ORIGINAL ARTICLE

Sleep health, diseases, and pain syndromes: findings from an electronic health record biobank

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Abstract

Study Objectives: Implementation of electronic health record biobanks has facilitated linkage between clinical and questionnaire data and enabled assessments of relationships between sleep health and diseases in phenome-wide association studies (PheWAS). In the Mass General Brigham Biobank, a large health system-based study, we aimed to systematically catalog associations between time in bed, sleep timing, and weekly variability with clinical phenotypes derived from ICD-9/10 codes.

Methods: Self-reported habitual bed and wake times were used to derive variables: short (<7 hours) and long (≥9 hours) time in bed, sleep midpoint, social jetlag, and sleep debt. Logistic regression and Cox proportional hazards models were used to test cross-sectional and prospective associations, respectively, adjusted for age, gender, race/ethnicity, and employment status and further adjusted for body mass index.

Results: In cross-sectional analysis ($n = 34,651$), sleep variable associations were most notable for circulatory system, mental disorders, and endocrine/metabolic phenotypes. We observed the strongest associations for short time in bed with obesity, for long time in bed and sleep midpoint with major depressive disorder, for social jetlag with hypercholesterolemia, and for sleep debt with acne. In prospective analysis ($n = 24,065$), we observed short time in bed associations with higher incidence of acute pain and later sleep midpoint and higher sleep debt and social jetlag associations with higher incidence of major depressive disorder.

Conclusions: Our analysis reinforced that sleep health is a multidimensional construct, corroborated robust known findings from traditional cohort studies, and supported the application of PheWAS as a promising tool for advancing sleep research. Considering the exploratory nature of PheWAS, careful interrogation of novel findings is imperative.

Statement of Significance

Through phenome-wide association scans, we identified robust cross-sectional associations and prospective associations for sleep health and a range of diseases and pain syndromes, including those underexamined in traditional cohort studies. Our findings support that sleep is a multidimensional construct, which includes duration, timing, and regularity, with each dimension exhibiting unique links to disease. Our results also highlight strengths and limitations of phenome-wide association studies using electronic health record biobanks as a tool for advancing sleep research. Overall, our findings expand our understanding of sleep disturbance as a common comorbidity for numerous diseases and catalogs clinical phenotypes where sleep may serve as a cost-effective and noninvasive disease marker.

Key words: sleep health; phenome-wide association study; electronic health records; epidemiology

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Introduction

Sleep is a complex and essential human behavior that performs multiple restorative functions for the brain and the periphery and thus is necessary for overall health and well-being [1, 2]. It is also increasingly recognized that sleep is a multidimensional construct [3], which includes duration, quality, timing, and regularity and that attaining adequate, restorative, and consistent sleep is important for physical and mental health, quality of life, and productivity [4]. In large epidemiologic cohort studies, indices of suboptimal sleep, including short and long sleep duration [5–9], later timing [10], and variability in duration and timing [11, 12] associate with impaired health including adverse effects on daytime functioning, mood regulation, metabolic, cardiovascular, neurological, and immunological function [5–8, 13–16]. Conversely, sleep disturbance may also serve as a marker or a symptom of poor health and disease onset [17] or medication side effects. Sleep research from traditional epidemiologic cohort studies, however, has often been limited in breadth of sleep domains as well as scope in terms of disease outcomes.

Evaluating the relationships between sleep variables and clinical phenotypes is now possible with the implementation of large electronic health record (EHR) biobanks across healthcare systems [18]. EHR biobanks bridge clinical information to health questionnaire data and biological specimens, creating opportunities to derive “virtual” patient cohorts enriched for diseases with relevant data for big data research [19]. For patients within a healthcare system with temporal data, EHR biobanks further provide infrastructure enabling longitudinal analyses. Sleep research using EHR biobanks remains sparse. Leveraging EHR biobanks provide opportunities to confirm known sleep–disease relationships, identify previously undocumented disease links [20], and interrogate sleep as a risk factor for disease onset.

Through phenome-wide association studies (PheWAS), EHRs have been examined to systematically assess relationships between genetic [21, 22] and nongenetic [23, 24] exposures and clinical phenotypes through a hypothesis-free approach [25, 26]. For example, nongenetic PheWAS for rheumatic diseases [23, 24] and hematological traits [27] verified known associations and identified novel links. Whether nongenetic sleep PheWAS using EHR biobanks will advance knowledge of disease pathophysiology remains an open question. The first published nongenetic sleep-related PheWAS included 3,652 patients recruited from a sleep clinic and identified that sleep duration was associated with mental and neurological disorders [18]. Our assessment of self-reported sleep duration and 21 validated disease phenotypes in 30,251 adults supported links between sleep duration and metabolic and psychiatric disorders [28]. Here, we continue to evaluate this high-throughput method by expanding to five self-reported sleep variables (short and long time in bed [a proxy for sleep duration], sleep midpoint, social jetlag [29], and sleep debt [11]) and by considering their cross-sectional ($n = 34,651$) and prospective ($n = 24,065$) associations with 506 clinical phenotypes. We hypothesize that cross-sectional and prospective analytical approaches will provide complementary but distinct information regarding sleep as a risk factor or marker of disease.

Methods

Mass General Brigham Biobank

The Mass General Brigham Biobank (formerly Partners HealthCare Biobank) is a health system-based virtual cohort

study from the Mass General Brigham hospitals in Boston, MA with EHR and genetic data supplemented with a baseline electronic lifestyle and health survey [30–32]. Recruitment for the Mass General Brigham Biobank launched in 2010 and is active at participating clinics at Brigham and Women's Hospital, Massachusetts General Hospital, Spaulding Rehabilitation Hospital, Faulkner Hospital, McLean Hospital, and Newton-Wellesley Hospital or electronically through Patient Gateway, a secure online portal for patients. Recruitment strategy has been described previously [30]. Briefly, patients were recruited from inpatient stays, emergency department settings, and outpatient visits, including waiting rooms from high-volume clinics, and phlebotomy and pathology, research, and imaging and radiology sites. To further promote patient inclusion, the Biobank website and all recruitment and consent materials are fully translated into Spanish [30] and feature pictures of people from diverse backgrounds. The overall demographic of the Biobank reflects the race/ethnicity distribution of the population that receives care at these hospitals [30]. All recruited patients provided written informed consent upon enrollment, and the study protocol was approved by the Mass General Brigham Institutional Review Board.

A total of 101,741 participants were enrolled in the Biobank as of April 20, 2019 (start date of analysis). Following Biobank enrollment, study participants were invited to complete the Health Information Questionnaire by email that included questions on sleep. The current analysis was restricted to 38,929 participants who have responded to the questionnaire (38.3% of Biobank responded; $n = 62,793$ excluded) and who were ≥ 18 years at enrollment ($n = 19$ excluded) (Figure 1). In general, questionnaire responders were more likely to be older, more women, more white, and have lower 10-year survival probability than nonresponders (for responders and nonresponders, respectively, mean ages were 57.6 and 55.2 years; % men were 40.4% and 45.6%; % white were 89.5% and 82.6%; Charlson comorbidity index, % with 10-year survival probability $\geq 90.15\%$ were 34.3% and 38.3%) (Table 2). Only 158 participants responded to Spanish translations of the questionnaire. The Charlson comorbidity index is a validated index that combines the presence and severity of comorbidities with age to predict the 10-year survival probability [33].

Sleep and covariate measures

In the Health Information Questionnaire, sleep was assessed with the questions, “In considering your longest sleep period, what time do you usually go to bed on WEEKDAYS or WORK or SCHOOL days?” and “In considering your longest sleep period, what time do you usually wake up on WEEKDAYS or WORK or SCHOOL days?” Similar questions were asked for “WEEKENDS or DAYS OFF.” Responses were in half-hour increments.

Time in bed, sleep timing, and sleep variability variables were derived using self-reported bed and wake times as described in Table 1. First, weighted average weekly time in bed (a proxy for sleep duration) was computed from self-reported weekday and weekend bed and wake times with 5/7 weighting for weekdays and 2/7 for weekends. If either weekday or weekend time in bed was missing, then weekly time in bed was set as the nonmissing weekend or weekday time in bed, respectively. Weekly time in bed was then categorized as short (< 7 hours per night), recommended (7 to < 9 hours per night; referent group), or long (≥ 9 hours per night). Sleep midpoint, a measure of sleep timing or an individual's chronotype [34], was calculated as the midpoint

Figure 1. Flow chart of Mass General Brigham Biobank participants included in the present analysis.

