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Per-and polyfluoroalkyl substances and disrupted sleep: mediating roles of proteins

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ABSTRACT

Background: Per-and polyfluoroalkyl substances (PFAS) contamination may disrupt sleep through disrupted metabolic and immune functions. The study aims to investigate the association and potential mechanism between PFAS and sleep.

Methods: We included 136 young adults recruited between 2014-2018 and 76 were re-assessed between 2020-2022. Additional 8 participants only had complete data between 2020-2022. Plasma PFAS (PFOS, PFOA, PFHxS, PFHpS, PFPeS, PFNA, PFDA) were measured at both visits using liquid-chromatography high-resolution mass spectrometry. Plasma proteins were measured by Olink® Explore 384 Cardiometabolic and Inflammation Panel I. Sleep duration was self-reported at both visits along with follow-up sleep disturbance and sleep-related impairment using validated instruments. We utilized multiple linear regression to explore the association between individual PFAS (in tertile) and these sleep outcomes. PFAS associated with sleep outcomes were subjected to computational toxicology analysis using the Comparative Toxicogenomics Database and Toxicology in the 21st Century database to identify potential genetic links between them. Mediation analysis using proteomic data was then performed to confirm the findings from computational toxicology analysis.

Results: At baseline, one tertile increase in PFDA was associated with 0.39 (95 % CI: 0.05, 0.73) hours of shorter nightly sleep duration, and, at follow-up, PFHxS and PFOA were associated with 0.39 (95 % CI: 0.05, 0.72) and 0.32 (95 % CI: 0.01, 0.63) hours shorter sleep duration, respectively. One tertile increase in PFOS exposure was associated with a 2.99-point increase in sleep disturbance scores (95 % CI: 0.67, 5.31) and a 3.35-point increase in sleep-related impairment scores (95 % CI: 0.51, 6.20). Computational toxicology and mediation analyses identified potential mediating roles for several proteins in the PFAS-sleep associations, including 11-beta-dehydrogenase isozyme 1 (HSD11B1), cathepsin B (CTSB) and several immune system-related proteins.

Conclusion: Future large scale epidemiological and mechanistic studies should confirm our findings and test effect measure modification of the associations by age.

Introduction

Sleep deprivation and sleep disorders can exert an immediate impact on daily activities, mood, and health (Colten et al., 2006). Over the long term, sleep disturbance is linked to adverse effects in different parts of the human body, including the heart, liver, and brain (Dutil et al., 2018). However, a significant proportion of adults fail to obtain an adequate amount of sleep (Adjaye-Gbewonyo et al., 2022). Although some of these effects are due to known demographic, social, and behavioral risk factors, they do not fully explain differences in insufficient sleep and sleep quality (Grandner et al., 2015). Addressing modifiable factors that contribute to poor sleep is vital in mitigating the risk of these negative

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health outcomes and informing public health interventions to promote sleep health.

Per-and polyfluoroalkyl substances (PFAS) constitute a group of chemicals commonly used in consumer products due to their water- and stain-resistant properties. They are pervasive in the population and possess a long half-life in the human body (Andrews and Naidenko, 2020; Li et al., 2018). Three previous studies (in pregnant women, infants, and early childhood) in China showed that both individual PFAS and PFAS mixtures are associated with worse sleep disturbance (Huang et al., 2023, 2022; Xie et al., 2022). Yet, studies using data from the US National Health and Nutrition Examination Surveys (NHANES) showed mixed results. Guo et al. found an inverse association between PFAS mixture and trouble falling asleep using NHANES data from 2005-2014 while Shiue et al. found a positive association with wake-up at night, unrested during the day, and leg jerks in sleeping using NHANES data from 2005-2006 (Guo et al., 2023; Shiue, 2017). The discrepancies suggest that the effects of PFAS on sleep may vary across populations and sleep measures.

PFAS is hypothesized to have the ability to cross the blood-brain barrier (BBB) and disrupt the levels of neurotransmitters (e.g., dopamine, glutamate, and serotonin) and calcium homeostasis, which are all important for sleep health (Brown-Leung and Cannon, 2022; Carbone et al., 2023; Gvilia, 2010). PFAS may also indirectly affect sleep through disrupted immune and metabolic function (Asif et al., 2017; Beans, 2021; Chen et al., 2020; Morselli et al., 2012). For example, cytokines such as interleukin 1 (IL-1) and tumor necrosis factor (TNF) can participate in the regulation of sleep, specifically non-rapid eye movement sleep stage (Imeri and Opp, 2009). In addition, many studies have linked sleep duration and quality to metabolic function through effects in glucose homeostasis (i.e., regulation of growth hormone, glucagon, and cortisol), which further contributes to obesity and diabetes (Morselli et al., 2012). A recent report by the National Academies of Sciences, Engineering, and Medicine points out the gap in the neurological impact of PFAS (Guidance on PFAS Exposure, Testing, and Clinical Follow-Up, 2022). Identifying potential molecular pathways between PFAS and sleep may further our understanding of PFAS neurotoxicity.

High-throughput proteomics data emerged as a powerful tool to profile thousands of proteins and identify differential protein expression and dysregulated molecular pathways due to environmental exposures including PFAS research (Chen et al., 2024; Dunder et al., 2023; Salihovic et al., 2020). Proteomics data can capture modifications beyond transcriptomes and genomes, and proteomics profiling showed PFAS associated with pro-inflammation and immunoregulation, which are important for sleep as well (Chen et al., 2024; Imeri and Opp, 2009).

In the present study, our primary objective (Step 1) was to leverage a prospective cohort of young adults to assess the association between multiple PFAS and sleep duration, disturbance, and impairment. To gain more insight into the potential molecular mechanisms, our secondary objective (Step 2) was to evaluate the current body of evidence through a data mining approach in two toxicological databases including Comparative Toxicogenomics Database (CTD) and Toxicology in the 21st Century (Tox21). The goal of data mining is to screen potential genetic targets that are shared between PFAS and sleep disorders as well as the toxicity of each PFAS. These genetic targets are genes that are identified in the toxicological studies when screening toxicity of individual chemicals and the expression of genes or associated transcript/proteins could be up or down regulated due to exposure to the chemical in the study. To confirm the genetic targets generated through computational toxicology analysis, we further assessed the potential mediating roles of proteins associated with suspected genetic targets of PFAS in the association between PFAS and measures of sleep duration and quality (Step 3). Our approach provides a more comprehensive understanding of the relationship between PFAS and sleep and, by integrating multiple data sources, we have significantly enhanced the inferential strength of our findings.

Method

Study population

We included study participants from the Metabolic and Asthma Incidence Research (Meta-AIR) study (Kim et al., 2019) who were recruited between 2014 and 2018 from the Southern California Children's Health Study (CHS) (McConnell et al., 2015). Meta-AIR study participants were selected based on having a history of overweight or obesity (defined as age- and sex-specific BMI $> 85^{th}$ percentile; BMI was obtained between age 14 and 15), and free of diabetes. We included participants (n=136) who provided biospecimens and completed sleep-related questions. A subset of study participants (n=76) was re-examined and n = 8 only had data between 2020 and 2022. This study was approved by the USC Institutional Review Board (HS-19-00338). We selected this cohort because 1) they were relatively healthy and identifying causes of disrupted sleep pattern could lead to interventions to prevent worsening adverse health outcomes and 2) sleep patterns change frequently in young adults (Owens et al., 2014).

