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# Sleep disorders as risk factors for calcific aortic stenosis.

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ABSTRACT

*Background and Aims:* Circadian disruption and sleep disorders have been shown to increase the risk for many cardiovascular diseases. Their association specifically with valvular heart disease, however, is inconclusive. In this study we test the association between sleep disorders and the future incidence of aortic stenosis using two large electronic health record (EHR) databases datasets (the TriNetX network and the All *of* Us study). We also explore biochemical data for potential mechanistic insights into that association.
*Methods:* We fitted Cox proportional hazards models to quantify the risk of future incidence of AS in patients with sleep disorders. We also explored clinical laboratory test datasets for biochemical signals that might explain the association, running mediation analyses.
*Results:* In our fully adjusted Cox models, we find that having any sleep disorder increases the risk for the future incidence of AS (HR: 1.15 95 % CI: 1.13–1.18). Changes in lipid profile mediate a proportion of that association.
*Conclusion:* Sleep disorders are associated with an increased risk of AS incidence. That association is independent of classical cardiovascular risk factors even though dyslipidemia plays a large role in mediating this risk.

## 1. Introduction

Modern lifestyles are full of disruptors of our normal sleep-wake rhythms, such as artificial light, noise, trans meridian travel, as well as social and professional demands. Sleep disturbances show high prevalence, for example, 36.8 % of respondents to a CDC survey reported a short sleep duration (<7 h) in 2022 [1]. A clear signal emerged from epidemiological studies linking disrupted sleep-wake rhythms (measured by sleep time, sleep duration, or working as a shift-worker) to an increased risk of cardiovascular disease (CVD) [2–4]. Sleep disorders (diagnosed and self-reported) have also been linked to an increased risk of various cardiovascular diseases [5–7]. These studies do not include valvular disease as a clinical outcome measure. To date, only one study from the UK-biobank tests the association between disrupted sleep wake rhythms and aortic stenosis (AS) and concludes that self-reported insomnia is linked to the development of AS [8].

AS is strongly associated with aging and is estimated to be prevalent in 5–10 % of adults older than 65 years; its incidence is predicted to increase along with prolonged life expectancy [9]. AS has an overlapping risk factor profile with atherosclerosis which highlights a shared pathogenic processes with the initiation phase of AS. Circadian disruption and sleep disorders have a well-established link to higher risks of coronary artery disease [2,3,7]. We thus hypothesized that circadian disruption caused by sleep disorders increases the risk for AS development.

The main objective of this study is to test the association between sleep disorders and the future incidence of aortic stenosis using multiple statistical methods and two large electronic health record (EHR) databases; The TriNetX Diamond Network and the All *of* US study. Because valvular heart disease has not been studied in a circadian pre-clinical context, we leverage biochemical data for potential mechanistic insights into that association as a secondary objective.

## 2. Methods

### 2.1. Patients

The data used in this study were downloaded on April 27, 2023, from the TriNetX Diamond Network which provided access to electronic

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medical records from approximately 108 million patients across 92 healthcare organizations in the United States. For our testing cohort, we obtained EHR data from 8.8 million patients above age 50, with a measurement of height and weight, and with a diagnosis of sleep disorders (ICD10 code G47, ICD9 code 327) and from a random sample of 8.8 million patients who meet the same criteria but without a diagnosis of sleep disorders.

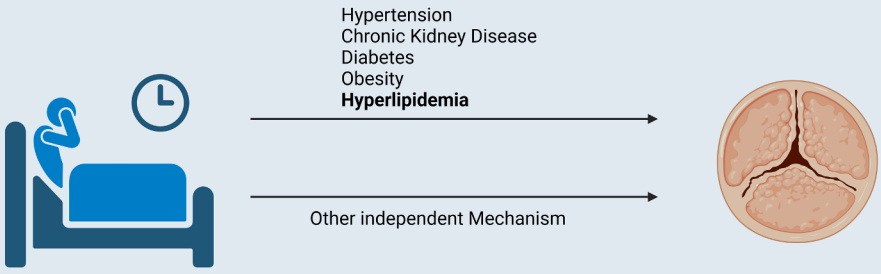
For our validation cohort we used data from the All *of* Us study (data version 7) containing EHR data from 392,259 participants in the United States, 70,070 of whom have been diagnosed with a sleep disorder.