Table 1. Description of self-reported sleep variables included in the present analysis

Variable	Definition	Calculation
Short time in bed	Time in bed <7 hours per night compared to the referent group (7 to <9 hours per night).	Weighted average weekly time in bed was computed from self-reported weekday and weekend bed and wake times with 5/7 weighting for weekdays and 2/7 for weekends.
Long time in bed	Time in bed ≥ 9 hours per night compared to the referent group (7 to <9 hours per night).	
Sleep midpoint	A measure of sleep timing and an individual's chronotype	Midpoint of self-reported bed and wake times on weekends.
Social jetlag	A measure of weekly sleep timing variability	Difference in self-reported weekend and weekday sleep midpoint.
Sleep debt	A measure of weekday-weekend sleep duration variability and also weekday sleep deprivation.	Difference between self-reported weekend and weekday time in bed.

of self-reported bed and wake times on weekends in order to limit the influence of external demands. Social jetlag, a measure of weekly sleep timing variability [29], was calculated as the difference in self-reported weekend and weekday sleep midpoint. Sleep debt, a measure of weekday-weekend sleep duration variability and weekday sleep deprivation [11], was calculated as the difference in self-reported weekend and weekday time in bed.

Additional covariates included age, gender, self-reported height and weight, self-reported race and ethnicity, employment status, smoking status, and education attainment. Body mass index (BMI) was calculated as weight (kg)/height² (m²) using self-reported measures. Missing BMI values and

possibly erroneous BMI values >100 or <15 kg/m² likely resulting from inaccurate self-reported weight or height were replaced with values derived from a clinical visit with a date nearest to Biobank enrollment. Employment was assessed by the question, "Which of the following best describes your usual work schedule?" with the following response options: Day shift, afternoon shift, night shift, split shift, irregular shift/on-call, rotating shifts, or don't work. Smoking status was assessed by the question, "Have you smoked at least 100 cigarettes in your lifetime?" with the following response options: yes, currently smoke; Yes, smoked in past, but quit; no have not smoked more than 100 cigarettes. Education attainment was assessed by the question,

“What is the highest grade in school that you finished?” with the following options: Grade school (1–4 years); Grade school (5–8 years); Some high school (9–11 years); High school diploma or GED (finished high school); Some college; 2-year college or vocational school; 4-year college; Masters, doctoral, or professional degree. Missing categorical variables were imputed using a missing indicator approach.

Clinical phenotypes

Clinical phenotypes were determined from ICD-9 and -10 billing codes in the EHR since 1986 generated from all inpatient or outpatient encounters at any Mass General Brigham facility [30]. Same-day duplicated diagnoses, non-ICD 9/10 codes, and codes from excluded participants were removed. Similar ICD-9 and ICD-10 were grouped, and then further collapsed to one of 1,857 disease PheWAS categories (“phecodes”) based on clinical similarity, as determined previously (<https://phewascatalog.org/phecodes>) [35]. Cases and controls sets for every tested phenotype were unique to that association test.

For cross-sectional analyses, all phenotypes irrespective of date of Biobank enrollment were considered. In order to improve the positive predictive values for clinical phenotypes [20, 36], participants with at least two phecodes on two separate days for a phenotype were considered cases for that outcome. Participants with no relevant code for that phenotype and with no code for any relevant exclusionary phenotype were presumed to be free of disease and thus considered controls. Relevant exclusionary phenotypes are curated lists of related conditions specific to each outcome (i.e. for Crohn’s disease, exclusionary diseases included ulcerative colitis and other related gastrointestinal complaints) aimed at generating robust control groups with limited case contamination to increase statistical power for finding associations [37, 38] and are described in the PheWAS catalog [20]. Participants with one code (i.e. code on 1 day) for a phenotype or a code for any relevant exclusionary phenotype were excluded from analysis for that outcome.

For prospective analyses, incident diseases were defined as two new incident phecodes on two separate dates ≥ 1 year after Biobank enrollment, and the date of the first occurrence for that phecode was used. Participants with no code from the EHR for that outcome and with no code for any other relevant exclusionary phenotype at any time were presumed to be free of disease and set as controls for analysis of that outcome. Participants with any code from the EHR prior to and within the first year of Biobank enrollment for the phenotype or its relevant exclusionary phenotypes or only one new incident phecode ≥ 1 year after Biobank enrollment were excluded for analysis of that outcome. Censoring dates for controls were either death date or the last available date of any medical encounter used in this analysis (April 20, 2019). If death date was unknown, then the date of the last medical encounter was used instead. Thus, participants contributed person-time of follow-up from the date of Biobank enrollment (i.e. date of questionnaire) until first occurrence of the disease for cases, or death or the date of last medical encounter for controls.

Statistical analysis

The analytical data set was comprised of all Biobank adult participants with sleep data. Likely improbable self-reported bed and

wake times from participants who were not shift workers were revised. Specifically, self-reported bed times between 08:00 am and 02:00 pm (weekday $n = 910$; weekend $n = 1,601$) and self-reported wake times between 06:00 pm and 12:00 am (weekday $n = 411$; weekend $n = 764$), likely resulting from am/pm misreporting, were flipped (i.e. am to pm and vice versa). In addition, improbable calculated weekday or weekend time in bed < 3 or > 18 hours (weekday $n = 250$; weekend $n = 166$), consistent with earlier investigations [39], was set to missing.

Furthermore, participants were excluded if (1) self-reporting any afternoon shift, night shift, split shift, irregular shift/on-call, or rotating shifts ($n = 3,940$ excluded), (2) missing a pair of bed/wake times following corrections ($n = 336$), or (3) with no links to medical data ($n = 2$) (Figure 1). Prospective analyses were further restricted to a subset of participants seeking regular care at Mass General Brigham ($n = 10,262$ excluded) with further exclusion of participants with deaths within 1 year of enrollment ($n = 324$ excluded). Regular care was determined by the frequency of healthcare encounters where participants with at least two encounters, one occurring within the year prior to consent date (i.e. survey date) and another occurring between 2 and 5 years, were considered “regular.”

The following five self-reported sleep variables were examined: short vs. recommended sleep (binary variable), long vs. recommended sleep (binary variable), sleep midpoint (continuous), social jetlag (continuous), and sleep debt (continuous). Analyses related to social jetlag and sleep debt were restricted to working participants only.

In cross-sectional analyses, associations between self-reported sleep variables and clinical phenotypes were examined using logistic regression with adjustments for age at survey completion, gender, race and ethnicity, and employment status, and then further adjusted for BMI, smoking status, or education attainment, using the PheWAS R package [38]. Stratified analyses were conducted based on the following factors: (1) gender (men and women) and (2) race/ethnicity (white, Asian, black). Diseases that only impact one sex, including some genitourinary, neoplasms, and pregnancy complications related outcomes, were only considered in stratified analyses. In sensitivity analyses, only diagnoses made 1 year or 5 years before and after Biobank enrollment were included in the PheWAS. In prospective analyses, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident phenotype comparing short (< 7 hours) and long (≥ 9 hours) time in bed, with 7–8 hours serving as a reference group. Models were adjusted for age, gender, race and ethnicity, and employment status (for all sleep variables, except social jetlag and sleep debt), and then further adjusted for BMI, smoking status, or education attainment.

Only clinical phenotypes with at least 1% case prevalence (i.e. n cases ≥ 347) or incidence (i.e. n cases ≥ 241) in the analytical sample were analyzed. Accordingly, cross-sectional or prospective associations were considered significant at Bonferroni p -value cutoffs accounting for the total number of tested outcomes (i.e. cross-sectional analysis p -value = $0.05/506$ tested outcomes with at least 1% case prevalence = 9.89×10^{-5} ; prospective analysis p -value threshold = $0.05/40$ tested outcomes with at least 1% case incidence = 1.25×10^{-3}). In cross-sectional PheWAS stratified by gender or race/ethnicity, p -value thresholds were adjusted to reflect the number of tested outcomes with at least 1% case prevalence (men p -value = 9.52×10^{-5} ; women p -value = 9.11×10^{-5} ; white p -value = 9.88×10^{-5} ; Asian

p -value = 1.20×10^{-4} ; black p -value = 8.36×10^{-5}). As sleep exposures were derived from the same set of self-reported sleep variables and therefore not independent, p -values were not adjusted for the number of tested exposures. All analyses were conducted using R (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Cross-sectional PheWAS

Our cross-sectional analytical sample included 34,651 adult participants who have responded to the optional health questionnaire from the Mass General Brigham Biobank and met all other inclusionary criteria (mean age 54.5 years; 40.5% men) (Figure 1, Table 2). Self-reported time in bed was normally distributed with a mean of 8.1 hours ($SD = 1.3$ hours) per night, and 12.1% (<7 hours per night; $n = 4,204$), 71.6% (7 to <9 hours per night; $n = 24,818$), and 16.2% (≥ 9 hours per night; $n = 5,629$) had short, recommended, and long time in bed, respectively. In aggregate, the 34,651 participants had 8,798,754 ICD-9/10, of which 7,703,145 codes mapped to a clinical phenotype and corresponded to 892,272 phecodes with at least two distinct diagnostic code dates.