Written informed assent and consent were obtained from participants and their parents, respectively.

Plasma-level PFAS concentrations

Details on the method for quantification of these environmental pollutants were published elsewhere (Goodrich et al., 2023). Briefly, we used liquid chromatography–high-resolution mass spectrometry (LC-HRMS) to determine the levels of PFAS. Raw data were extracted, aligned, batch-effect corrected, and imputed with the limit of detection (LOD). Among the 24 PFAS that could be quantified using the method, we quantified 7 PFAS, which were perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluoroheptane sulfonic acid (PFHpS), perfluoropentane sulfonic acid (PFPeS). In addition, the same 7 PFAS were measured at follow-up. We then converted the concentration (ng/mL) of these pollutants into tertiles to improve model fit and account for potential non-linear associations which is consistent with previous studies (Guo et al., 2023; Huang et al., 2023). The complete list of PFAS and their LODs is available in Supplemental Table 1.

Sleep health

At baseline and follow-up, self-reported sleep duration was collected. In addition, two sleep outcomes, including sleep disturbance and sleep impairment in the past 7 days, were measured at follow-up by the 8-item short forms developed from the Patient-Reported Outcomes Measurement Information System (PROMIS™) Sleep Disturbance and Sleep-Related Impairment item banks. The short forms are comparable to the full item forms and the sleep disturbance and sleep-related impairment item banks have been previously validated (Forrest et al., 2018; Yu et al., 2011). Sleep disturbance measures problems with falling and staying asleep and sleep-related impairment measures daytime sleepiness, difficulties waking up, and their impact on mood and behavior. The instruments were measured on a Likert scale ranging from 1 (Not at all) to 5 (Very much) and the higher the score is, the worse the sleep disturbance/impairment is. The raw scores were then transformed into a t-score. For sleep duration, we further categorized sleep duration as not enough sleep (<7 vs ≥ 7 h) based on clinical recommendations for enough sleep (Watson et al., 2015).

Covariates

We included the following variables a priori as potential confounders based on prior literature (Guo et al., 2023; Huang et al., 2023): ethnicity (non-Hispanic White, Hispanic, or Other), sex (male or female), age

(continuous; measured at baseline and follow-up), parental education (high school and below or above high school), Healthy Eating Index (HEI) 2015 (continuous; measured at baseline and follow-up) derived from 24-hour recalls, using Nutrition Data System for Research (NDSR) (University of Minnesota) at baseline and Automated Self-Administered 24-hour (ASA24) (NCI) at follow up, physical activity (self-perceived physical activity [continuous; the scale of 1 (least active) to 9 (most active)] measured at baseline and metabolic equivalents [low, medium, and high] measured at follow-up) derived from self-reported number of minutes/week spent on various activities (Mendes et al., 2018), cigarette smoking (ever vs never), alcohol drinking (ever vs never). We used a single imputation ("mice" package in R) to impute missing values of the HEI and self-perceived level of physical activity (Buuren and Groothuis-Oudshoorn, 2011; Little and Rubin, 2019).

Step 1: Association study

The analytic workflow is presented in Fig. 1. We used multiple linear regression to assess the cross-sectional associations between PFAS exposures (per one tertile increase) measured and sleep measurements at a baseline or follow-up visit. We controlled for baseline covariates (ethnicity, sex, parental education, age, physical activity, cigarette smoking, alcohol drinking, HEI) when assessing outcomes measured at baseline, and time-fixed covariates (ethnicity, sex, parental education) and covariates measured at follow-up (age, physical activity, cigarette smoking, alcohol drinking, HEI) for outcomes measured at follow-up. A directed acyclic graph (DAG) is included in Supplemental Fig. 1. To assess the joint effect of the PFAS mixture on sleep outcome, we used quantile g-computation ("qgcomp" package in R) (Keil et al., 2020). The mixture effect was interpreted as per tertile increase in all PFAS. In addition, we assessed whether individual PFAS and PFAS mixtures were associated with not enough sleep (<7 h) using logistic regression.

Since PFAS have long half-lives in the human body (Li et al., 2018), we further assessed whether PFAS measured at baseline were associated with sleep duration over time. We used the generalized estimating equation (GEE) model ("geepack" in R) to conduct repeated measure analysis with exchangeable correlation structure and standard error estimated using a robust sandwich estimator. We adjusted for both time-fixed covariates and time-varying covariates (age, HEI, cigarette smoking, drinking). Since the physical activity was measured differently at baseline and follow-up, we only controlled for the follow-up level of physical activity. We also included interaction terms between PFAS and follow-up time in the model. We adjusted for multiple testing for all models using the false discovery rate (FDR) method at the threshold of 0.20 (Benjamini and Hochberg, 1995). We additionally conducted sensitivity analysis using linear mixed model ("lme4" in R).

Since there are sex and racial/ethnic differences in sleep (Billings et al., 2021; Meers et al., 2019), we perform stratified analysis by sex or ethnicity for each PFAS and three main sleep outcomes (duration, disturbance, and impairment).

Since neighborhood socioeconomic status (SES) may influence number of PFAS exposure sources and neighborhood SES may also influence sleep health, we conducted sensitivity analysis by including area deprivation index (ADI) at census block group level in the model. ADI was downloaded from Neighborhood Atlas and the index ranks neighborhoods by socioeconomic disadvantage (Kind and Buckingham, 2018; University of Wisconsin School of Medicine and Public Health, 2015).

Since season/temperature may influence sleep pattern, we additionally conducted a sensitivity analysis by controlling for season (Months in May to October vs Months in November to April).

Step 2: Computational toxicology analysis

CTD is a publicly available database that aims to understand the mechanisms of health effects of environmental exposures. As of September 2023, the database contains 50 million toxicogenomic relationships including 2.8 million chemical-gene interactions, 32.2 million gene-disease associations, 0.4 million phenotype-based

