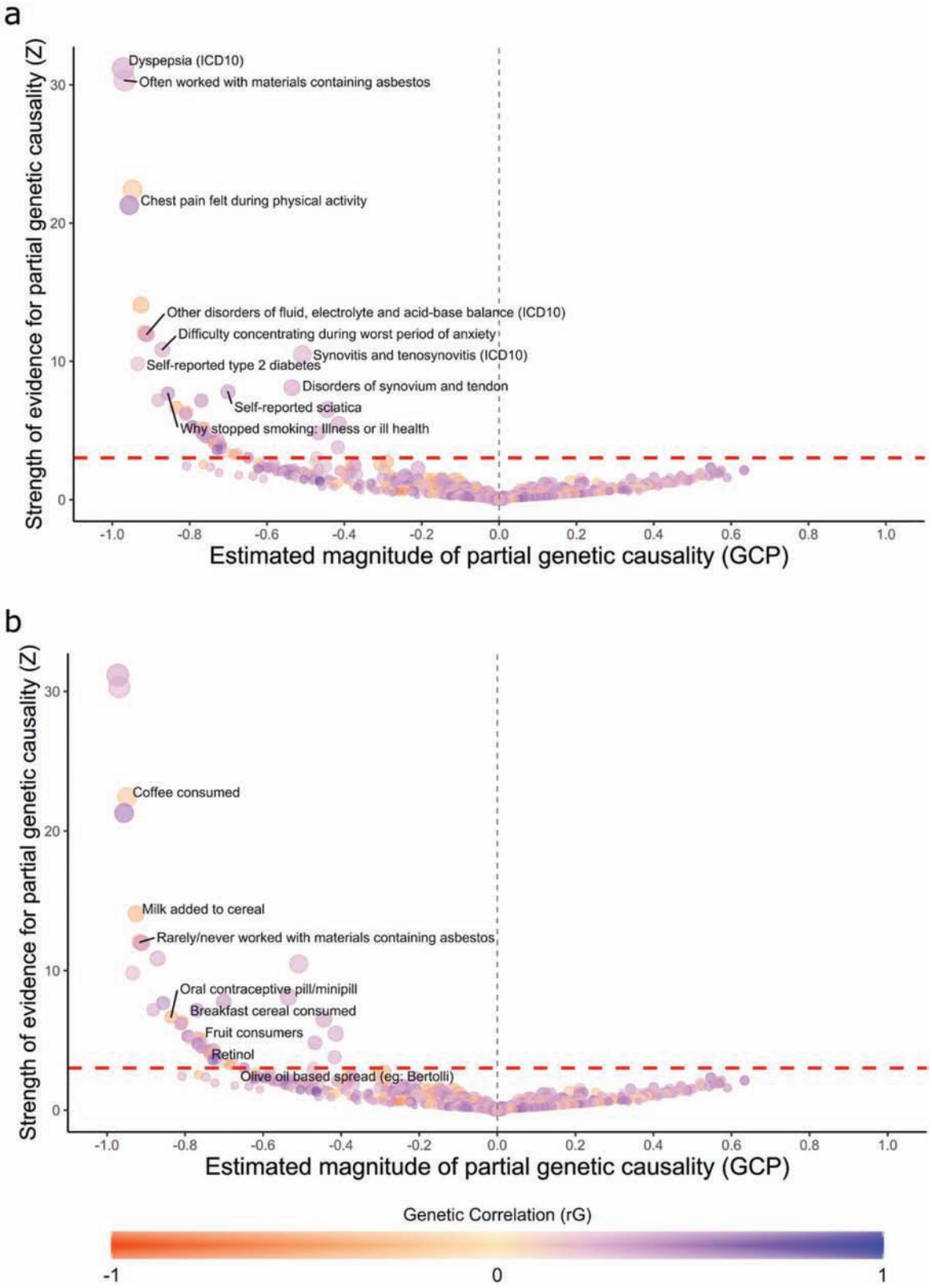

Figure 2. Causal associations for insomnia. Causal architecture plots depicting the LCV exposome-wide analysis results. Dots represent traits with a significant genetic correlation with the trait of interest. The x-axis shows the GCP estimate, while the y-axis shows the GCP absolute Z-score (statistical significance). The red dashed lines represent the statistical significance threshold (FDR < 5%), while the grey dashed lines represent the division for traits causally influencing a sleep trait (on the left) and traits causally influenced by the sleep trait (on the right). Showing separately results for traits that increased risk for insomnia (A) and decreased risk for insomnia (B). An explanation for how to interpret these plots is available in Figure 1.