A total of 506 distinct clinical phenotypes with at least 1% case prevalence in the analytical sample (i.e. ≥ 347 prevalent

cases per category) were tested. The most prevalent phenotypes were pain in joint (40.9% prevalent cases) and essential hypertension (38.2% prevalent cases). In cross-sectional PheWAS, we identified 484 distinct associations in aggregate, of which 14.7%, 11.0%, 10.7%, and 10.3% of findings were for circulatory system, mental disorders, respiratory, and endocrine/metabolic phenotypes, respectively. In addition, 51.0% and 37.4% of tested phenotypes classified as mental disorders and neurological, respectively, had associations with self-reported sleep variables. Fewest associations were evident for hematopoietic (2.2% of identified associations) and sense organ (2.2% of identified associations) phenotypes, and clinical phenotypes classified as infectious diseases, congenital anomalies, and pregnancy complications were underrepresented in our PheWAS.

Of all PheWAS findings, 29.3% and 33.7% of identified associations were for short and long time in bed, respectively, of which almost all were positive associations (Figure 2; Supplementary Tables S1 and S2). Associations were notable for circulatory system, endocrine/metabolic, mental disorders, and neurological phenotypes. The strongest evidence for association for short time in bed was seen with higher odds of obesity (odds ratio [95% CI] = 1.85 [1.7, 2.01]; $p = 2.45 \times 10^{-45}$), morbid obesity (2.15 [1.92, 2.41]; 3.35×10^{-39}), and chronic pain (1.72 [1.56, 1.89]; 5.00×10^{-28}), and the largest effect was observed

Table 2. General characteristics of Mass General Brigham Biobank participants included in the present analyses

	Cross-sectional analysis (n = 34,651)	Prospective analysis (n = 24,065)
Age, years	54.5 (16.3)	55.47 (15.8)
Gender, n men (%)	14,042 (40.5)	9,609 (39.9)
Hispanic, n (%)	636 (1.8)	417 (1.7)
Race, n (%)		
Asian	844 (2.4)	516 (2.1)
Black	838 (2.4)	528 (2.2)
White	31,172 (90.0)	21,869 (90.9)
Other	447 (1.3)	305 (1.3)
Unknown	1,350 (3.9)	847 (3.5)
Retired, n (%)	11,889 (34.3)	8,862 (36.8)
Education, n (%)		
Grade school, high school diploma, or GED	3,052 (8.8)	1,900 (7.9)
Some college, 2-year college, or vocational school	6,956 (20.1)	4,751 (19.7)
Four-year college	10,670 (30.8)	7,259 (30.1)
Masters, doctoral, or other professional degrees	13,852 (40.0)	10,084 (41.9)
Smoking status, n (%)		
Current	1,581 (4.6)	1,056 (4.4)
Past	12,636 (36.5)	9,046 (37.6)
Never	20,434 (58.9)	13,963 (58.0)
Charlson comorbidity index, 10-year survival probability $\geq 90.15\%$, n (%)*	12,055 (34.8)	6,892 (28.6)
BMI, kg/m ²	27.4 (6.04)	27.4 (6.03)
Time in bed, hours	8.1 (1.3)	8.1 (1.3)
Short sleep, n (%)	4,204 (12.1)	2,971 (12.3)
Long sleep, n (%)	5,629 (16.2)	3,891 (16.2)
Sleep midpoint, hours	3.2 (1.0)	3.2 (1.0)
Social jetlag, hours	0.8 (0.8)	0.8 (0.8)
Sleep debt, hours	0.7 (1.2)	0.7 (1.2)

Values are means (SDs), unless noted otherwise. Time in bed (a proxy for sleep duration) was calculated as the self-reported weighted average weekly time in bed. Sleep midpoint was calculated as the midpoint of self-reported bed and wake times on weekends. Social jetlag was calculated as the difference in self-reported weekend and weekday sleep midpoint. Sleep debt was calculated as the difference between self-reported weekend and weekday time in bed.

*Charlson comorbidity index predicts 10-year survival in patients with multiple comorbidities. Prospective analyses were restricted to a subset of participants seeking regular care at Mass General Brigham.

Figure 2. Manhattan plots of cross-sectional phenome-wide association findings for self-reported (a) short (<7 hours) and (b) long (≥9 hours) time in bed. Time in bed (a proxy for sleep duration) was calculated as the self-reported weighted average weekly time in bed. The y-axis is color-coded phecodes organized by broad clinical phenotype categories and the x-axis is p -value of association ($-\log_{10}(P)$). The vertical red line depicts genome-wide significance using Bonferroni correction for all tested phenotypes. Each data point (i.e. arrow) represents an association between the sleep exposure and a tested phenotype. Upward arrows denote positive associations (i.e. more short sleep, more long sleep; odds ratio [OR] > 1), and downward arrows denote negative associations (i.e. less short sleep, less long sleep; OR < 1). Only associations with $p \leq 1 \times 10^{-10}$ are annotated. Full results denoted on this figure can be found in tabular form in [Supplementary Tables S1 and S2](#).

for substance addiction and disorders (2.19 [$1.82, 2.64$]; 6.38×10^{-17}). Long time in bed most strongly associated with higher odds of mental health disorders, particularly major depressive disorder (2.39 [$2.21, 2.59$]; 1.72×10^{-103}), depression (2.24 [$2.07, 2.42$]; 1.66×10^{-92}), and anxiety disorder (1.96 [$1.81, 2.12$]; 1.98×10^{-61}), with the largest effects observed for bipolar (3.16 [$2.75, 3.63$]; 3.91×10^{-58}) and posttraumatic stress disorder (2.89 [$2.43, 3.44$]; 2.02×10^{-32}). Of 66 shared phenotypes associating with both short and long time in bed, 65 phenotypes, including cardiometabolic, psychiatric, neurological, among others, showed consistent positive associations with both variables. The remaining shared phenotype, benign neoplasm of colon,

was among 11 other neoplasms with associations for long time in bed. Both short and long time in bed were associated with higher odds of several sleep-related disease phenotypes, including sleep apnea, insomnia, and restless legs syndrome, but long time in bed associations with restless legs syndrome did not retain significance after accounting for multiple comparisons ([Table 3](#)). In general, associations, including those for sleep-related diseases, remained similar after adjusting for BMI, smoking status, and education attainment and when restricting analyses to only diagnoses made within 1 year or 5 years prior to and after Biobank enrollment ([Supplementary Tables S1 and S2](#)).