Further exclusion criteria applied to both data sources were hidden sex, a diagnosis of congenital aortic valve disease, a non-physiologic BMI (<12 or >50), the presence of a procedural code for any aortic valve procedure without the presence of an AS diagnosis, and a diagnosis of AS before age 66. All diagnostic, procedural, or prescription codes used in this study are listed in Supplemental Table 1.

Our study was deemed exempt from IRB review by the institutional review board at the University of Pennsylvania (Protocol # 853,440). Using data from TriNetX is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is de-identified per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data are de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert refreshed on December 2020. All *of* US participants provided informed consent before participation [10].

## Central Illustration: Sleep disorders as risk factors for calcific aortic stenosis.

**Study Objective**: Are sleep disorders associated with an increased incidence of aortic valve stenosis?
**Study Sample:** 7,788,859 patients from the TriNetX network and 87,135 patients from the All *of* US study.
**Methods:** Cox Proportional Hazards Models and clinical labs analysis from EHR data




**Adjusted Models**

| Disorder | HR (95% CI) |
|---|---|
| Any Sleep Disorder | 1.15 (1.13 to 1.18) |
| Sleep Apnea | 1.20 (1.17 to 1.24) |
| Circadian Rhythm Sleep Disorder | 1.08 (0.84 to 1.39) |
| Insomnia | 0.98 (0.94 to 1.03) |
| Hypersomnia | 1.18 (1.07 to 1.31) |
| Parasomnia | 1.03 (0.78 to 1.35) |
| Narcolepsy | 1.28 (1.03 to 1.60) |
| Sleep Movement Disorders | 1.19 (1.07 to 1.33) |




### Key Findings:

- Patients with sleep disorders were at a higher risk to develop aortic stenosis in the future
- Patients with sleep disorders have an unfavorable cardiometabolic risk factor profile particularly hyperlipidemia that partly but not entirely explains the association.

Central Illustration

### 2.2. Statistical analysis

To test whether sleep disorders qualify as risk factors for AS, we fitted Cox proportional hazards models seperately to patient cohorts from the TriNetX network and the All *of* US research program. We applied the same methodology to both data sources independently. The outcome of the model was specified as the incidence of non-rheumatic aortic valve stenosis, as assessed by the first occurance of the ICD10 codes I35.0 or I35.2. Because the older ICD9 classification grouped non-rheumatic aortic valve diseases broadly under code 424.1, we considered the first occurrence of the ICD9 code as the first occurrence of AS only if the patient record subsequently contained the ICD10 codes 135.0 or I35.2. We specified a diagnosis of sleep disorder as our main exposure of interest. We included hypertension, hyperlipidemia, chronic kidney disease, BMI, diabetes, and sex at birth as covariates in the models. Sleep disorders and the covariates of interest were defined as the first occurrence of an ICD code in the medical record. Supplemental Table 1 specifies all the codes used to define and extract medical record data. Based on previous work on AS risk factors and because of its strong association with aging [11], we specified the exposure and covariate cutoff time as age 65 and started our follow up time (time 0) a year later at age 66 to decrease the risk of reverse causation. We ended the follow up time at age 80 due to the sparse proportion of patients in the medical record reaching an age above 80. Starting our follow up time at a later age also decreases the risk of confounding by congenital aortic valve disease which leads to earlier incidence of AS [12].We used each patient's age as the time component of the model, and data were censored at the time of a patient's death or the year 2020. Supplemental figure 1 schematically summarizes the temporal design behind our main cox proportional hazards model. We tested the proportional hazards assumption by plotting Schoenfeld residuals [13]. Covariates where the assumption was violated were included as time varying coefficients. When analyzing the incidence of any sleep disorder, the earliest date of any sleep diagnosis was considered the date of sleep disorder incidence in patients with more than one sleep disorder diagnosis. We also stratified our analysis by sleep disorder type based on the ICD classification.