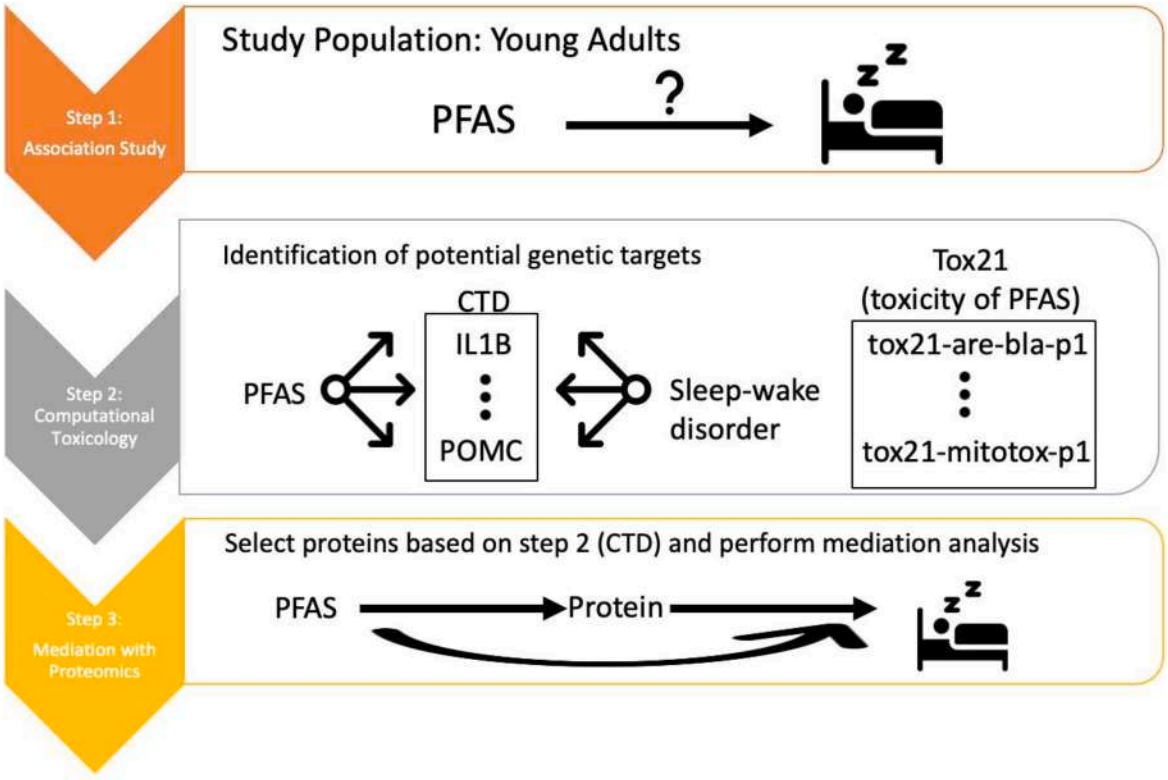

Fig. 1. Analytic workflow.

interactions, 3.4 million chemical-disease associations, along with relationships among chemical, disease, gene ontology (GO), pathway (Davis et al., 2023). In addition, the relationships in CTD are either direct (e.g., evidence directly links chemical and gene) or inferred (e.g., chemical and gene are linked via an intermediate event). For any inferred association, CTD also provides an inference score (0 to infinite), and the higher the score is, the more atypical the connection is (King et al., 2012).

Tox21 Consortium generates publicly available quantitative high throughput screening (qHTS) 10K library data on the toxicity of over 760,000 chemicals using roughly 70 high-throughput assays that cover about 125 biological processes in the body (Huang, 2016; Huang et al., 2018, 2016; Hur et al., 2018). Toxicity profiling is based on a wide range of assays including cardiotoxicity, counter screen, cytotoxicity, developmental toxicity, gene toxicity, G protein-coupled receptors (GPCR), metabolism, neurotoxicity, nuclear receptor (NR), and stress response (SR) panels. Details on assay target, cell line, cell type, and target category for each protocol used in the toxicity profiling are included in Supplemental Table 2. Tox21 used various cell types primarily in liver and kidney and cervical and breast cancer cells.

Based on the previously described association study, we selected PFAS associated with any of the sleep outcomes (with FDR-adjusted p value <0.20) to conduct the following analysis. We performed computational toxicology analysis using data available from CTD and Tox21 database.

We selected sleep-wake disorder (MeSH: d012893) as the disease of interest in the computational toxicology analysis. The sleep-wake disorder is defined as an abnormal sleep-wake schedule or pattern associated with the circadian rhythm and the disorder is closely related to duration, timing, and quality of sleep. In addition, the disease term from CTD is presented as a polyhierarchical tree, and sleep-wake disorder is the ancestor of many sleep-related disorders on the disease hierarchy. We did not include specific disease such as insomnia or obstructive sleep apnea since the study was exploratory and aimed at capturing more comprehensive list of genes that were associated with sleep. In addition, our age group is relatively healthy and therefore, did not have choose a specific disease to test in this step.

To identify the potential mechanism between selected PFAS and sleep-wake disorder, we first queried CTD to generate chemical-gene or chemical-gene-associated-protein relationships for each of the PFAS. This step identified a list of genetic targets of each PFAS. We then queried CTD to generate a list of genes associated with sleep-wake disorder. These genes are either marker/mechanism genes for sleep-wake disorders or non-marker genes, which are suggestively associated with sleep-wake disorders. Lastly, we filtered out genes that are shared by both PFAS and sleep-wake disorder. The final list of genes will then be used for mediation analysis using proteomics data in the next step.

In CTD, we additionally queried the database to generate GO terms that are statistically enriched (Benjamini-Hochberg adjusted p value<0.05) among genes/proteins associated with each of the PFAS. We further assessed whether these GO terms contain “sleep” or “circadian”.

Using the Tox21 Activity Profiler available from the Tox21 Toolbox, we extracted toxicity data for each of the selected PFAS tested with 68 available assays by uploading the CAS registry number of these PFAS. We used the point-of-departure method to describe the toxicity of the PFAS (value range of log10(M)*(-1)) (Wang, 2018). A value of 1e-4 means there is inconclusive evidence for toxicity. A value of 0 means a chemical is inactive in the assay tested. The higher the value is, the more potent/toxic a chemical is.

Step 3: Proteomics and mediation analysis

To test the genetic targets identified in the previous computational toxicology analysis (Step 2), we used proteomics data to perform mediation analysis in the associations between PFAS and sleep outcomes identified in Step 1 (association study).

We used the Proximity Extension Assay (PEA) technology coupled with next-generation sequencing (NGS) readout on Illumina instruments through Olink® to measure proteins in plasma. Briefly, PEA technology by Olink uses pairs of antibodies linked to unique DNA oligonucleotides to detect target proteins. When antibodies bind to a protein, their oligonucleotides are brought into proximity, allowing DNA polymerase to extend one oligonucleotide using the other as a template. The resulting DNA is amplified and sequenced using NGS on Illumina instruments, enabling highly sensitive and specific quantification of multiple proteins simultaneously (Haslam et al., 2022; Petrera et al., 2021). At baseline, we used Olink® Explore 384 Cardiometabolic I ($n = 384$) to measure the concentration of proteins in plasma among all participants. At follow-up, we used both Olink® Explore 384 Cardiometabolic I and Inflammation Panel I ($n = 768$) for all participants. Protein columns with over 50 % of the observations below limit of detection (LOD) were moved (n column removed = 38 at baseline and 63 at follow-up). Data values below the LOD were reported for all samples by Olink. Raw protein concentration was then log2 transformed.

We selected proteins coded from genes identified in CTD (Step 2). We conducted multiple independent mediation analyses (“mediation” package in R) to assess the mediating role of each of these proteins in the association between individual PFAS and sleep (Tingley et al., 2014). The mediation analysis was done separately for baseline and follow-up participants. We estimated average direct effect (ADE), average causal mediation effect (ACME), and total effect. We included mediation results which showed consistent direction of estimates for ADE, ACME, and total effect. We controlled for the same covariates in the mediation analysis as in the cross-sectional analysis and the same covariates were controlled for in both the mediator model and outcome models. We did not adjust for multiple comparisons given that individual hypotheses were generated for each selected gene/protein based on computational toxicology analysis.