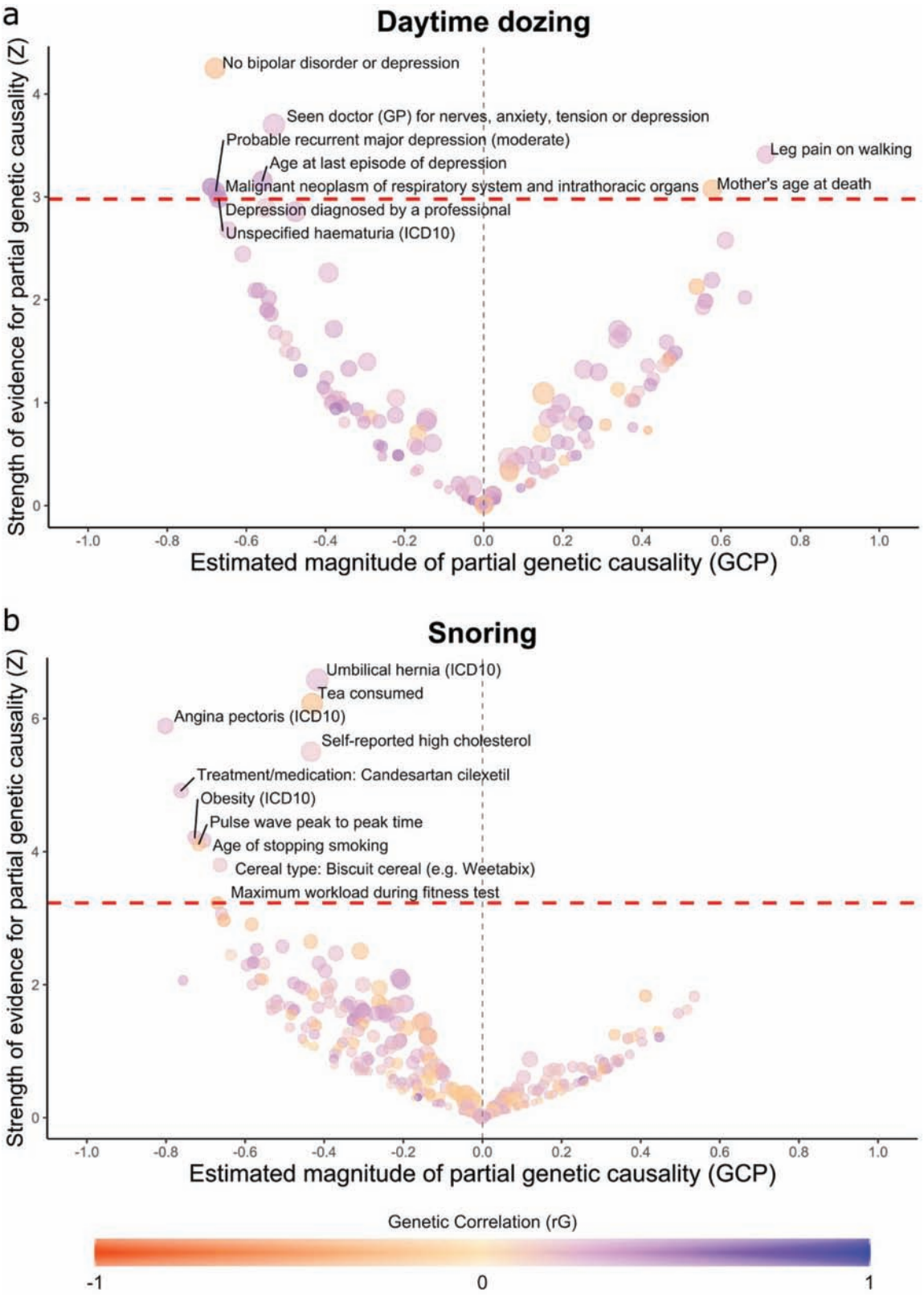

Figure 3. Causal associations for daytime dozing and snoring. Causal architecture plots depicting the LCV exposome-wide analysis results. Dots represent traits with a significant genetic correlation with the trait of interest. The x-axis shows the GCP estimate, while the y-axis shows the GCP absolute Z-score (statistical significance). The red dashed lines represent the statistical significance threshold (FDR < 5%), while the grey dashed lines represent the division for traits causally influencing a sleep trait (on the left) and traits causally influenced by the sleep trait (on the right). Showing results for daytime dozing (A) and snoring (B). An explanation for how to interpret these plots is available in Figure 1.

Table 3. Traits with a causal relationship with sleep-related traits

Trait 1	Trait 2	GCP	GCP se	GCP pval	r_G	r_G se	r_G pval
Dozing	No bipolar disorder or depression	−0.678	0.159	2.13E−05	−0.323	0.089	2.79E−04
Dozing	Seen doctor (GP) for nerves, anxiety, tension or depression	−0.530	0.143	2.15E−04	0.274	0.060	5.80E−06
Dozing	Leg pain on walking	0.713	0.209	6.44E−04	0.266	0.089	2.72E−03
Dozing	Age at last episode of depression	−0.559	0.177	1.59E−03	0.403	0.141	4.25E−03
Dozing	Malignant neoplasm of respiratory system and intrathoracic organs	−0.689	0.222	1.95E−03	0.569	0.179	1.49E−03
Dozing	Mother's age at death	0.577	0.187	2.10E−03	−0.314	0.104	2.51E−03
Dozing	Probable recurrent major depression (moderate)	−0.676	0.221	2.22E−03	0.372	0.132	4.82E−03
Dozing	Depression diagnosed by a professional	−0.674	0.222	2.46E−03	0.345	0.082	2.25E−05
Dozing	Unspecified hematuria (ICD10)	−0.669	0.224	2.90E−03	0.463	0.101	4.12E−06
Getting up	Episodal and paroxysmal disorders	−0.823	0.052	4.64E−55	−0.215	0.071	2.30E−03
Getting up	Easily tired during worst period of anxiety	−0.659	0.063	4.43E−25	−0.343	0.116	3.11E−03
Getting up	Manifestations of mania or irritability: Increased creativity	−0.655	0.080	3.64E−16	−0.299	0.109	6.16E−03
Getting up	Tinnitus: Some of the time	−0.816	0.132	6.38E−10	−0.354	0.107	8.94E−04