To make sure that our results also apply to patients with sleep disorder diagnoses at different ages, we fitted a Cox proportional hazards model. Sleep disorders are used as time varying covariates. The sleep disorder diagnosis status of a patient can vary across the follow up period of 66 to 80 years of age provided it is at least a year prior to the development of AS, should a patient develop AS in the follow up period. We also fit Cox proportional hazards models with sleep and covariate cutoffs at age 50 and a follow up period between age 51 and 80.

Because of their strong association we used the mediation package in R to quantify the degree to which cardiovascular risk factors confounded the association between sleep disorders and AS [14]. We used a survival regression model quantifying the association between the risk factor and the development of AS after age 66 and a logistic regression model quantifying the association between having a sleep disorder and the risk factor of interest for the mediation analysis. We also further assessed the influence of each risk factor on AS development at the population level. We used our adjusted main Cox proportional hazards model to calculate the population attributable fraction (PAF) for all covariates in the model using the graphPAF package in R to quantify further the impact of each covariate on the development of AS [15]. PAF describes the fraction of disease cases attributable to a specific exposure [16].

To provide clues to further study valvular heart disease in a circadian context we explored biochemical signals potentially explicative of the association between sleep disorders and AS and divided the patients in the TriNetX data into 4 cohorts: (i) those with a sleep disorder diagnosis before age 65 and incident AS after age 66, (ii) those with no prior sleep disorder but incident AS, (iii) those with prior sleep disorders but no incident AS, and (iv) heathy patients with neither prior sleep disorder nor incident AS. We then examined all clinical lab tests in the database performed prior to age 65 and eliminated any outlier values (beyond 1.5 times the interquartile range from the first and second quartiles), and excluded tests not represented across all 4 cohorts. Measurements after age 65 were also eliminated. Multiple test values prior to age 65 for a specific lab test in a single patient were averaged. We then ran a linear regression analysis with the lab test numeric value as the dependent variable and the cohort as the independent variable such that all cohorts are compared to the sleep disorder and incident AS cohort. We selected the lab tests where the Benjamini-Hochberg adjusted $p$-value ($q$-value) was $<0.1$ and the fold change in the lab numeric value was $\geq 5\%$ for all the three comparisons to make sure the resulting labs are not selected based solely on a low $p$-value due to a large sample size. To quantify further the effect each of the statistically significant differences in lab results have on the association between sleep disorders and AS, we repeated the above-described mediation analysis while replacing our covariates of interest with the labs surviving our $q$-value and fold-change cutoff.

Data management and all analyses were performed using R versions (4.3 and 4.4).

## 3. Results

### 3.1. Multiple sleep disorders are associated with an increased risk for AS incidence

In the TriNetX database, patients with sleep disorders had a significantly higher prevalence of cardiovascular risk factors, cardiovascular disease, and a significantly higher BMI (Table 1). 10.6 % of the studied sample from TriNetX presented with a sleep disorder diagnosis before age 65. The mean age of diagnosis was $62.7 \pm 2.4$ years with sleep apnea as the most prevalent diagnosis (7.1 %, Table 2). There were 133,419 cases of incident AS between ages 66 and 80 with a mean follow up time of $7.9 \pm 4.9$ years. Our unadjusted Cox proportional hazards models showed an increased risk of AS incidence with any sleep disorder (HR: 2.61, 95 % CI: 2.55–2.67) which remained significant when each individual sleep disorder was interrogated (Fig. 1, Supplemental Figure 2). Here, sleep apnea showed the strongest signal (HR: 3.04, 95 % CI: 2.96–3.12). The significant risk association between AS incidence and any sleep disorder and sleep apnea survived our adjusted model (HR: 1.15 95 % CI: 1.13–1.83 and HR: 1.20 95 % CI: 1.17–1.24, respectively) where we controlled for various cardiovascular risk factors. Additional candidate sleep disorders linked to AS incidence included hypersomnia (HR: 1.18, 95 %CI: 1.07–1.31), narcolepsy (HR: 1.28 95 % CI:1.03–1.60) and sleep movement disorders (HR: 1.19 95 % CI: 1.07–1.33, Fig. 1). Supplemental Figure3 shows how we arrived at our population of interest from the TriNetX data.