Results

Study population description

Table 1a shows the characteristics of the study participants at baseline and follow-up. The mean age of the study participants at baseline was 19 years old and the mean age at follow-up was 24 years old. Study participants were mostly Hispanic (58 %), had parents’ education above high school (67 %), drank alcohol (70 %), and smoked (63 %), and had a similar proportion of males and females. There was not much difference in the characteristics of the study population between baseline and follow-up except that slightly more participants ever drank alcohol ($p<0.01$) and HEI was slightly lower at follow-up than baseline ($p=0.008$). The average follow-up time was 4.02 years (SD: 1.07 years). Table 1b shows the baseline and follow-up characters only among those who were re-examined and Table 1c shows the comparison of baseline characteristics between those who were re-examined and those who were lost to follow-up.

Participants slept on average 8.04 (SD: 1.49) hours at baseline and 6.86 (SD: 1.16) hours at follow-up. The average sleep disturbance score at follow-up was 48.02 (SD: 7.44) and the average sleep impairment score was 50.36 (SD: 9.07). The sleep duration at baseline was somewhat correlated with sleep duration at follow-up (Intraclass correlation coefficients with average fixed raters: 0.38, $p=0.019$). Sleep duration at follow-up was negatively correlated with sleep disturbance score and sleep-related impairment score (Pearson $r=-0.26$, $p=0.02$; $r=-0.28$, $p=0.02$, respectively).

Plasma level concentrations of each PFAS chemical as well as the cutoff values for each tertile are presented in Supplemental Table 3. We observed higher concentrations of PFOS, PFOA, and PFHxS among participants at baseline, and PFAS levels were reduced overall at follow-up except for PFDA (See Supplemental Table 4). Supplemental Table 5 also shows plasma levels of PFAS by ethnicity and sex. Most of the

Table 1a
Characteristics of study population at baseline and follow-up.

Characteristic		Baseline (N = 136)	Follow-up (N = 84)[1]	p value[2]
Race/ethnicity	n (%)			0.78
White		49 (36 %)	30 (36 %)	
Hispanic		79 (58 %)	47 (56 %)	
Other		8 (5.9 %)	7 (8.3 %)	
Male Sex	n (%)	75 (55 %)	41 (49 %)	0.44
Age (years)	Mean (SD)	19.44 (1.30)	23.96 (0.81)	< 0.01
Parental education above high school	n (%)	91 (67 %)	57 (67 %)	1.00
Healthy Eating Index	Mean (SD)	53.38 (13.26)	49.37 (12.58)	0.03
Missing		13	1	
Never Smoking	n (%)	50 (37 %)	31 (37 %)	1.00
Never Drinking	n (%)	41 (30 %)	10 (12 %)	<0.01
Self-perceived physical activity	Mean (SD)	6.30 (1.99)	NA	NA
Missing		9		
Physical Activity based on metabolic equivalents per hour	n (%)			NA
Low (≥1.5 to 2.99)		NA	16 (19 %)	
Medium (3 to 5.99)		NA	21 (25 %)	
High (≥6)		NA	47 (56 %)	
Duration of nightly sleep (hours)	Mean (SD)	8.04 (1.49)	6.86 (1.16)	< 0.01
Not Enough Sleep (<7 h)	n (%)	26 (19 %)	29 (35%)	< 0.01
Sleep Disturbance[3]	Mean (SD)	NA	48.02 (7.44)	NA
Sleep Impairment[3]	Mean (SD)	NA	50.36 (9.07)	NA

[1] 76 were followed again at this visit and 8 had their first visit at this visit.
[2] Wilcoxon rank sum test was performed for continuous variables and Pearson's Chi-squared test was performed for categorical variable.
[3] Sleep disturbance measures problems with falling and staying asleep and sleep-related impairment measures daytime sleepiness, difficulties waking up, and their impact on mood and behavior.

Table 1b
Sub-cohort with both baseline and follow-up data (n=76).

Characteristic		Baseline	Follow-up	p value[1]
Age (years)	Mean (SD)	19.45 (1.20)	23.95 (0.80)	<0.001
Healthy Eating Index	Mean (SD)	54.66 (13.15)	49.97 (12.80)	0.008
Never Smoking	n (%)	51 (67 %)	46 (61 %)	0.4
Never Drinking	n (%)	25 (33 %)	7 (9.2 %)	<0.001
Duration of nightly sleep (hours)	Mean (SD)	7.97 (1.55)	6.94 (1.14)	<0.001
Not Enough Sleep (<7 h)	n (%)	16 (21 %)	23 (30 %)	0.2

[1] Wilcoxon rank sum test was performed for continuous variables and Pearson's Chi-squared test was performed for categorical variable.

chemical levels were the same across ethnic groups and sex. PFOS and PFOA baseline were higher in White than in Hispanic participants (mean [SD] for PFOS: 3.81 [1.66] vs 3.57 [1.76] ng/mL and for PFOA: 1.56 [0.50] vs 1.35 [0.46] ng/mL) and the similar difference was observed for PFAS measured at follow-up.

Step 1: Association study

Fig. 2 shows that one tertile increase in PFDA at baseline was associated with an average of 0.39 h of less nightly sleep at baseline (95 % CI: -0.73, -0.05 h per one tertile increase, FDR-p value: 0.20), and a similar relationship was observed for PFHxS and PFOA at follow-up and shorter sleep duration at follow-up (PFHxS: -0.39 [-0.72, -0.05] hours per one tertile increase, FDR-p value: 0.11; PFOA: -0.32 [-0.63, -0.01] hours,

Table 1c
Baseline characteristics of study population that were and were not lost to follow-up.

Characteristic		Baseline (N = 76)	Follow-up (N = 60)	p value[1]
Race/ethnicity	n (%)			0.5
White		28 (37%)	21 (35%)	
Hispanic		42 (55%)	37 (62%)	
Other		6 (7.9%)	2 (3.3%)	
Male Sex	n (%)	36 (47%)	39 (65%)	0.04
Age (years)	Mean (SD)	19.45 (1.20)	19.43 (1.42)	0.8
Parental education above high school	n (%)	53 (70%)	38 (63%)	0.4
Healthy Eating Index	Mean (SD)	54.69 (13.24)	51.34 (13.18)	0.2
Missing		1	12	
Never Smoking	n (%)	51 (67%)	35 (58%)	0.3
Never Drinking	n (%)	25 (33%)	16 (27%)	0.4
Self-perceived physical activity	Mean (SD)	6.36 (2.08)	6.22 (1.86)	0.4
Missing		4	5	
Duration of nightly sleep (hours)	Mean (SD)	7.97 (1.55)	8.14 (1.42)	0.5
Not Enough Sleep (<7 h)	n (%)	16 (21%)	10 (17%)	0.5

[1] Wilcoxon rank sum test was performed for continuous variables and Pearson's Chi-squared test was performed for categorical variable.

FDR-p value: 0.11). PFAS mixture was suggestively associated with 0.59 and 0.40 h of reduced sleep at baseline and follow-up (-0.59 [-1.24, 0.06] and -0.4 [-0.81, 0], respectively). As shown in Fig. 3, only PFOS was suggestively associated with insufficient sleep (<7 h) at follow-up (OR [95 % CI]: 2.25 [1.04, 4.89] hours, FDR-p value: 0.28). Fig. 4 shows that, at follow-up, PFOS was associated with a higher level of sleep disturbance and sleep-related impairment (beta [95 % CI]: 2.99 [0.67, 5.31], FDR-p value: 0.10; 3.35 [0.51, 6.2], FDR-p value: 0.10, respectively). PFDA was associated with a higher level of sleep disturbance (beta [95 % CI]: 2.05 [-0.01, 4.12], FDR-p value: 0.19). Full summary statistics are shown in Supplemental Tables 6 to 8.