Getting up	Taken unprescribed medication for depression (more than once)	−0.588	0.098	2.65E−09	−0.468	0.145	1.25E−03
Getting up	Age at first episode of depression	−0.789	0.150	1.51E−07	0.435	0.100	1.21E−05
Getting up	Self-reported anxiety/panic attacks	−0.273	0.062	1.22E−05	−0.311	0.077	4.95E−05
Getting up	Panic attacks diagnosed by a professional	−0.499	0.122	4.75E−05	−0.247	0.074	7.62E−04
Getting up	Treatment/medication: Citalopram	−0.700	0.182	1.20E−04	−0.266	0.088	2.34E−03
Getting up	Ever had prolonged feelings of sadness or depression	0.680	0.216	1.66E−03	−0.368	0.041	4.46E−19
Getting up	Been in serious accident believed to be life-threatening	−0.595	0.193	2.04E−03	−0.233	0.079	3.14E−03
Snoring	Umbilical hernia (ICD10)	−0.417	0.063	4.55E−11	0.252	0.092	5.72E−03
Snoring	Tea consumed	−0.430	0.069	4.92E−10	−0.309	0.078	6.58E−05
Snoring	Angina pectoris (ICD10)	−0.801	0.136	3.90E−09	0.257	0.052	8.56E−07
Snoring	Self-reported high cholesterol	−0.433	0.078	3.75E−08	0.172	0.043	6.45E−05
Snoring	Treatment/medication: Candesartan cilexetil	−0.761	0.154	8.71E−07	0.254	0.074	5.55E−04
Snoring	Obesity (ICD10)	−0.727	0.172	2.54E−05	0.265	0.104	1.06E−02
Snoring	Age of stopping smoking	−0.704	0.168	3.06E−05	0.270	0.098	5.75E−03
Snoring	Pulse wave peak to peak time	−0.716	0.174	3.82E−05	−0.240	0.069	5.60E−04
Snoring	Cereal type: Biscuit cereal (e.g. Weetabix)	−0.663	0.174	1.44E−04	0.185	0.059	1.89E−03
Snoring	Maximum workload during fitness test	−0.670	0.207	1.24E−03	−0.364	0.081	7.43E−06
Sleep duration	Semi skimmed milk consumed	−0.848	0.096	1.53E−18	0.356	0.128	5.39E−03
Sleep duration	Disorders of synovium and tendon + bursopathies	−0.826	0.100	2.39E−16	−0.326	0.112	3.80E−03
Sleep duration	Treatment/medication: Movicol oral powder	−0.851	0.120	1.46E−12	−0.437	0.153	4.12E−03
Sleep duration	Primary gonarthrosis (Bilateral)	−0.789	0.147	9.34E−08	−0.350	0.125	5.17E−03
Sleep duration	Factors influencing health status and contact with health services	−0.689	0.203	6.94E−04	−0.204	0.072	4.70E−03
Napping	Triglycerides	−0.833	0.108	1.30E−14	0.159	0.037	1.52E−05