Results from the mediation analysis shows significant and negative average causal mediation effects (ACME) and average direct effects (ADE) indicating that the presence of a sleep disorder is significantly associated with smaller AS free survival time independent from the tested covariates, but that these covariates mediate a proportion of that association (Table 3).

While sleep disorders are attributed to a smaller proportion of AS cases developed during the follow up period (population attributable fraction, PAF: 4.35 %, 95 % CI, 3.75–4.82) compared to other cardiovascular risk factors such as a BMI $\geq$ 30 (PAF: 33.2 %, 95 % CI, 32.7–33.9), they still inflict a similar burden to chronic kidney disease (PAF 4.4 %, 95 % CI: 4.2 −4.67) in the population forming the TriNetX database (Table 4).

In the All *of* Us cohort, 957 cases of incident AS were present after age 66 with a mean follow up time of $7.7 \pm 4.5$ years. The adjusted Cox proportional hazards model confirmed the increased risk for AS development in patients diagnosed with any sleep disorder (HR: 1.40, 95 % CI: 1.12–1.77 in the fully adjusted model. Supplemental Figure 4). Due to the small number of events for several sleep disorders, we did not expand the modeling across each of the sleep disorder categories. We did not conduct a laboratory test analysis due to sample size limitations for

**Table 1**
Characteristics of the two patient populations in the TriNetX network and in the All of US study from data collected before age 65.

| Data Source | TriNetX | | | All *of* US | | |
|---|---|---|---|---|---|---|
| Variable | No Sleep Disorder before 65 n (%) | Any Sleep Disorder before 65 n (%) | *p*-value | No Sleep Disorder before 65 n (%) | Any Sleep Disorder before 65 n (%) | *p*-value |
| n | 6793,998 | 994,861 | | 79,296 | 7839 | |
| Hypertension | 1234,532 (18.2) | 715,083 (71.9) | <0.001 | 17,101 (21.6) | 5714 (72.9) | <0.001 |
| Diabetes | 559,336 (8.2) | 363,414 (36.5) | <0.001 | 6670 (8.4) | 2970 (37.9) | <0.001 |
| Hyperlipidemia | 1199,135 (17.6) | 704,398 (70.8) | <0.001 | 17,662 (22.3) | 5910 (75.4) | <0.001 |
| CVD | 152,9450 (22.5) | 822,529 (82.7) | <0.001 | 22,693 (28.6) | 6797 (86.7) | <0.001 |
| CKD | 127,164 (1.9) | 113,264 (11.4) | <0.001 | 1835 (2.3) | 1078 (13.8) | <0.001 |
| Sex (M) | 3066,843 (45.1) | 476,420 (47.9) | <0.001 | 35,657 (45.0) | 3495 (44.6) | 0.524 |
| Race | | | <0.001 | | | <0.001 |
| Asian/Pacific Islander | 45,192 (0.7) | 5005 (0.5) | | 1660 (2.1) | 98 (1.3) | |
| Black or African American | 337,984 (5.0) | 58,869 (5.9) | | 10,623 (13.4) | 1136 (14.5) | |
| More than one | | | | 686 (0.9) | 70 (0.9) | |
| Unknown | 2987,988 (44.0) | 391,263 (39.3) | | 9952 (12.6) | 862 (11.0) | |
| White | 3422,834 (50.4) | 539,724 (54.3) | | 56,375 (71.1) | 5673 (72.4) | |
| BMI mean(sd) | 30.15 (5.78) | 33.22 (5.73) | <0.001 | 29.53 (6.01) | 33.94 (7.41) | <0.001 |

**Table 2**
Prevalence of sleep disorders before age 65 and the mean age at diagnosis in the studied population from the both the TriNetX Network and the All of US study.