Based on the longitudinal analysis using GEE model shown in Supplemental Table 9, only PFOA at baseline was suggestively associated with reduced sleep duration over time but the negative effects of PFOA at baseline on sleep were reduced over time (main effect: beta [95 %CI]: -0.35 [-0.74, 0.03]; interaction term with time: 0.11 [0.02, 0.20]). The results were very similar when using linear mixed model (See Supplemental Table 10).

There were no differences in the associations between PFAS and sleep outcomes by race/ethnicity or sex (See Supplemental Tables 11 and 12).

When we additionally adjusted area deprivation index, the effect estimates were fairly similar to our main analysis although only PFDA was significantly negatively associated with sleep duration at baseline (See Supplemental Tables 13 and 14).

When we additionally adjusted season, the effect estimates were similar to our main analysis (See Supplemental Tables 15 and 16).

Step 2: Computational toxicology analysis

In our computational toxicology analysis, we selected four PFAS: PFDA, PFOA, PFOS, and PFHxS based on their associations with any sleep outcome in the association study. Through screening in CTD, we identified 161 genes associated with both sleep-wake disorder and PFDA, 583 for PFHxS, 3981 for PFOA, and 7231 for PFOS (See Fig. 5). Among these marker and non-marker genes, PFOS, PFOA, and PFDA were inferred to have associations with sleep-wake disorders through marker genes of sleep-wake disorder including IL1B, POMC, BHLHE41, and CHRNB2. These PFAS predominantly increase the expression of the IL1B gene, and the secretion of proteins produced from the IL1B gene

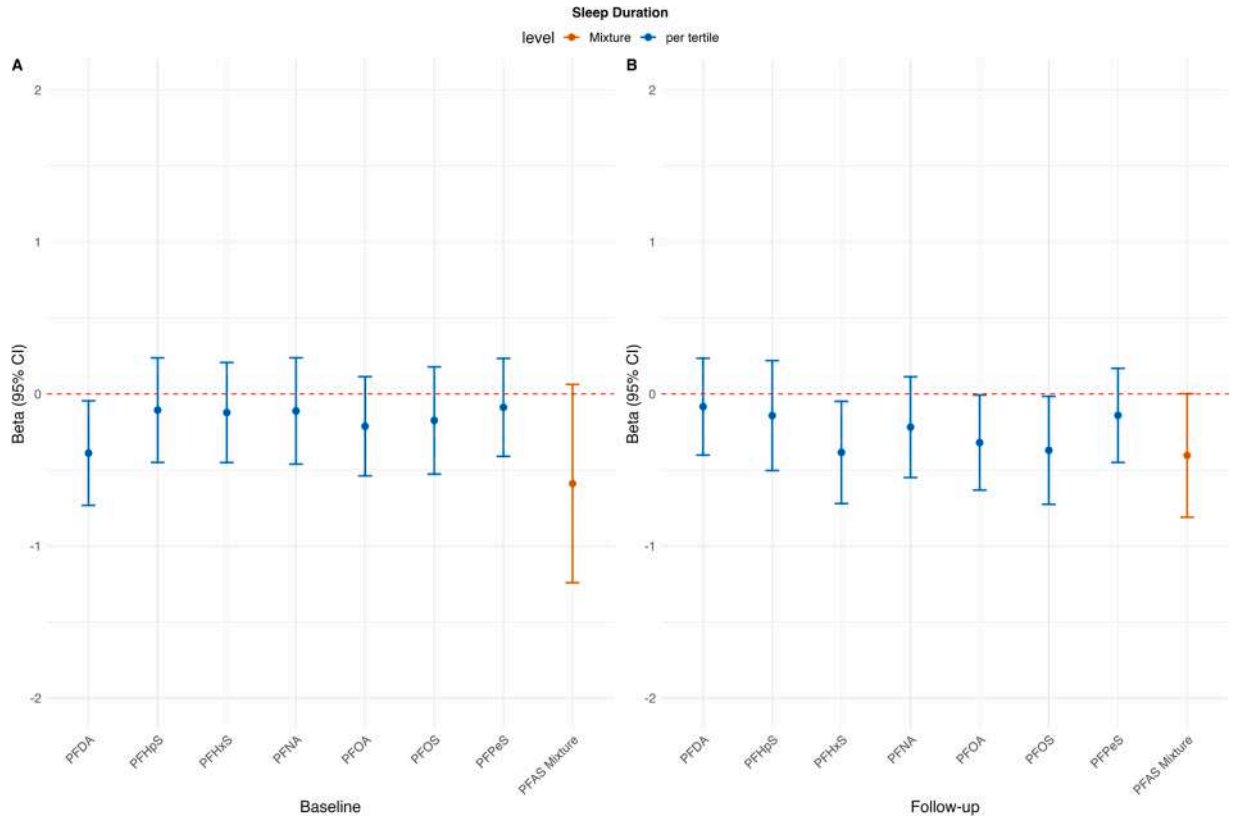

Fig. 2. Point estimates and 95 % confidence interval of the mean difference in nightly sleep duration (hours) per tertile increase in PFAS measured baseline (A) or follow-up (B).

*We controlled baseline covariates (race/ethnicity, sex, parental education, age, physical activity, cigarette smoking, alcohol drinking, HEI) when assessing outcomes measured at baseline, and time-fixed covariates (race/ethnicity, sex, parental education) and covariates (age, physical activity, cigarette smoking, alcohol drinking, HEI) measured at follow-up for outcomes measured at follow-up. We additionally controlled the time to follow-up visits when assessing sleep outcomes measured at follow-up.

while decreasing the expression of POMC, BHLHE41, and CHRNB2 genes (See Supplemental Table 17).

There were 4135 enriched GO terms associated with PFOS, 3406 with PFOA, 1016 with PFDA, and 909 with PFHxS in CTD. Among those terms, PFOS and PFOA are associated with four sleep-related GO terms including circadian behavior, circadian regulation of gene expression, circadian rhythm, and regulation of circadian rhythm while PFDA and PFHxS were only associated with circadian rhythm (See Supplemental Table 18).

In Tox21, PFDA, PFOA, and PFOS were screened for their toxicity using 68 different assays and PFHxS was not screened by Tox21. Fig. 6 depicts the toxicity level for the four included PFAS. All included PFAS increased activity of the human Nrf2 transcriptional factor, which is a biomarker for oxidative stress. These PFAS also all decreased the activity of the human estrogen receptor alpha transcriptional factor, a biomarker for sex hormone homeostasis. PFOA increased the activity of the human peroxisome proliferator-activated receptor (PPAR) delta transcriptional factor, a biomarker for lipid homeostasis, and increased PPAR gamma transcriptional factor activities.