Table 3. Cross-sectional associations of self-reported sleep variables with selected sleep-related disease phenotypes (n = 34,651)

Disease category (phecode)	Short time in bed (<7 hours)		Long time in bed (≥9 hours)		Sleep midpoint (per hour)		Social jetlag (per hour)		Sleep debt (per hour)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Sleep disorders (327)										
Primary model	1.94	4.68 × 10⁻¹⁴	1.63	3.52 × 10⁻⁰⁹	1.05	1.35 × 10 ⁻⁰¹	1.08	3.18 × 10 ⁻⁰²	1.01	8.61 × 10 ⁻⁰¹
	(1.63, 2.31)		(1.39, 1.92)		(0.98, 1.12)		(1.01, 1.16)		(0.90, 1.13)	
BMI-adjusted	1.91	1.90 × 10⁻¹³	1.61	8.95 × 10⁻⁰⁹	1.05	1.55 × 10 ⁻⁰¹	1.08	3.91 × 10 ⁻⁰²	1.01	9.19 × 10 ⁻⁰¹
	(1.61, 2.28)		(1.37, 1.90)		(0.98, 1.12)		(1.00, 1.15)		(0.90, 1.12)	
Sleep apnea (327.3)										
Primary model	1.65	5.29 × 10⁻¹³	1.47	2.24 × 10⁻⁰⁹	1.05	4.23 × 10 ⁻⁰²	1.03	2.72 × 10 ⁻⁰¹	0.97	4.20 × 10 ⁻⁰¹
	(1.44, 1.89)		(1.29, 1.66)		(1.00, 1.11)		(0.98, 1.09)		(0.89, 1.05)	
BMI-adjusted	1.57	1.79 × 10⁻¹⁰	1.42	5.73 × 10⁻⁰⁸	1.04	9.61 × 10 ⁻⁰²	1.03	3.58 × 10 ⁻⁰¹	0.96	3.43 × 10 ⁻⁰¹
	(1.37, 1.80)		(1.25, 1.62)		(0.99, 1.10)		(0.97, 1.08)		(0.88, 1.05)	
Obstructive sleep apnea (327.32)										
Primary model	1.65	2.03 × 10⁻¹⁹	1.37	1.91 × 10⁻⁰⁹	1.05	1.51 × 10 ⁻⁰²	1.07	1.35 × 10 ⁻⁰³	0.99	7.59 × 10 ⁻⁰¹
	(1.48, 1.85)		(1.24, 1.52)		(1.01, 1.09)		(1.03, 1.12)		(0.93, 1.06)	
BMI-adjusted	1.57	2.53 × 10⁻¹⁵	1.33	1.14 × 10⁻⁰⁷	1.04	3.64 × 10 ⁻⁰²	1.06	4.55 × 10 ⁻⁰³	0.98	5.21 × 10 ⁻⁰¹
	(1.40, 1.76)		(1.20, 1.48)		(1.00, 1.09)		(1.02, 1.11)		(0.91, 1.05)	
Insomnia (327.4)										
Primary model	1.65	6.27 × 10⁻¹⁵	1.47	4.06 × 10⁻¹¹	1.00	9.69 × 10 ⁻⁰¹	0.98	4.77 × 10 ⁻⁰¹	0.88	1.55 × 10 ⁻⁰³
	(1.45, 1.86)		(1.31, 1.64)		(0.96, 1.04)		(0.93, 1.03)		(0.82, 0.95)	
BMI-adjusted	1.64	1.32 × 10⁻¹⁴	1.46	6.29 × 10⁻¹¹	1.00	9.39 × 10 ⁻⁰¹	0.98	4.58 × 10 ⁻⁰¹	0.88	1.34 × 10 ⁻⁰³
	(1.44, 1.85)		(1.30, 1.64)		(0.95, 1.04)		(0.93, 1.03)		(0.82, 0.95)	
Restless legs syndrome (327.71)										
Primary model	1.79	3.78 × 10⁻⁰⁶	1.44	2.30 × 10 ⁻⁰³	0.97	4.60 × 10 ⁻⁰¹	1.01	8.67 × 10 ⁻⁰¹	0.91	2.50 × 10 ⁻⁰¹
	(1.40, 2.28)		(1.14, 1.81)		(0.88, 1.06)		(0.91, 1.12)		(0.77, 1.07)	
BMI-adjusted	1.75	8.52 × 10⁻⁰⁶	1.42	3.01 × 10 ⁻⁰³	0.97	4.57 × 10 ⁻⁰¹	1.00	9.50 × 10 ⁻⁰¹	0.91	9.10 × 10 ⁻⁰¹
	(1.37, 2.24)		(1.13, 1.80)		(0.88, 1.06)		(0.91, 1.11)		(0.77, 1.06)	

Time in bed (a proxy for sleep duration) was calculated as the self-reported weighted average weekly time in bed. Values are HRs (95% CI). Primary model was adjusted for age, gender, race and ethnicity, and employment status (for all sleep variables except social jetlag and sleep debt). Associations were considered significant at Bonferroni p-value cutoffs accounting for the total number of tested phenotypes and significant results are presented in bold. Results from stratified and sensitivity analyses and for all other clinical phenotypes are shown in [Supplementary Tables S1–S5](#).

Of all PheWAS findings, 19.8% of associations were for sleep midpoint, and were notable for circulatory system and neoplasms associations with earlier sleep midpoint and mental disorders associations with later sleep midpoint ([Figure 3](#); [Supplementary Table S3](#)). Among the most robust associations were later sleep midpoint associations with higher odds of major depressive disorder (1.25 [1.21, 1.29] per hour; 2.55×10^{-40}) and depression (1.2 [1.17, 1.24]; 6.81×10^{-31}), and lower odds of essential hypertension (0.84 [0.82, 0.86]; 4.24×10^{-48}) and hyperlipidemia (0.86 [0.84, 0.88]; 4.67×10^{-32}). Associations remained similar in sensitivity analyses.

Among working participants, associations were further evident for social jetlag and sleep debt, respectively, and notable for circulatory system and genitourinary phenotypes ([Figure 3](#); [Supplementary Tables S4](#) and [S5](#)). Higher social jetlag was most strongly associated with lower odds of hypercholesterolemia (0.78 [0.75, 0.83] per hour; 5.69×10^{-21}), and hyperlipidemia (0.82 [0.78, 0.85]; 2.21×10^{-20}), with the largest positive and negative effects observed for acne (1.4 [1.3, 1.5]; 6.41×10^{-19}) and cataract (0.66 [0.6–0.73]; 6.41×10^{-19}), respectively. In addition, higher sleep debt was most strongly associated with higher odds of acne (1.14 [1.09–1.2] per hour; 1.60×10^{-7}), with the largest effect, albeit smaller relative to the other sleep variables, observed for attention deficit hyperactivity disorder (1.18 [1.1, 1.26]; 1.20×10^{-6}). No associations were evident for sleep-related disease phenotypes for sleep midpoint, social jetlag, and sleep debt ([Table 3](#)).

In PheWAS stratified by gender (men and women), disease associations were persistent for many self-reported sleep variables ([Supplementary Tables S1–S5](#)). In addition, clinical phenotypes relevant to a single sex were evident in stratified analyses, including associations between earlier sleep midpoint and lower sleep jetlag with cancer of prostate among men and associations between short time in bed, higher sleep jetlag, and higher sleep midpoint with pain and other symptoms associated with women genital organs and excessive or frequent menstruation among women. PheWAS stratified by race (white, Asian, and black) corroborated findings from the larger PheWAS. Overall, there were fewer associations in the Asian and black subpopulations, likely as a result of small sample sizes (<5% of the Biobank) ([Supplementary Tables S1–S5](#)).

Prospective PheWAS

The sample for the prospective cohort analysis consisted of 24,065 participants. Over a median follow-up of 2.73 years (interquartile range: 1.82–3.98 years), 1,787,484 ICD codes occurred at least 1 year after Biobank enrollment, of which 323,946 ICD codes had not occurred prior to and up to 1 year after enrollment. The 323,946 ICD codes mapped to 137,137 clinical phenotypes, of which 57,198 had at least two distinct incident diagnostic codes ([Figure 1](#)). In the prospective cohort, self-reported time in bed was normally distributed with a mean of 8.1 hours ($SD = 1.3$

Figure 3. Manhattan plots of cross-sectional phenome-wide association findings for self-reported (a) sleep midpoint, (b) social jetlag, and (c) sleep debt. Sleep midpoint was calculated as the midpoint of self-reported bed and wake times on weekends. Social jetlag was calculated as the difference in self-reported weekend and weekday sleep midpoint. Sleep debt was calculated as the difference between self-reported weekend and weekday time in bed. The y-axis is color-coded phecodes organized by broad clinical phenotype categories and the x-axis is p -value of association ($-\log_{10}(P)$). The vertical red line depicts phenome-wide significance using Bonferroni correction for all tested phenotypes. Each data point (i.e. arrow) represents an association between the sleep exposure and a tested phenotype. Upward arrows denote positive associations (odds ratio [OR] > 1), and downward arrows denote negative associations (OR < 1). Full results denoted on this figure can be found in tabular form in [Supplementary Tables S3–S5](#).

hours) per night, and 12.3% (<7 hours per night; $n = 2,971$), 71.5% (7 to <9 hours per night; $n = 17,203$), and 16.2% (≥ 9 hours per night; $n = 3,891$) had short, recommended, and long time in bed, respectively ([Table 2](#)).