| | TriNetX | | | All *of* US | | |
|---|---|---|---|---|---|---|
| Sleep Disorder | Number Diagnosed Before Age 65 | Percent Diagnosed Before Age 65 | Mean Age at Diagnosis (± SD) | Number Diagnosed Before Age 65 | Percent Diagnosed Before Age 65 | Mean Age at Diagnosis (± SD) |
| AnySleep Disorder | 772,085 | 10.58 % | 62.74 (±2.4) | 7839 | 9 % | 60.67 (±3.9) |
| Sleep Apnea | 517,569 | 7.09 % | 62.76 (±2.2) | 5628 | 6.46 % | 60.67 (±3.5) |
| Circadian Rhythm Sleep Disorder | 6497 | 0.09 % | 62.93 (±2.3) | 180 | 0.21 % | 60.71 (±3.9) |
| Insomnia | 274,981 | 3.77 % | 52.9 (±2.4) | 2519 | 2.89 % | 61.52 (±3.7) |
| Hypersomnia | 35,288 | 0.48 % | 63.21 (±2.5) | 685 | 0.79 % | 63.21 (±3.9) |
| Parasomnia | 6261 | 0.09 % | 63.25 (±2) | 109 | 0.13 % | 61.37 (±3.6) |
| Narcolepsy | 5937 | 0.08 % | 62.28 (±3.2) | 82 | 0.09 % | 57.33 (±6) |
| Sleep Movement Disorders | 29,407 | 0.40 % | 63.08 (±2) | 488 | 0.56 % | 61.1 (±3.1) |

each individual test. Supplemental Figure 5 shows how we arrived at our population of interest from the All *of* Us study and Supplemental Table1 shows the characteristics of the patient population from data collected before age 65. As we observed in the TriNetX database, the All *of* Us cohort showed a similar trend of a higher prevalence of cardiovascular risk factors and cardiovascular disease diagnoses, among patients with sleep disorders. All *of* US study patients had a similar sleep disorder prevalence with slightly younger diagnosis ages compared to the TriNetX network (Table 2).

Fitting the Cox proportional hazards models with having a sleep disorder as a time varying covariate still demonstrates a significantly higher risk for developing AS in both the TriNetX network and the All *of* Us study (HR: 1.57, 95 % CI: 1.55–1.59 and HR: 1.92, 95 %CI: 1.66–2.24 in fully adjusted models from the TriNetX and the All *of* US data respectively, Supplemental Table 2). Changing the follow up time of our main model to start at 56 with covariate data at 55 also showed similar significant associations in both datasets (Supplemental Table 2).

Taken together, patients with sleep disorders are at an increased risk of developing AS. This association is independent from cardiovascular risk factors that mediate a proportion of this association.

### 3.2. Changes in lipid metabolism play a role in the increased risk

After running a linear regression analysis with the lab numeric value as the dependent variable and the cohort as the independent variable such that all four cohorts are compared to the healthy cohort (i), four lab tests, namely HDL, LDL, total cholesterol, and triglycerides, survived the multiple testing correction at a $q$-value $\leq 0.1$ while satisfying a fold change $\geq 5$ % in all three comparisons with the disease group (AS incidence after age 66 and sleep disorder before age 65, Supplemental Table3). Fig. 2 shows the distributions of the numeric value of each of the four lab tests across each of the four cohorts. The distribution of HDL cholesterol was lower and that of triglycerides was higher in the AS and sleep cohort, indicating less favorable lipid profiles (Supplemental Table4). LDL and total cholesterol were lower in the diseased cohort. This observation might be driven by statin use which, while effective in lowering LDL, does not seem to decrease AS progression [17,18]. Indeed, 77 % of patients in the AS incidence and prior sleep disorder cohort were on statins before age 65, a significantly higher proportion than the other cohorts (Chi-squared $p$ value $< 0.001$, Supplemental Figure 6). For HDL, LDL, total cholesterol and triglycerides, the mediation analysis showed significant and negative average direct effects