The table shows all traits with a significant (FDR < 5%) GCP for daytime dozing, dozing, ease to get up in the morning, snoring, sleep duration, and napping. Nominally significant genetic correlations for all sleep-related traits are reported in Supplementary File S1.

replicated with GSMR and survived Bonferroni *p*-value correction (Supplementary File S2). Similarly, of the 11 associations tested with traditional MR methods, the inferred causal relationships for *unspecified hematuria (ICD10)* increasing daytime dozing, *high cholesterol* increasing snoring, and *triglycerides* increasing napping were replicated. However, none of these associations survived Bonferroni *p*-value correction. (Supplementary File S2).

Discussion

This study provides new insights into the determinants and consequences of seven sleep-related traits. We examined potential causal associations between sleep-related phenotypes and 1,527 traits and identified 84 significant inferred causal relationships based on genetic evidence. Overall, our results suggest that changes in sleep variables were predominantly the consequence, rather than the cause, of other underlying phenotypes and diseases.

We identified inferred causal genetic influences of several conditions on insomnia risk. Consistent with previous studies [30, 31], gastrointestinal disorders such as *dyspepsia* and *other gastritis*, including *duodenitis*, and respiratory diseases, increased the risk of insomnia. The effects of asthma on insomnia have been described before, showing that uncontrolled asthma is a risk factor for insomnia [32, 33]. Additionally, *COPD* and *ILD*, also showed a causal effect on increased insomnia risk. Exposure to *asbestos, dust, and substances containing solvents such as paint, thinners, and glues* was also a causal factor for insomnia. Asbestos and solvents are hazardous chemicals that induce an inflammatory response in the respiratory system and may lead to *pulmonary fibrosis* [34], *ILD* [35], *COPD* [36], and lung cancer [37, 38].

Previous studies have described the relationships between socioeconomic status (SES) and chronic disease [39–41] highlighting the role of the occupation and work environment of individuals [40, 42] where people with lower SES are exposed more often to chemicals and toxins in their workplace, damaging their health [39, 40, 43]. For example, previous studies have identified a higher occurrence of COPD among people with low SES [41]. Notably, in our study, other occupations and work environments such as *workplace is often full or chemicals or other fumes* and *workplace often had a lot of diesel exhaust* presented a significant genetic correlation (Supplementary File S1). However, our results did not support a causal association (Supplementary