A total of 40 distinct clinical phenotypes had at least 1% incidence (i.e. ≥ 241 incident cases per category). The largest incident phenotype were pain in limb ($n = 1,743$ incident cases), “other tests” ($n = 1,323$ incident cases), and chronic pain ($n = 1,003$ incident cases). Short time in bed was associated (all $p_{\text{adj}} < 0.05$) with higher incidence of acute pain (HR [95% CI] = 1.46 [1.20, 1.78]), tobacco use disorder (1.42 [1.18, 1.71]), sciatica (1.72 [1.3, 2.27]), and edema (1.69 [1.25, 2.28]) ([Table 4](#)). Associations remained similar upon further adjustment for BMI, except for edema, and smoking status or education attainment, except for tobacco use disorder ([Supplementary Table S6](#)). No longitudinal associations were evident for long time in bed ([Table 4](#); [Supplementary Table S6](#)).

Furthermore, each additional hour of later sleep midpoint was associated (all $p_{\text{adj}} < 0.05$) with higher incidence of major

depressive disorder (1.30 [1.14, 1.49] per hour) ([Table 5](#)). Similarly, among working participants, each additional hour of social jetlag and sleep debt were associated (all $p_{\text{adj}} < 0.05$) with higher incidence of major depressive disorder (social jetlag: 1.54 [1.27, 1.84] per hour; debt: 1.23 [1.09, 1.38] per hour) ([Table 5](#)). Associations with incident major depressive disorder retained significance upon further adjustment for BMI, smoking status, or education attainment ([Supplementary Table S7](#)). No other longitudinal associations were observed at the Bonferroni p -value threshold.

Discussion

Our study in a large health system-based virtual cohort supports unique associations between self-reported sleep variables that define key aspects of sleep health and diverse health outcomes. In 34,651 adults, we showed that time in bed, sleep timing, and weekly variability derived from self-reported usual

bed and wake times associate with prevalent and incident diseases identified from EHR. Overall, our application of PheWAS (1) identified a number of cross-sectional and prospective associations largely in agreement with earlier findings, (2) cautiously cataloged several preliminary links with other diseases and pain syndromes that were underexamined in traditional cohort studies, and (3) highlighted strengths and important limitations of PheWAS using EHR biobanks for advancing sleep research.

Our PheWAS findings corroborate well-established links between sleep variables and diseases primarily from traditional epidemiologic cohort studies, and in doing so, provide support for use of PheWAS for advancing sleep research. Our cross-sectional PheWAS for self-reported time in bed, a proxy for sleep duration, supports well-established positive associations between short and long sleep duration and obesity [40], type 2 diabetes [5], hypertension [41], cardiovascular disease [42], and depression [43]. As expected, sleep disorders showed positive associations with self-reported short and long time in bed, but not sleep timing or variability. In addition leveraging longitudinal data from EHR, we were able to supplement cross-sectional PheWAS with prospective analyses providing some insight on sleep disturbance as a potential risk factor for incident disease. For example, despite our modest follow-up duration, we observed that later sleep timing and weekly variability in sleep timing and duration positively associate with major depressive disorder, consistent with the current literature [44–46]. Associations for major depressive disorder were evident in both cross-sectional and prospective analyses and suggests suboptimal sleep as an antecedent risk factor for depression, as previously noted [45].

Our systematic interrogation of associations with hundreds of clinical phenotypes in a patient population 10× larger than earlier studies [18] revealed novel links between self-reported sleep and diseases where sleep has been largely underrecognized. Novel signals from our catalog of disease associations with suboptimal sleep may suggest diseases and physiological functions sensitive to dysregulation of sleep and may indicate disorders likely to impact sleep regulation where sleep intervention may be warranted. For example, among our findings are novel links between long time in bed, sleep timing, and social jetlag with malignancies, particularly secondary malignancies [47, 48]. Fatigue is common in malignancies and is reported by patients before, during, and after therapy [49]. Findings related to earlier sleep timing and lower social jetlag with higher odds of neoplasms support the possibility of patients seeking earlier sleep times, particularly on weekends, to overcome fatigue. Whether these changes in sleep patterns (duration and timing) serve as markers of continued debilitating health or reflect treatment (e.g. chemotherapy and radiotherapy) side effect cannot be determined from PheWAS. Thus, novel PheWAS findings should be treated as preliminary and require further careful assessments and out-of-sample interrogations. In addition, infectious diseases, congenital anomalies, and pregnancy complications phenotypes were underrepresented in our PheWAS and require further examination.

Directionality of cross-sectional and prospective PheWAS findings from EHR should be interpreted cautiously. Despite cross-sectional findings persisting in sensitivity analyses when codes were restricted to a time frame of 1 or 5 years since Biobank enrollment, diagnoses could have incurred prior to or after Biobank enrollment and sleep assessment. Directionality from prospective PheWAS may result from more diligent coding over time where first occurrence of the code does not reflect new

disease onset, for example as observed for associations with incident tobacco use disorder, or incompleteness of medical histories within an open healthcare network, such as Mass General Brigham. Here, we identified cross-sectional associations between short and long time in bed and earlier sleep timing with acute and chronic pain. We further identified prospective links between short time in bed and acute pain. The cross-sectional findings could reflect a bidirectional and reciprocal relationship between sleep and pain, suggesting that sleep disturbances can both initiate and amplify pain by negatively affecting endogenous pain modulation, mood, and pain-related coping mechanisms [50]. The prospective finding is consistent with the possibility of short sleep as a risk factor for amplified pain sensitivity [50], supporting ongoing interest in testing sleep extension as an effective, low-cost, and nonpharmacologic strategy in pain management [50, 51]. Given the impetus for health centers to reduce opioid use, determining directionality of our results could support the use of EHR to identify individuals with sleep disturbance who may benefit from such trials. Nonetheless, causality and directionality cannot be inferred through PheWAS alone, and both cross-sectional and prospective findings may be influenced by medication use or other unexamined confounders.

Optimal methods for ascertaining sleep exposure in PheWAS remain to be determined. We relied on patient-reported questionnaires to obtain standardized data on behaviors not readily captured by EHR. Our assessment of bed and wake times questions derived from the Sleep Heart Health Study [52] enabled us to expand our scope to other important and often unexamined sleep variables, including timing and weekly variability. However, these measures have not been validated in our clinical cohort, and self-reported bed and wake times are susceptible to reporting and recall biases and reduced precision partly due to rounding [53, 54]. In addition, wake-bed time difference may reflect time in bed, and estimates of sleep duration using this interval are known to overestimate actigraphy-derived total sleep time as it disregards sleep latency [53, 54]. Indeed, the prevalence of long time in bed (≥ 9 hours per night) in our clinical cohort is almost double the prevalence of long sleep duration of the US population (16.2% in Biobank vs. 8.6% in US National Health Interview Survey 2012 [55]), likely a result of our assessment of bed and wake times or also possibly reflecting fatigue stemming from disease or medication use in this patient cohort. We were previously successful in replicating sleep duration genetic discoveries in the Mass General Brigham Biobank despite fundamental population and methodological differences in self-reported sleep duration ascertainment [28]. Thus, while findings related to time in bed may reflect sleep duration associations, all derived self-reported sleep variables in the present analysis are prone to inaccuracies. We were also limited to a single assessment of sleep via questionnaire upon enrollment. Repeated measures in future PheWAS are necessary to determine the stability and trajectory of baseline measures particularly in a patient population [56]. Furthermore, supplementing future biobanks with objective sleep measures, including actigraphy and polysomnography, incorporating routine evaluation of sleep variables in clinical assessments, or determining habitual sleep from genetic profiles may offer more robust estimates.