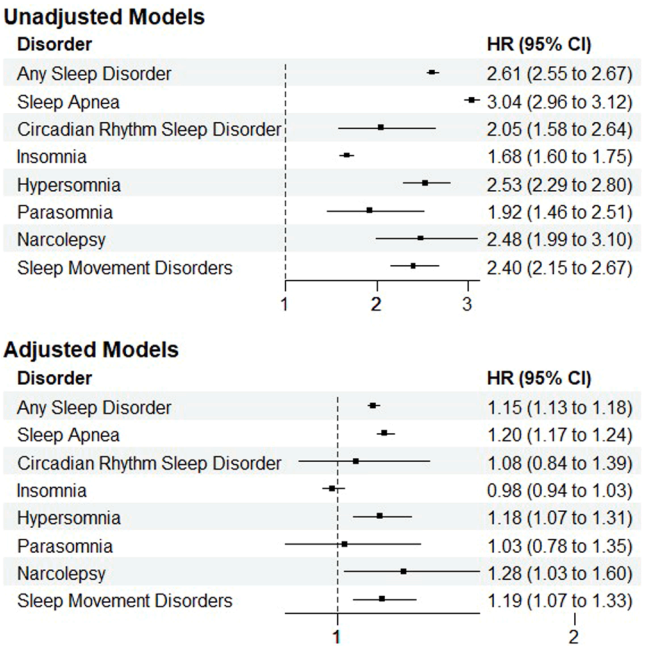



**Fig. 1.** Hazard ratios from unadjusted cox proportional hazards models (Top) and adjusted models (Bottom) testing the association between sleep disorders and incident aortic stenosis in the TriNetX database. Adjusted for hypertension, hyperlipidemia, diabetes, chronic kidney disease, sex at birth, and BMI.

**Table 3**
Results from the mediation analysis quantifying the effects cardiovascular risk factors have on the association between sleep disorders and incident aortic stenosis. Data from the TriNetX database. ACME: Average causal mediation effects of sleep disorders on aortic stenosis through the risk factor ADE: average direct effect of sleep disorders on aortic stenosis. Negative estimates imply shorter disease free survival times. CKD: chronic kidney disease.

| | ACME | | ADE | |
|---|---|---|---|---|
| Risk Factor | Estimate | *p*-value | Estimate | *p*value |
| Hypertension | −14.77 | <0.001 | −15.26 | <0.001 |
| Hyperlipidemia | −13.10 | <0.001 | −18.05 | <0.001 |
| Diabetes | −8.68 | <0.001 | −21.53 | <0.001 |
| CKD | −3.08 | <0.001 | −31.52 | <0.001 |
| BMI | −7.58 | <0.001 | −30.62 | <0.001 |

**Table 4**
Population attributable fraction (PAF) of sleep disorders and the different cardiovascular risk factors. The PAF was calculated from adjusted main cox proportional hazards model based on data from the TriNetX network using the graphPAF package in R. PAF: population attributable fraction, CI: confidence interval.

| Risk Factor | PAF (%) | 95 % CI |
|---|---|---|
| Sleep Disorders | 4.35 | 3.75–4.82 |
| Chronic Kidney Disease | 4.4 | 4.2–4.67 |
| Hyperlipidemia | 7.52 | 6.6–8.32 |
| Diabetes | 11.9 | 11.5–12.4 |
| Hypertension | 18.8 | 18.0–19.6 |
| BMI ≥ 30 | 33.2 | 32.7–33.9 |

(ADE, *p*-values < 0.02 for all) indicating that sleep disorders are associated with a shorter AS free survival time independent from these lipid differences. The analysis also showed negative and significant causal mediation effects (ACME, *p-values* < 0.01 for all) indicating that a proportion of this association is mediated by changes in these lipid parameters (Table 5). In addition to the fully adjusted Cox proportional hazards models, both covariate and laboratory test mediation analyses support the conclusion that sleep disorders are independently associated with an increased risk for AS incidence.

## 4. Discussion

Using two separate databases, we report an increased risk for AS development in patients with a diagnosis of any sleep disorder. This statistically significant association was mainly driven by sleep apnea, hypersomnia, narcolepsy, and sleep movement disorders and remained robust when the model was controlled for traditional cardiovascular risk factors, suggesting that sleep disorders independently contribute to the AS risk profile. We further find that the increased risk is largely associated with a higher prevalence of classical cardiovascular risk factors and particularly dyslipidemia. We conclude that while dyslipidemia plays a role in mediating the increased risk for AS development, patients with sleep disorders are also at an increased risk for AS incidence through an independent mechanism. While sleep disorders were not attributed to the largest proportion of AS cases as compared to the classical cardiovascular risk factors, they are still an important modifiable target in cardio-protection. A population-based study reported 85 % of incident AS cases required hospitalization for severe AS which underscores the need for preventive care targeting modifiable risk factors [19].