Additionally, PFDA can increase activity in estrogen-related receptors (sex hormone). PFOS showed both mitochondrial toxicity by increasing mitochondrial membrane permeability and developmental toxicity by decreasing the activity of Transforming Growth Factor-β (TGF-β). A full description of the toxicity level of each PFAS and their associated assays are included in Supplemental Table 19.

Step 3: Proteomics and mediation analysis

Four PFAS (PFDA and sleep duration at baseline, PFOA and sleep duration at follow-up, PFOS and sleep disturbance and sleep-related impairment at follow-up, and PFHxS and sleep duration at follow-up) were further included in the mediation analysis using proteomics data. From the potential target genes (Step 2), we explored mediation pathways using 11 proteins for PFDA, 42 for PFHxS, 246 for PFOA, and 327 for PFOS, based on the availability of proteomics data.

Our analysis revealed that corticosteroid 11-beta-dehydrogenase isozyme 1 (HSD11B1) mediated 37 % of the total effect of PFOA on sleep duration at follow-up. The total effect of PFOA on sleep duration was estimated as beta [95 % CI]: -0.33 [-0.68, 0.07], with an ACME of beta [95 % CI]: -0.14 [-0.27, -0.03] for HSD11B1 (See Supplemental Table 20).

Shown in Supplemental Tables 21 and 22, we observed that cathepsin B (CTSB) mediated the association between PFOS and sleep disturbance (ACME: 1.36 [0.04, 4.42]) and the following proteins mediated the association between PFOS and sleep-related impairment: interleukin-6 receptor subunit beta (IL6ST) (ACME: 1.95 [0.34, 4.23]), dickkopf-related protein 3 (DKK3) (ACME: 1.65 [0.04, 3.96]), ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5) (ACME: 1.37 [0.05, 3.08]), scavenger receptor cysteine-rich domain-containing group B protein (SSC4D) (ACME: 1.76 [0.19, 4.91]), and tyrosine-protein kinase receptor (TYRO3) (ACME: 1.83 [0.06, 4.84]).

None of the identified proteins mediated the associations between PFDA and PFHxS and sleep durations. Full summary statistics are included in Supplemental Tables 23 and 24.

Discussion

On April 10, 2024, EPA announced the Maximum Contaminant

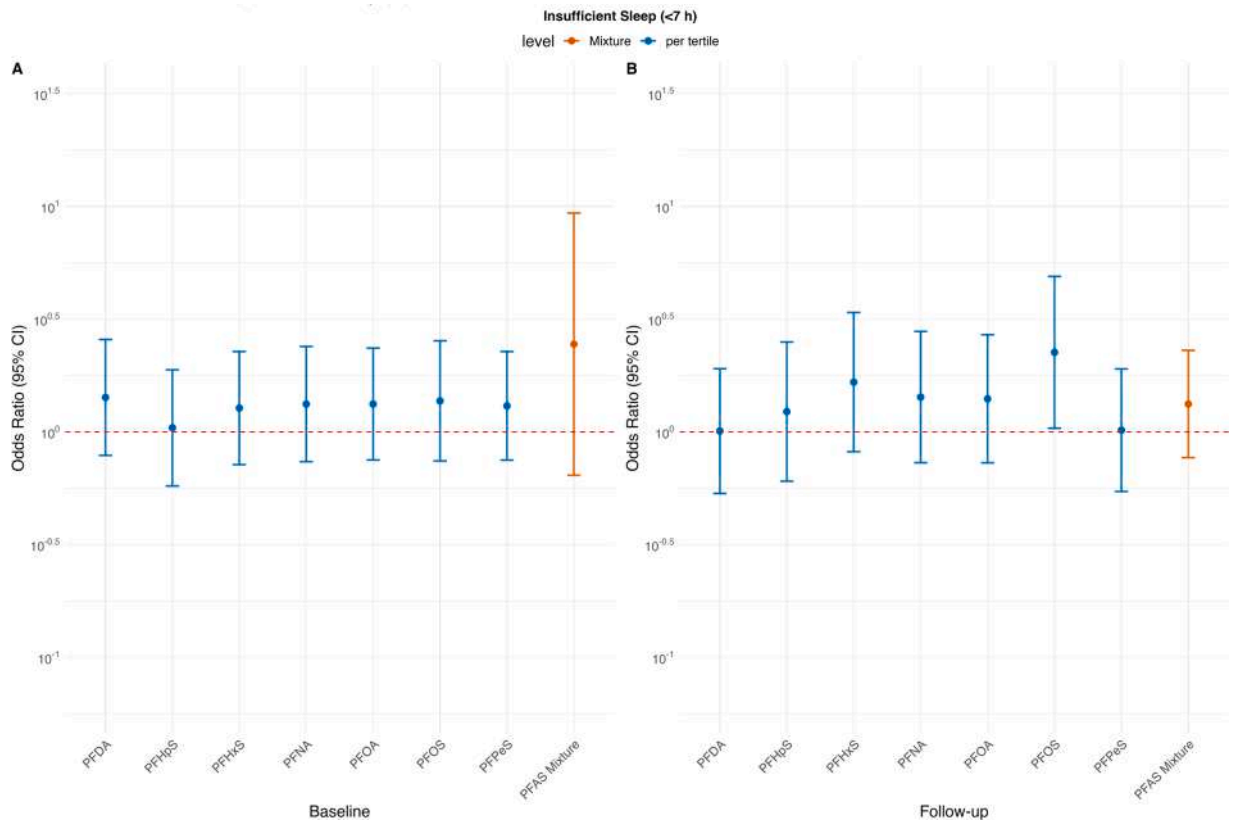

Fig. 3. Point estimates and 95 % confidence intervals of the odds ratio of insufficient sleep (less than 7 h) per tertile increase in PFAS measured baseline (A) or follow-up (B).

*We controlled baseline covariates (race/ethnicity, sex, parental education, age, physical activity, cigarette smoking, alcohol drinking, HEI) when assessing outcomes measured at baseline, and time-fixed covariates (race/ethnicity, sex, parental education) and covariates (age, physical activity, cigarette smoking, alcohol drinking, HEI) measured at follow-up for outcomes measured at follow-up. We additionally controlled the time to follow-up visits when assessing sleep outcomes measured at follow-up.

Levels (MCLs) for PFAS including PFOA, PFOS, PFHxS, PFNA, and HFPO-DA with individual MCLs, and PFAS mixtures and the National Academies of Sciences, Engineering, and Medicine recommended clinical guidance for patients with simple additive sum of serum PFAS levels of MeFOSAA, PFHxS, PFOA, PFDA, PFUnDA, PFOS and PFNA (Guidance on PFAS Exposure, Testing, and Clinical Follow-Up, 2022). Therefore, understanding the health impact of these PFAS is urgently needed. While PFAS have been extensively studied and linked to various health outcomes, only a limited number of studies have explored their impact on sleep health (Bell et al., 2021; Wallace et al., 2023). Sleep health plays a crucial role in maintaining overall human health, spanning across multiple bodily systems, and is especially important for neurological and metabolic function (Dutil et al., 2018; Iranzo and Santamaria, 2015; Palagini et al., 2022). Our current study employs a comprehensive approach by integrating data from a prospective cohort study involving young adults, information from two toxicology databases, CTD and Tox21, and proteomics data collected from the study participants. Our study revealed that PFDA, PFOA, and PFHxS were associated with shorter sleep duration while PFOS was associated with higher scores of sleep disturbance and sleep-related impairment. The following computational toxicology analysis suggests genes that are associated with these PFAS, and sleep-wake disorders, and these genes are used to select proteins for additional mediation analysis. Our mediation analysis showed several metabolic and immune function-related proteins mediated the association between these PFAS and sleep outcomes. Our approach can improve the inferential power of either association study or computational toxicology analysis, and better inform the targeted mediation analysis of molecular pathways for testing hypotheses that are driven by existing literature.