Our study has some limitations. The low response rate to the optional Health Information Questionnaire (38.3% of the cohort) from a single healthcare network inadvertently yielded a partially biased sample of older, more women, more white, and less healthy participants, as has been noted in other large

Table 4. Prospective associations of self-reported short and long time in bed with incident clinical phenotypes (n = 24,065)

Disease category (phecode)	Group	Short time in bed (<7 hours)			
		Total cases/ person-years	Incidence rate	HR (95% CI)	P
Benign neoplasm of colon (208)	Neoplasms	108/9.1	11.92	1.17 (0.95, 1.45)	0.14
Benign neoplasm of skin (216)	Neoplasms	51/4	12.61	0.86 (0.64, 1.16)	0.32
Radiotherapy (196)	Neoplasms	61/5	12.29	1.21 (0.91, 1.59)	0.19
Chemotherapy (197)	Neoplasms	64/5.2	12.43	1.33 (1.01, 1.75)	0.04
Vitamin D deficiency (261.4)	Endocrine/metabolic	39/2.9	13.67	1.16 (0.82, 1.64)	0.40
Intestinal disaccharidase deficiencies and disaccharide malabsorption (271.3)	Endocrine/metabolic	43/3.7	11.7	1.38 (0.98, 1.93)	0.06
Other anemias (285)	Hematopoietic	28/1.8	15.52	0.76 (0.51, 1.12)	0.17
Tobacco use disorder (318)	Mental disorders	142/11.5	12.4	1.42 (1.18, 1.71)	0.0002
Major depressive disorder (296.22)	Mental disorders	33/2.2	14.72	1.23 (0.85, 1.79)	0.27
Pain in limb (773)	Neurological	263/21.5	12.26	1.21 (1.06, 1.38)	0.01
Chronic pain (338.2)	Neurological	135/10.8	12.54	1.18 (0.98, 1.42)	0.08
Acute pain (338.1)	Neurological	127/10.8	11.73	1.46 (1.2, 1.78)	0.0001
Other headache syndromes (339)	Neurological	61/5.1	11.91	1.33 (1.01, 1.77)	0.04
Abnormality of gait (350.2)	Neurological	42/3.2	13.05	1.62 (1.15, 2.28)	0.01
Dizziness and giddiness (light-headedness and vertigo) (386.9)	Sense organs	51/3.7	13.7	1.09 (0.81, 1.48)	0.56
Cataract (366)	Sense organs	41/3.3	12.54	1.33 (0.95, 1.88)	0.10
Essential hypertension (401.1)	Circulatory system	53/4	13.23	1.22 (0.91, 1.64)	0.18
Nonspecific chest pain (418)	Circulatory system	47/3.4	13.93	1.15 (0.84, 1.57)	0.38
Arrhythmia (cardiac) NOS (427.5)	Circulatory system	40/2.8	14.15	1.15 (0.82, 1.62)	0.41
Abnormal findings examination of lungs (514)	Respiratory	75/6.1	12.29	1.19 (0.93, 1.53)	0.17
GERD (530.11)	Digestive	52/3.9	13.26	1.35 (1, 1.83)	0.05
Disorder of skin and subcutaneous tissue NOS (689)	Dermatologic	32/2.4	13.22	0.75 (0.52, 1.09)	0.13
Other dyschromia (694.2)	Dermatologic	32/2.4	13.24	0.8 (0.55, 1.16)	0.24
Disturbance of skin sensation (687.4)	Dermatologic	46/3.9	11.83	1.61 (1.16, 2.23)	0.005
Other disorders of bone and cartilage (733)	Musculoskeletal	112/7.9	14.14	1.06 (0.86, 1.29)	0.59
Pain in joint (745)	Musculoskeletal	79/5.8	13.5	1.07 (0.84, 1.36)	0.58
Osteoarthritis, localized, primary (740.11)	Musculoskeletal	65/5	13.02	1.17 (0.9, 1.53)	0.25
Spondylosis without myelopathy (721.1)	Musculoskeletal	41/3.4	12.09	1.32 (0.94, 1.85)	0.11
Abdominal pain (785)	Symptoms	68/4.8	14.05	1.09 (0.84, 1.41)	0.53
Malaise and fatigue (798)	Symptoms	62/4.8	12.98	1.18 (0.9, 1.56)	0.23
Back pain (760)	Symptoms	56/4.3	12.98	1.16 (0.87, 1.55)	0.31
Other abnormal blood chemistry (790.6)	Symptoms	55/4.1	13.48	1.3 (0.97, 1.74)	0.08
Sciatica (764)	Symptoms	65/5.3	12.28	1.72 (1.3, 2.27)	0.0002
Cervicalgia (761)	Symptoms	54/4.4	12.37	1.61 (1.19, 2.18)	0.002
Edema (782.3)	Symptoms	56/4.5	12.54	1.69 (1.25, 2.28)	0.0002
Syncope and collapse (788)	Symptoms	33/2.6	12.7	0.91 (0.63, 1.32)	0.61
Nausea and vomiting (789)	Symptoms	32/2.5	12.62	1.01 (0.69, 1.48)	0.94
Myalgia and myositis unspecified (770)	Symptoms	45/3.3	13.64	1.62 (1.17, 2.26)	0.004
Fracture of unspecified bones (809)	Injuries and poisonings	45/3.4	13.36	1.39 (1, 1.93)	0.05
Other tests (1010)	Unspecified	202/15	13.43	1.18 (1.01, 1.38)	0.03

Time in bed (a proxy for sleep duration) was calculated as the self-reported weighted average weekly time in bed. Association analyses were restricted to 40 disease categories with at least 1% incidence in the analytical sample and ordered by disease group. Values are HRs (95% CI). Analyses were adjusted for age, gender, race and ethnicity, and employment status. Incidence rates are per person-years. Associations were considered significant at Bonferroni *p*-value cutoffs accounting for the total number of tested diseases and significant results are presented in bold. Associations adjusted for BMI or education attainment are shown in [Supplementary Table S6](#). GERD, gastroesophageal reflux disease; NOS, not otherwise specified.

biobanks [57]. Our biased sample and our limited external validity potentially limit generalizability of our findings to other populations. In addition, as only 10% of our population are nonwhite, reflecting the overall demographic of hospitals in the Mass General Brigham network but not the greater Boston area, our findings for Asian and black populations were generally limited. Continued active enrollment of diverse populations in biobanks, as in the All of Us Research Program, is imperative [58]. Whereas the use of ICD billing codes to define cases enabled the

systematic scan of over 500 diseases in our PheWAS, ICD codes are prone to missingness in the context of an open healthcare network and inaccuracy and error contributing to ascertainment bias [59]. Validation of case definitions using natural language processing and machine learning algorithms or with an external source such as payor data may be useful in limiting false-positive cases in future studies [60]. In addition, while the phecode scheme used in the present analysis has built-in exclusion criteria to prevent contamination by cases in the control