Circadian rhythms are present in all physiologic and behavioral functions, amongst the most prominent of which is the sleep-wake cycle [20]. These rhythms are the result of endogenous molecular clocks that are self-sustained transcriptional and translational feedback loops [21]. Molecular clocks are found in most cells and tissues and influence cellular function by regulating transcription of large sets of genes [22]. While being self-sustained, peripheral clocks are synchronized by a central master clock in the suprachiasmatic nucleus via hormonal or neural cues [22]. Similar to other peripheral tissues, the molecular clock machinery is present in the heart and the vasculature and is synchronized with the clocks of other tissues by hormonal, neural, and food signals [23]. As a consequence, cardiovascular function varies rhythmically across the 24h day ranging from electrophysiology, to blood pressure, to contractility, metabolic states, and remodeling and injury responses [23–26]. In light of our results implicating lipid markers, it is important to note that lipid metabolism is under circadian control and varies rhythmically throughout the day [27]. Knocking out components of the molecular clock in animal models has led to increased atherosclerotic burden and the development of different cardiomyopathies [23,28]. However, a potential impact of clocks on valvular physiology and disease has largely remained unaddressed.

Sleep apnea emerged with the largest effect size in our analysis of seven specific sleep disorder phenotypes. We speculate that a multiplicity of factors could be relevant to this observation. Obesity is an important risk factor for sleep apnea and is accompanied by metabolic dysfunction both of which are aortic stenosis risk factors [9,29]. The periods of breathlessness in sleep apnea increase sympathetic tone at night via chemoreflex stimulation by hypoxia, leading to both hypertension and metabolic dysfunction [29]. A third factor is the disruption of normal circadian rhythms by apneic episodes and sympathetic activation. For hypersomnia and sleep movement disorders, evidence also suggests the involvement of circadian misalignment and dysautonomia [30].

Genetic disruption of clock genes in rodents led to various metabolic consequences such as increased body weight, hyperglycemia, hyperinsulinemia, and hyperlipidemia [31]. Epidemiological studies have linked inadequate sleep to diabetes [32], hypertension [33], obesity [34], and hyperlipidemia [35]. In a study from the UK biobank, sleep apnea was associated with coronary heart disease, and metabolic risk factors (especially dyslipidemia) played a mediating role [36]. We see a similar effect where patients with sleep disorders had a higher prevalence of cardiometabolic risk factors and were at a higher risk for developing aortic stenosis.