Our results are consistent with previous studies conducted in infants, children, adolescents, and pregnant women and we included a summary table of previous studies in Supplemental Table 25. For instance, a study involving 4,127 pregnant women in China found that individual PFAS was associated with an increased risk of sleep disturbance, lower sleep efficiency, and shorter sleep duration across three trimesters. Moreover, PFAS mixtures were linked to poor sleep quality and the use of sleep medicine (Huang et al., 2022). Our analysis of the PFAS mixture showed a suggestive reduction of sleep duration and an increase in the level of sleep disturbance and sleep-related impairment. However, we may lack the statistical power to detect the mixture effect that was statistically significant. In addition, other studies involving infants and 4-year-old girls indicated that prenatal exposure to PFAS was associated with an elevated risk of sleep disturbance (Huang et al., 2023; Xie et al., 2022). One previous study in Belgium also showed PFAS were associated with day-time sleepiness among adolescents (van Larebeke et al., 2022).

Conversely, a recent study using data from NHANES spanning from 2005 to 2014 did not identify any association between PFAS and sleep health. It even revealed an inverse association between PFAS mixtures and sleep disorders (Guo et al., 2023). These findings contradicted those of another study conducted by Shiue et al. using NHANES data, which identified specific PFAS such as 2-(N-Methyl perfluorooctane sulfonamido) acetate (MeFOSA) and perfluorobutanesulfonic acid (PFBS) as being associated with worse sleep outcomes (Shiue, 2017). Given that the NHANES study population represents the general U.S. population, with a median age of approximately 45 years, it is plausible that the effects of PFAS on sleep outcomes may not be as evident as in historically marginalized populations. Our study, conducted in young adults aligns with the findings in pregnant women, infants, and children (Choi et al.,

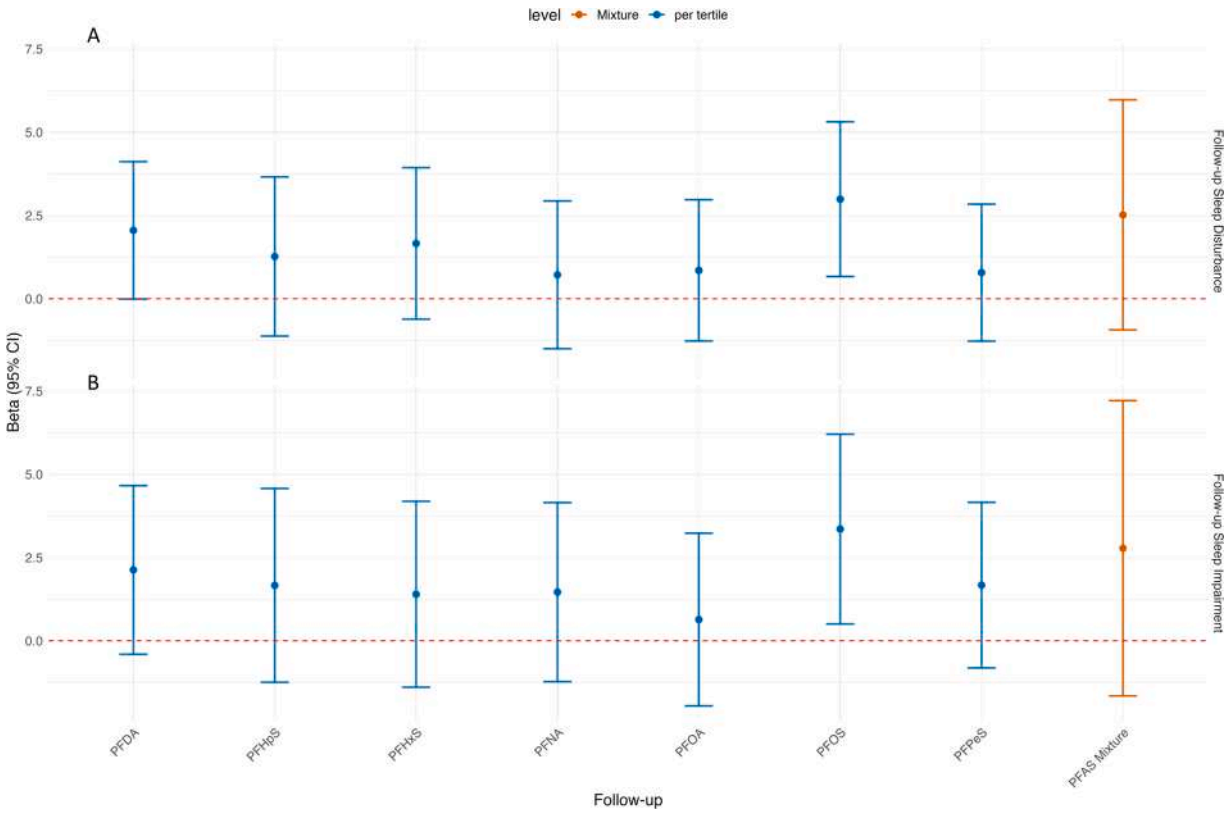

Fig. 4. Point estimates and 95% confidence intervals of mean difference in sleep disturbance (A) and sleep-related impairment scores (B) per tertile increase in PFAS at follow-up.
*We controlled time-fixed covariates (race/ethnicity, sex, parental education) and covariates (age, physical activity, cigarette smoking, alcohol drinking, HEI) measured at follow-up for outcomes measured at follow-up.

2024; Huang et al., 2023, 2022; Xie et al., 2022).

The age group our study focused on, young adults (age 19 to 24), offers a unique time window for interventions including the removal of PFAS exposures to prevent the long-term health impacts of disrupted sleep due to PFAS exposure. Our study also fills the gap of literature in PFAS and sleep research by studying young adults. Unlike young children or teens, young adults' sleep habit is less structured and less dependent on the parents, which allows for variability in sleep behavior for studying impact of PFAS on sleep in this age group. Future studies should aim to validate potential effect modification by age group to understand the mixed results for PFAS and sleep health and refine more precise windows of susceptibility.

Mostly long-chain PFAS including PFOA, PFOS, and PFDA was associated with shorter sleep duration or worse sleep quality except for PFHxS, and evidence was less clear based on chemical group (carboxylic or sulfonic acid). It is important to note that only a few short-chain PFAS were quantified in our study and concentrations of these short-chain PFAS were less than long-chain PFAS. Previous studies suggested mixed results for the toxicity of these short-chain PFAS in comparison to long-chain PFAS. For example, among sulfonic acid, developmental neurotoxicity was higher as chain length increased but not for developmental toxicity based on Zebrafish model (Gaballah et al., 2020). Therefore, PFAS chain-length could matter more for neurotoxicity leading to greater sleep disruption. It is also likely that these short-chain PFAS had less time to accumulate in the blood and therefore, the associated health effect may not be evident. Short-chain and ultrashort chain PFAS are now dominant in the indoor home environment (Zheng et al., 2023). In addition, PFOS has a longer half-life compared with other PFAS (Li et al., 2018), which could lead to prolonged health effects and PFOS. PFOS may also have a greater ability to penetrate BBB and dysregulate the brain system more than other PFAS (Hu et al., 2023; Wang et al., 2010; Xie et al., 2024). Therefore, PFOS may be more important for sleep health.