Recommended time in bed (7, 8 hours)				Long time in bed (≥ 9 hours)			
Total cases/ person-years	Incidence rate	HR (95% CI)	P	Total cases/ person-years	Incidence rate	HR (95% CI)	P
497/38.3	12.98	1.00 (ref)	—	87/6.4	13.67	0.77 (0.61, 0.97)	0.03
333/24.1	13.8	1.00 (ref)	—	56/4.1	13.52	0.73 (0.54, 0.97)	0.03
273/22.6	12.09	1.00 (ref)	—	67/5.4	12.42	1.1 (0.84, 1.44)	0.50
266/21.7	12.26	1.00 (ref)	—	66/5.3	12.48	1.1 (0.83, 1.44)	0.51
201/14.4	13.95	1.00 (ref)	—	48/3.6	13.19	1.11 (0.81, 1.53)	0.50
169/13.6	12.44	1.00 (ref)	—	36/2.9	12.53	0.95 (0.66, 1.37)	0.80
213/16.6	12.82	1.00 (ref)	—	45/3.1	14.49	0.97 (0.7, 1.34)	0.85
588/45.2	13.01	1.00 (ref)	—	162/12.1	13.43	1.27 (1.06, 1.51)	0.01
166/12.1	13.73	1.00 (ref)	—	45/3.2	13.91	1.6 (1.14, 2.23)	0.01
1220/94	12.98	1.00 (ref)	—	260/19.3	13.5	0.94 (0.82, 1.07)	0.35
693/53.8	12.87	1.00 (ref)	—	175/13.6	12.86	1.16 (0.98, 1.37)	0.09
524/42.6	12.29	1.00 (ref)	—	105/8.7	12.11	0.92 (0.75, 1.14)	0.46
258/18.8	13.72	1.00 (ref)	—	60/4.3	14.08	1.05 (0.79, 1.4)	0.73
159/11.8	13.47	1.00 (ref)	—	47/3.5	13.6	1.3 (0.94, 1.81)	0.12
267/20.3	13.12	1.00 (ref)	—	63/4.3	14.66	1.11 (0.84, 1.47)	0.45
180/14.8	12.12	1.00 (ref)	—	56/4.3	13.02	1.27 (0.94, 1.72)	0.13
272/19.6	13.85	1.00 (ref)	—	78/5.4	14.51	1.51 (1.17, 1.95)	0.002
268/19.8	13.57	1.00 (ref)	—	60/4.3	14.06	1.07 (0.81, 1.42)	0.64
210/15.7	13.39	1.00 (ref)	—	49/3.4	14.35	1.16 (0.85, 1.59)	0.34
360/26	13.84	1.00 (ref)	—	86/6.1	14.05	1.12 (0.88, 1.42)	0.34
241/18.8	12.84	1.00 (ref)	—	61/4.7	12.86	1.33 (1, 1.77)	0.05
237/17.4	13.65	1.00 (ref)	—	46/3.4	13.37	0.87 (0.63, 1.19)	0.38
228/16.1	14.14	1.00 (ref)	—	37/2.5	14.61	0.75 (0.53, 1.06)	0.10
172/13.6	12.65	1.00 (ref)	—	33/2.7	12.28	0.92 (0.63, 1.34)	0.66
657/49.1	13.37	1.00 (ref)	—	126/9.4	13.39	0.78 (0.64, 0.94)	0.01
477/34.5	13.84	1.00 (ref)	—	81/5.7	14.14	0.75 (0.59, 0.96)	0.02
318/25	12.7	1.00 (ref)	—	61/5.1	11.91	0.84 (0.64, 1.11)	0.22
185/13.6	13.64	1.00 (ref)	—	34/2.5	13.86	0.86 (0.59, 1.24)	0.41
395/28.3	13.98	1.00 (ref)	—	88/6.2	14.26	1.11 (0.88, 1.41)	0.37
298/21.7	13.76	1.00 (ref)	—	73/5.5	13.19	1.22 (0.94, 1.59)	0.13
291/21.9	13.26	1.00 (ref)	—	71/5.2	13.64	1.19 (0.92, 1.55)	0.19
240/18.9	12.71	1.00 (ref)	—	50/3.7	13.38	0.99 (0.73, 1.35)	0.96
217/16.2	13.39	1.00 (ref)	—	56/4.1	13.6	1.16 (0.86, 1.56)	0.34
201/14.9	13.49	1.00 (ref)	—	51/3.8	13.46	1.21 (0.88, 1.65)	0.24
187/15.5	12.09	1.00 (ref)	—	62/4.5	13.65	1.57 (1.18, 2.11)	0.002
195/15.6	12.53	1.00 (ref)	—	58/4.8	12.02	1.33 (0.99, 1.79)	0.06
183/12.9	14.21	1.00 (ref)	—	62/4.3	14.35	1.58 (1.18, 2.11)	0.002
165/11.8	14.01	1.00 (ref)	—	43/3	14.1	1.19 (0.85, 1.68)	0.31
192/15.7	12.21	1.00 (ref)	—	54/4.4	12.2	1.27 (0.93, 1.72)	0.13
929/64.8	14.34	1.00 (ref)	—	192/14.6	13.17	0.95 (0.81, 1.11)	0.49

group [37], controls may still have other disease conditions that may influence findings. Given the high prevalence of some disease outcomes included in the PheWAS, the reported odds ratios may possibly overestimate the prevalence ratio and thus should be interpreted cautiously [61]. In our PheWAS, we limited our statistical adjustment to several key confounders, but avoided more comprehensive adjustments that could introduce problems related to measurement error (and imprecision), missing data, and inadvertent inclusion of a collider, which would have

introduced confounding. However, residual confounding may influence the relationships observed between sleep and diseases and should be further interrogated in future disease-specific studies using clearly defined directed acyclic graphs.

In summary, our findings from PheWAS in a large hospital-system virtual cohort reinforce that sleep is a multidimensional construct with diverse relationships to diseases and pain syndromes. Our findings corroborated robust known findings, thus supporting the application of nongenetic PheWAS

Table 5. Prospective associations of sleep midpoint, social jetlag, and sleep debt with incident clinical phenotypes (n = 24,065)

Disease category (phecode)	Group	Sleep midpoint (per hour)			
		Total cases/ person-years	Incidence rate	HR (95% CI)	P
Benign neoplasm of colon (208)	Neoplasms	676/52.3	12.93	0.93 (0.86, 1)	0.05
Benign neoplasm of skin (216)	Neoplasms	431/31.7	13.6	1.1 (1, 1.2)	0.05
Radiotherapy (196)	Neoplasms	391/32.1	12.19	0.91 (0.83, 1.01)	0.07
Chemotherapy (197)	Neoplasms	385/31.1	12.36	0.94 (0.85, 1.04)	0.22
Vitamin D deficiency (261.4)	Endocrine/metabolic	282/20.4	13.8	1.18 (1.05, 1.33)	0.01
Intestinal disaccharidase deficiencies and disaccharide malabsorption (271.3)	Endocrine/metabolic	241/19.6	12.27	1.03 (0.91, 1.17)	0.66
Other anemias (285)	Hematopoietic	275/20.5	13.4	1.06 (0.94, 1.2)	0.33
Tobacco use disorder (318)	Mental disorders	874/67.2	13	0.95 (0.89, 1.02)	0.15
Major depressive disorder (296.22)	Mental disorders	233/16.8	13.87	1.31 (1.14, 1.5)	0.0001
Pain in limb (773)	Neurological	1694/131	12.93	0.99 (0.95, 1.04)	0.82
Chronic pain (338.2)	Neurological	975/76.2	12.8	1.03 (0.97, 1.1)	0.37
Acute pain (338.1)	Neurological	735/60.5	12.15	1.02 (0.95, 1.1)	0.62
Other headache syndromes (339)	Neurological	375/28	13.41	1.03 (0.93, 1.14)	0.55
Abnormality of gait (350.2)	Neurological	237/17.7	13.38	1.06 (0.94, 1.21)	0.33
Dizziness and giddiness (light-headedness and vertigo) (386.9)	Sense organs	367/27.2	13.51	1.1 (0.99, 1.22)	0.07
Cataract (366)	Sense organs	266/21.4	12.44	0.99 (0.88, 1.12)	0.88
Essential hypertension (401.1)	Circulatory system	392/28.1	13.95	0.98 (0.89, 1.09)	0.73
Nonspecific chest pain (418)	Circulatory system	364/26.6	13.68	1.02 (0.91, 1.13)	0.77
Arrhythmia (cardiac) NOS (427.5)	Circulatory system	294/21.5	13.68	0.97 (0.87, 1.09)	0.63
Abnormal findings examination of lungs (514)	Respiratory	507/37.2	13.62	0.95 (0.87, 1.04)	0.25
GERD (530.11)	Digestive	348/26.9	12.94	1.04 (0.93, 1.16)	0.51
Disorder of skin and subcutaneous tissue NOS (689)	Dermatologic	305/22.5	13.53	1 (0.89, 1.12)	0.96
Other dyschromia (694.2)	Dermatologic	288/20.5	14.05	0.99 (0.88, 1.11)	0.83
Disturbance of skin sensation (687.4)	Dermatologic	246/19.7	12.5	1.02 (0.9, 1.16)	0.77
Other disorders of bone and cartilage (733)	Musculoskeletal	871/64.9	13.42	1.02 (0.95, 1.09)	0.60
Pain in joint (745)	Musculoskeletal	630/45.5	13.83	1.01 (0.93, 1.09)	0.83
Osteoarthritis, localized, primary (740.11)	Musculoskeletal	437/34.5	12.68	0.96 (0.87, 1.06)	0.40
Spondylosis without myelopathy (721.1)	Musculoskeletal	257/19.3	13.34	0.99 (0.88, 1.12)	0.91
Abdominal pain (785)	Symptoms	536/38.4	13.95	1 (0.91, 1.09)	0.96
Malaise and fatigue (798)	Symptoms	422/31.2	13.54	1.03 (0.93, 1.13)	0.60
Back pain (760)	Symptoms	405/30.7	13.18	1.09 (0.98, 1.2)	0.10
Other abnormal blood chemistry (790.6)	Symptoms	335/26	12.88	0.99 (0.89, 1.11)	0.93
Sciatica (764)	Symptoms	324/24.5	13.21	1 (0.89, 1.11)	0.93
Cervicalgia (761)	Symptoms	297/22.4	13.25	0.98 (0.87, 1.1)	0.75
Edema (782.3)	Symptoms	298/24	12.4	0.99 (0.88, 1.1)	0.80
Syncope and collapse (788)	Symptoms	274/22.1	12.42	1.12 (1, 1.26)	0.05
Nausea and vomiting (789)	Symptoms	270/19.2	14.04	1.08 (0.96, 1.22)	0.21
Myalgia and myositis unspecified (770)	Symptoms	245/17.3	14.14	0.9 (0.8, 1.03)	0.12
Fracture of unspecified bones (809)	Injuries and poisonings	283/22.7	12.45	0.97 (0.86, 1.09)	0.59
Other tests (1010)	Unspecified	1293/92	14.06	1.08 (1.03, 1.15)	0.004

Association analyses were restricted to 40 disease categories with at least 1% incidence in the analytical sample and ordered by disease group. Values are HRs (95% CI). Analyses were adjusted for age, gender, race and ethnicity, and employment status. Incidence rates are per person-years. Associations were considered significant at Bonferroni *p*-value cutoffs accounting for the total number of tested diseases and significant results are presented in bold.