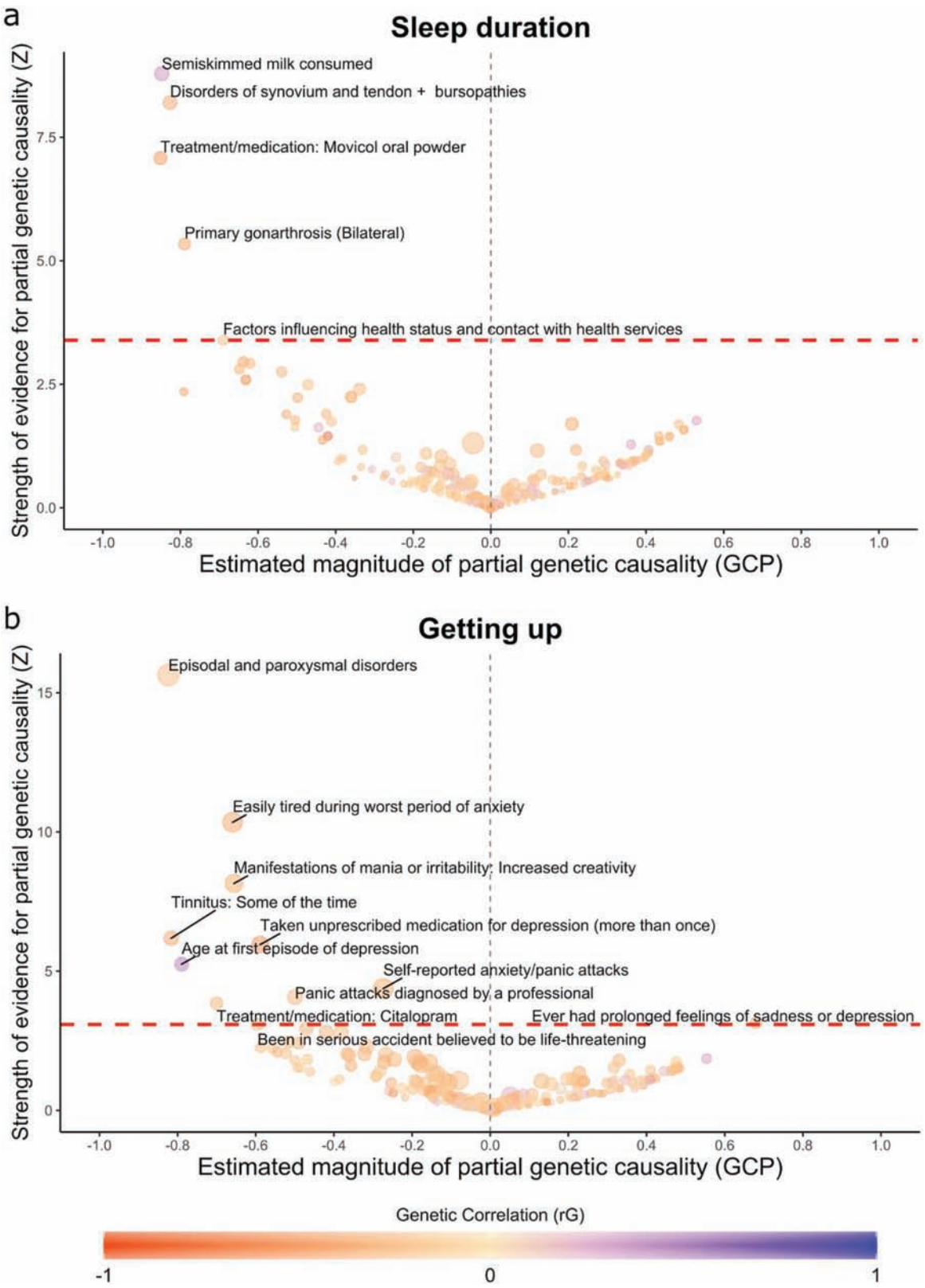

Figure 4. Causal associations for sleep duration and getting up. Causal architecture plots depicting the LCV exposome-wide analysis results. Dots represent traits with a significant genetic correlation with the trait of interest. The x-axis shows the GCP estimate, while the y-axis shows the GCP absolute Z-score (statistical significance). The red dashed lines represent the statistical significance threshold (FDR < 5%), while the grey dashed lines represent the division for traits causally influencing a sleep trait (on the left) and traits causally influenced by the sleep trait (on the right). Showing results for sleep duration (A) and ease of getting up (B). An explanation for how to interpret these plots is available in Figure 1.