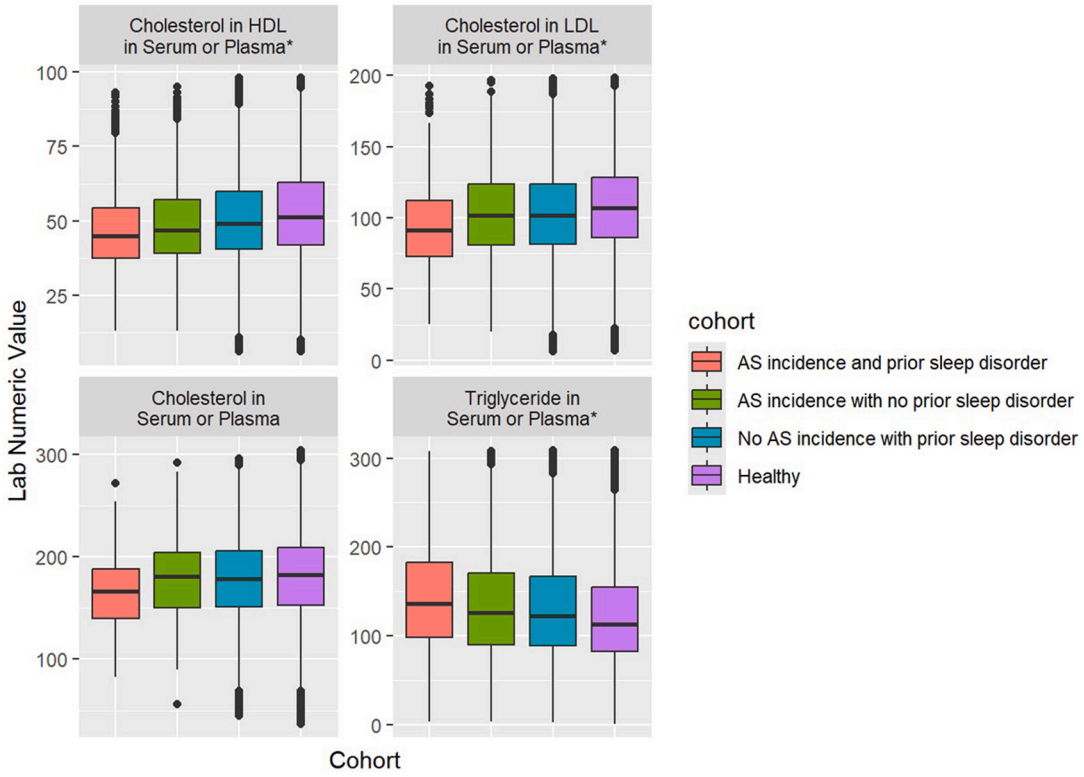



**Fig. 2.** Distribution of lab test numeric values with $q$-values $\leq 0.1$ and fold change $\geq 5$ % for all cohort comparisons with the healthy cohort. *$q$-value $\leq 0.05$. Based on data from the TriNetX database.

**Table 5**
Results from the mediation analysis quantifying the effects select laboratory measurements have on the association between sleep disorders and incident aortic stenosis. Data from the TriNetX database. ACME: Average causal mediation effects of sleep disorders on aortic stenosis through the risk factor ADE: Average direct effect of sleep disorders on aortic stenosis. negative estimates imply shorter disease free survival times.

| | ACME | | ADE | |
|---|---|---|---|---|
| Risk Factor | Estimate | P-value | Estimate | P-value |
| HDL | −3.19 | <0.001 | −15.21 | <0.001 |
| LDL | −2.10 | <0.001 | −18.71 | <0.001 |
| Cholesterol | −0.47 | <0.001 | −17.79 | 0.02 |
| Triglycerides | −2.15 | <0.001 | −14.93 | <0.001 |

Our study leverages large sample sizes of real-world EHR data from diverse populations across the US. The large sample size allowed a longitudinal design which provides confidence in the validity of observed associations. While we took measures to reduce the risk of reverse causation, it is not eliminated. Despite adjusting our models for known risk factors for AS, using two different datasets with differing populations, and including biochemical measurements in our analysis, their remains a risk for residual confounding by unknown or unmeasured variables. Further studies with designs permitting causal conclusions are needed. This study also relies on EHR data, which by its nature, targets a sicker population than the general population. This could have diluted some signals leading us to miss associations that might have had relevance in the general population. Another potential limitation is the possibility of an overlap in participating patients since both databases are large cohort studies based in the US.

## 5. Conclusion

Patients with sleep disorders are at a higher risk of developing AS, an association largely mediated by dyslipidemia. Our study also suggests the presence of a distinct mechanism linking sleep disorders to the development of AS that is independent from the traditional cardiovascular risk factors including dyslipidemia. The application of machine learning to refine and integrate sleep and image derived phenotypes with genetics will elucidate the mechanisms which underlie this apparent relationship. Thus, sleep disorders are potential modifiable risk factors for the development of AS.

## 6. Disclosures

G.A. FitzGerald is the McNeil Professor of Translational Medicine and Therapeutics and held a Merit Award from the American Heart Association (17MERIT33560013) during the performance of this work. C. Skarke is the Robert L. McNeil Jr. Fellow in Translational Medicine and Therapeutics. The other authors report no conflicts.

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## CRediT authorship contribution statement

**Nadim El Jamal:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Thomas G. Brooks:** Writing – review & editing, Methodology. **Carsten Skarke:** Writing – review & editing, Conceptualization. **Garret A. FitzGerald:** Writing – review & editing, Supervision, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Garret FitzGerald reports a relationship with American Heart Association Inc that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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*Code availability*

The code used in extracting variables, cleaning the data, and running all analyses is made freely available at https://zenodo.org/records/14883761.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.100958.

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