Associations adjusted for BMI or education attainment are shown in [Supplementary Table S7](#). GERD, gastroesophageal reflux disease; NOS, not otherwise specified.

as complementary to traditional epidemiologic cohort studies and a viable tool for advancing sleep research. Overall, the findings support sleep disturbance as a common comorbidity for numerous diseases, suggesting clinical phenotypes where sleep may serve as a cost-effective and noninvasive marker for disease onset. Novel findings from PheWAS, however, should be carefully interpreted and further examined. The growth and evolution of biobanks, specifically the incorporation of diverse data sources beyond billing codes, including

laboratory and imaging results, medication use, clinical documentation, and genetics, should continue to be explored in future sleep research for the purpose of identifying robust biomarkers of sleep disturbance and other clinically relevant disease associations [62].

Supplementary Material

Supplementary material is available at *SLEEP* online.

Social jetlag (per hour)				Sleep debt (per hour)			
Total cases/ person-years	Incidence rate	HR (95% CI)	P	Total cases/ person-years	Incidence rate	HR (95% CI)	P
424/32.9	12.89	1.04 (0.92, 1.18)	0.49	428/33.1	12.92	1.04 (0.96, 1.12)	0.33
279/20.4	13.68	1.11 (0.96, 1.29)	0.14	282/20.6	13.7	1 (0.91, 1.1)	0.95
216/17.5	12.31	0.9 (0.76, 1.07)	0.22	216/17.6	12.29	0.97 (0.88, 1.08)	0.62
204/16.4	12.47	0.91 (0.76, 1.08)	0.29	205/16.4	12.48	1 (0.9, 1.12)	0.95
170/12.3	13.79	1.18 (0.98, 1.42)	0.08	169/12.3	13.79	1.03 (0.91, 1.16)	0.69
141/11.4	12.35	1.08 (0.88, 1.34)	0.46	143/11.6	12.37	1.06 (0.93, 1.2)	0.41
130/9.7	13.46	1.02 (0.81, 1.28)	0.88	132/9.8	13.45	0.98 (0.85, 1.12)	0.72
384/28.7	13.37	0.92 (0.8, 1.06)	0.24	384/28.7	13.39	0.97 (0.89, 1.05)	0.43
130/9.2	14.05	1.54 (1.28, 1.84)	2.9 × 10⁻⁰⁶	132/9.4	14.07	1.23 (1.09, 1.38)	0.001
954/72.8	13.1	1.07 (0.99, 1.16)	0.09	955/72.9	13.1	1.02 (0.97, 1.07)	0.54
516/41.1	12.55	1.15 (1.03, 1.28)	0.01	518/41.2	12.56	1.03 (0.96, 1.11)	0.38
389/31.5	12.34	1.12 (0.99, 1.27)	0.08	391/31.6	12.38	1.05 (0.97, 1.14)	0.23
210/15.1	13.95	1.03 (0.87, 1.23)	0.71	213/15.3	13.88	1 (0.9, 1.12)	0.94
95/7	13.66	1.23 (0.96, 1.58)	0.10	93/6.7	13.85	1.09 (0.92, 1.28)	0.34
187/14.1	13.25	1.01 (0.83, 1.22)	0.93	187/14	13.35	1.09 (0.98, 1.23)	0.12
120/9	13.3	0.98 (0.77, 1.23)	0.84	119/9	13.29	0.99 (0.86, 1.15)	0.92
233/16.6	14	1.08 (0.91, 1.28)	0.38	233/16.7	13.97	1.09 (0.99, 1.21)	0.09
208/15.4	13.49	1.22 (1.02, 1.46)	0.03	208/15.4	13.52	1.1 (0.98, 1.22)	0.10
153/11.2	13.72	1.03 (0.83, 1.28)	0.77	153/11.2	13.72	0.96 (0.84, 1.1)	0.59
230/17.1	13.43	0.9 (0.76, 1.08)	0.26	232/17.3	13.43	0.97 (0.87, 1.08)	0.56
206/15.8	13.04	1.05 (0.87, 1.26)	0.60	205/15.7	13.04	1.02 (0.91, 1.15)	0.69
185/13.5	13.66	0.87 (0.72, 1.05)	0.15	189/13.8	13.67	0.95 (0.84, 1.06)	0.33
188/13.7	13.69	1.09 (0.91, 1.31)	0.35	190/13.8	13.76	1.01 (0.9, 1.14)	0.82
155/12.3	12.59	1.08 (0.88, 1.33)	0.45	157/12.5	12.51	1.03 (0.9, 1.16)	0.69
452/34.2	13.22	1.03 (0.91, 1.16)	0.66	453/34.3	13.22	1.04 (0.96, 1.12)	0.34
377/27.5	13.73	1.04 (0.91, 1.19)	0.60	383/27.9	13.73	1 (0.92, 1.09)	0.95
247/19.3	12.77	1.07 (0.91, 1.26)	0.43	248/19.5	12.72	1.02 (0.92, 1.13)	0.65
145/10.8	13.48	1.11 (0.9, 1.37)	0.32	147/11	13.37	1.07 (0.93, 1.22)	0.34
333/24.1	13.81	1.06 (0.92, 1.22)	0.42	333/24.1	13.79	0.99 (0.9, 1.09)	0.84
233/17.3	13.47	1.27 (1.09, 1.47)	0.002	236/17.5	13.48	1.07 (0.97, 1.18)	0.19
254/19	13.4	1.07 (0.91, 1.26)	0.41	255/19	13.41	1.01 (0.91, 1.12)	0.88
190/14.2	13.33	1.01 (0.84, 1.22)	0.94	191/14.3	13.36	1.05 (0.94, 1.18)	0.38
185/14	13.21	1.14 (0.96, 1.37)	0.14	185/14	13.21	1.08 (0.97, 1.21)	0.17
178/13.5	13.14	1.14 (0.95, 1.37)	0.17	179/13.7	13.07	1.03 (0.92, 1.16)	0.61
153/12.2	12.56	0.94 (0.76, 1.17)	0.58	152/12.1	12.58	0.92 (0.81, 1.05)	0.23
127/10	12.71	0.98 (0.78, 1.23)	0.83	128/10	12.74	1.02 (0.89, 1.17)	0.80
132/9.8	13.49	1.03 (0.83, 1.29)	0.78	133/9.8	13.52	0.95 (0.83, 1.09)	0.47
143/9.8	14.65	0.98 (0.79, 1.22)	0.87	145/9.9	14.68	1.05 (0.92, 1.2)	0.46
161/12.8	12.61	1.05 (0.86, 1.28)	0.66	161/12.8	12.59	1.01 (0.9, 1.15)	0.82
877/62.7	14	1.13 (1.04, 1.23)	0.003	876/62.7	13.98	1.02 (0.97, 1.07)	0.49

Data availability

Data cannot be shared publicly because of ethical restrictions to the data. Data are available from the Mass General Brigham Human Research Office/Institutional Review Board at Mass General Brigham (contact located at <https://www.partners.org/Medical-Research/Support-Offices/Human-Research-Committee-IRB/Default.aspx>) for researchers who meet the criteria for access to confidential data.

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Author contributions

The authors' contributions were as follows: H.S.D., B.E.C., G.S., R.S., S.R., and E.W.K.: designed the study; H.S.D. and G.S.: conducted research and contributed to statistical analyses; H.S.D., B.E.C., G.S., R.S., S.R., and E.W.K. interpreted data; H.S.D. wrote the manuscript; and all authors: read and approved the final version of the manuscript. H.S.D. is the guarantors of this work and, as such, had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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