File S1). Finally, no evidence for an inferred causal association of other SES measures such as townsend deprivation index was observed (Supplementary File S1). Therefore, our results would suggest that exposure to asbestos and solvents could lead to insomnia, perhaps as a consequence of the development of severe respiratory diseases such as *COPD*, *ILD*, and *asthma*.

Musculoskeletal conditions and connective tissue disorders also increased insomnia risk. *Synovitis* and *tenosynovitis* (ICD10), *disorders of synovium and tendon*, self-reported *sciatica*, *fibroblastic disorders* (ICD10), *self-reported cervical spondylosis*, *primary gonarthrosis (bilateral)*, and *knee pain for more than 3 months*, among others, could be used as a proxy for poor musculoskeletal and connective tissue health. Previous studies have found an association between shorter sleep duration and insomnia with chronic pain [44]. In the present study, *sciatica, primary gonarthrosis (bilateral)* and *disorders of synovium and tendon* were also causally associated with shorter sleep duration. We speculate that the discomfort and inflammation arising from problems in the musculoskeletal system and connective tissue may reduce sleep duration. However, more research is needed to understand the intricate relationship between pain and sleep.

Depression and anxiety are common among people with insomnia, and previous studies suggest that insomnia may increase the risk of depression and anxiety [45, 46]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), insomnia is considered a secondary symptom of major depression [47]. Although our results did not show a direct inferred causal relationship between insomnia and anxiety or depression diagnosis, the *frequency* in the use of Diazepam, a common medication for anxiety disorders [48] and a proxy for anxiety severity, had a causal association with insomnia. Also, *depression diagnosed by a professional* and *age at last episode of depression* among other depression-related traits, showed an inferred causal relationship increasing the risk for daytime dozing. This is expected, as excessive daytime sleepiness is a common symptom of depression [49, 50].

The relationship between insomnia and cardiometabolic diseases has been described before reaching an unclear set of conclusions. Most studies suggest that insomnia, particularly in the context of short sleep duration, poses a risk for cardiometabolic diseases, in particular, hypertension [51–54] and diabetes mellitus [52, 55]. In contrast, others suggest that insomnia symptoms are not positively associated with hypertension [56]. In the present study, results uncovered insomnia-increasing inferred causal relationships with cardiometabolic traits including self-reported type 2 diabetes, electrolyte and acid-base balance, as well as endocrine and metabolic diseases, indicating insomnia is most likely a consequence of these diseases. Furthermore, the inferred causal relationships found with *chest pain during physical activity, the use of treatment/medication: GTN 400 micrograms spray*, which is commonly prescribed for hypertension [57], and *small vessel stroke*, which is known to be a consequence of hypertension [58], suggest that the development of cardiometabolic disease may be causally associated with insomnia.

Variables such as *mouth ulcers* and *stopped smoking due to an illness or a doctor recommendation* also showed evidence of inferred causal relationship increasing insomnia risk. Nonetheless, these relationships are likely explained by a single causal effect on insomnia. Smoking cessation is accompanied by an abstinence phase, which is well-known as a risk factor for both, mouth ulcers [59, 60], and insomnia [60, 61]. We speculate that the apparent inferred causal relationship of mouth ulcers on insomnia is mediated through smoking cessation. Formally testing this hypothesis was outside the scope of the present study.

A negative association between the ease of getting up in the morning and depression has been reported previously [62]. Our results consistently showed inferred causal relationships for anxiety traits such as *panic attacks diagnosed by a professional* and *use of citalopram*, a common antidepressant [63, 64], increasing the difficulty to get out of bed in the morning. Further, the *age at the first episode of depression*, which is a proxy for the severity and recurrence of depression [65], showed an inferred causal relationship with getting up, where higher age increases the ease of getting up. Consistently, we identified an inferred causal relationship where the risk of *ever having prolonged feelings of sadness or depression* was lower for individuals who can effortlessly get up in the morning. These results agree with the fact that sleep problems and reduced energy are part of the diagnostic criteria for clinical depression.

Relationships between snoring and cardiometabolic traits have been reported before [15, 66]. We previously reported a causal link between BMI and snoring [15] and putative causal links of whole-body fat mass on snoring risk [15]. Other studies had also suggested that snoring is a risk factor for cardiometabolic traits such as hypertension [67] and angina pectoris [68]. In this study, we identified several factors that influence snoring risk, including *obesity* (ICD10), *angina pectoris* (ICD10), a known risk factor for coronary heart disease (CHD) [69, 70], *self-reported high cholesterol* and *use of candesartan*, a common drug for treating hypertension [71]. Although this suggests that coronary heart disease exerts an inferred causal relationship on snoring, we cannot currently rule out whether this is mediated through the genetic component for obesity that underlies CHD. The inferred causal relationship found for *triglycerides* causing *napping* is consistent with previous studies in the Chinese population [72]. However, no evidence was found between *napping* and *CHD* as described in other studies [72]. We hypothesize that well-powered GWAS would show a relationship with CHD and obesity, all known to correlate with triglyceride levels.

Poor replication of LCV results with sensitivity analyses is attributed to the limitations in the assumptions that must be met in MR methods. In particular, several phenotypes assessed in the present study have none or less than 10 genome-wide significant SNPs (Supplementary File S2), which limits the feasibility of implementing traditional MR methods. Further, given that a substantial proportion of the data used in this study comes from the UK Biobank cohort (see Methods), the requirement for independent samples could not be met.

Our observations are aligned with reports of LCV being a powerful a powerful tool to flag potential causal relationships in underpowered phenotypes that cannot be detected with MR [17, 18]. Therefore, we recommend interpreting LCV as a hypothesis generator to point out potential causal relationships that, when estimated with well-powered samples, could then be followed by other statistical methods to address causality such as MR methods.

Some limitations of the present study need to be acknowledged. First, our analyses only employed data from individuals of European ancestry from the UK Biobank cohort. Given that previous studies have highlighted ethnic differences in

sleep-related traits [73–76], the generalizability of the results may be limited. Also, despite the use of aggregated genetic information throughout the genome to increase statistical power in the LCV method, since the GCP estimates are still tied to the statistical power of the GWAS, the capacity to identify inferred causal effects for some traits is limited [76]. In addition, despite the inclusion of more than 1,500 traits, other causal associations not tested here may exist. Further, it is crucial to keep in mind the possible biases or designs of the GWAS involved. For instance, our results implicate several medication use GWAS, however, our results suggest these should be interpreted as a proxy for the underlying disease or symptom requiring the medication. Finally, our study highlights the challenge of dealing with non-pleiotropic horizontal associations, where a third trait may moderate the association between two other traits through a shared genetic component. An example is the association of cardiovascular disease-related phenotypes and snoring, which could be mediated through obesity. While we cannot rule out a direct causal association, the most likely explanation is that obesity causes both snoring and cardiovascular disease through a shared genetic component. This limitation is implicit in the bivariate nature of the LCV approach, and future developments on statistical genetics could leverage causal architecture statistical networks to disentangle confounding effects.

In summary, we provide evidence for inferred causal relationships for seven sleep-related traits and 1,527 other phenotypes. Our analyses uncovered the role of musculoskeletal and connective tissue disorders in increasing the risk for insomnia and shorter sleep duration. Also, we show the influence of depression on insomnia, getting up, and daytime dozing as well as the role of obesity and potentially cardiometabolic traits and diseases, causing an increased risk for insomnia, napping, and snoring. We also observed an influence of diet and lifestyle-related variables such as working with asbestos, thinner, or glues on respiratory diseases, which in turn increase insomnia risk. Altogether, our results generate testable hypotheses that, if confirmed, could inform the design of novel treatment and intervention strategies to support better sleep quality and overall health.

Supplementary material

Supplementary material is available at *SLEEP* online.

Acknowledgments

We thank our colleague Jackson Thorp for his valuable feedback and for proof-reading the manuscript.

Funding

AIC is supported by a UQ Research Training Scholarship from The University of Queensland (UQ). M.E.R. thanks the support of Australia's National Health and Medical Research Council and Australian Research Council (ARC) through a Research Fellowship (APP1102821). The funding agencies had no involvement in the design or implementation of the study.

Conflict of interest statement. None declared.

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