It is interesting to note that the effect of PFAS, specifically PFOA, is reduced over time and our results indicated that short-term exposure may be more important for sleep health. As described in our longitudinal analysis, the effect of PFOA measured at baseline on sleep duration reduced over time while PFOA measured at follow-up was associated with shorter sleep duration. The half-life of PFOA is about 3.5 years (Li et al., 2018) and our follow-up time is on average 4 years. Therefore, the effect of PFOA may not be evident at the time of follow-up but more recent exposure to PFOA still has an impact on sleep duration. Therefore, policies to address PFAS exposure should be considered with more timely urgency to better address health consequences that occur more proximally to exposure assessment timing.

The analyses conducted in the CTD have provided suggestive evidence linking PFOS, PFDA, and PFOA to sleep-wake disorders through the involvement of specific genes, primarily through the IL1B gene. The IL1B gene plays a crucial role in producing the IL-1B protein, which is a key player in the inflammatory response. Mutations in cytokine genes, including IL1B, have been associated with short sleep duration and sleep disturbance in previous studies (Alfaro et al., 2014; Illi et al., 2012). Furthermore, the interconnection between sleep and the immune system has long been recognized, making the inflammatory response a highly plausible pathway between PFAS and sleep (Besedovsky et al., 2019; Irwin, 2019).

Although we did not directly observe the mediating role of IL1B, we found several immune system-related proteins mediating the association between PFOS and sleep-related impairment including IL6ST, SSC4D, and TYRO3 (Cardoso et al., 2021; Lu and Lemke, 2001, p. 3; Unver and McAllister, 2018). One Mendelian randomization study suggested that IL6 signaling is the causal link between chronic inflammation and sleep

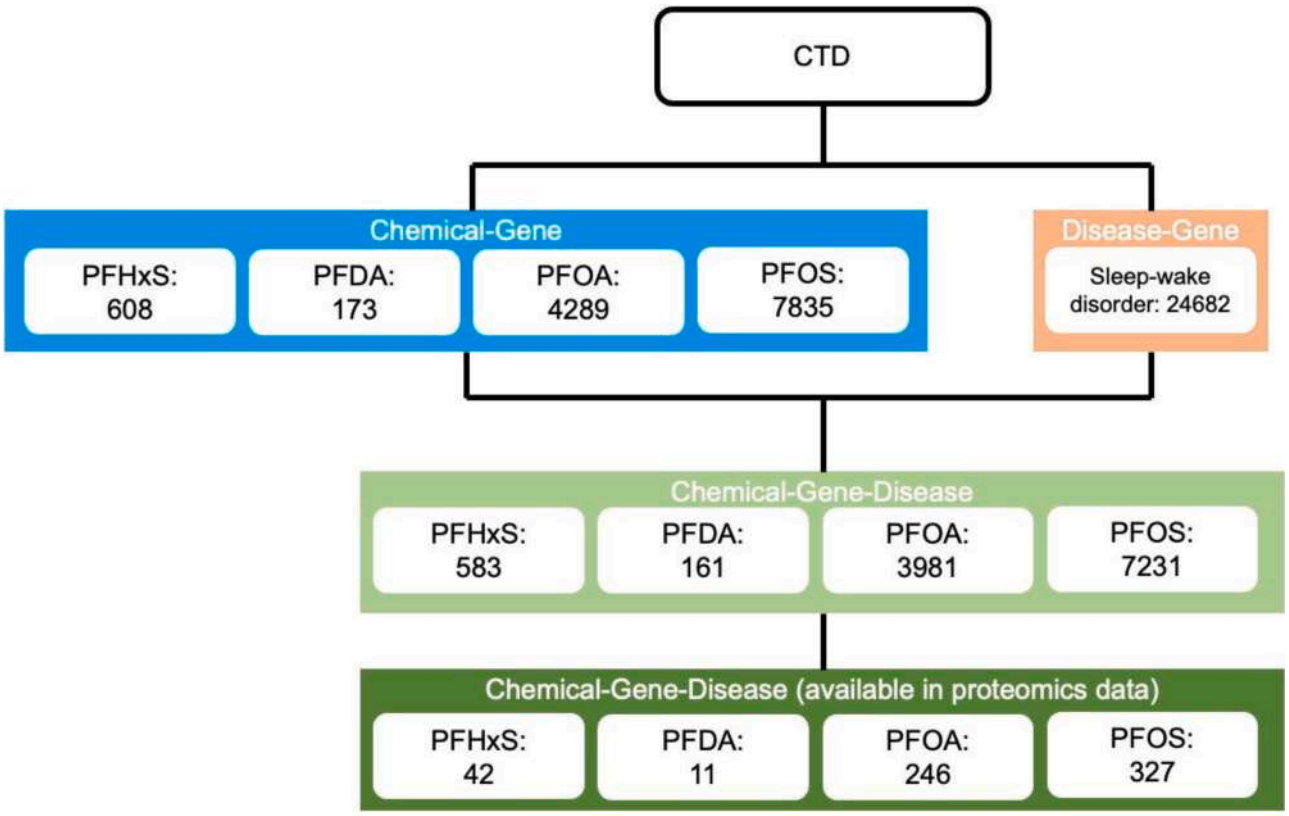

Fig. 5. Screening of potential genetic target shared by PFAS identified in the epidemiological study and sleep-wake disorder in the comparative toxicogenomics database (CTD).

duration (Iakunchykova et al., 2024). Proteins coded from SSC4D acts as a pattern recognition receptor for pathogens and involve in the development of the immune system and regulation of both innate and adaptive immune responses (Cardoso et al., 2021). TYRO3 is a member of the TAM family of transmembrane receptor tyrosine kinases and is responsible for many biological processes including immune regulation (Smart et al., 2018). TYRO3 is predominantly expressed in nervous system which makes the link between TYRO3 and sleep more likely although no previous study has assessed the link between TYRO3 and sleep directly. However, one recent study showed that TYRP3 can promote the functional maturation of glutamatergic synapses, which are the main excitatory synapses in the brain and is linked to sleep (Vogt et al., 2024). Therefore, our mediation analysis provided further support for the immune system-mediated pathway between PFAS and sleep health.

Both CTD and Tox21 suggest that PFAS may be linked to poor sleep health through their influence on metabolic function. Specifically, our analysis identifies the involvement of PPAR pathways, particularly PPAR γ signaling pathways, as potential mechanisms of PFAS toxicity. PPAR γ, for instance, is mostly expressed in adipose tissue and plays a role in lipid metabolism, insulin sensitization, and glucose metabolism (Ahmadian et al., 2013). Notably, PFOA exhibited toxicity in PPAR γ pathways indirectly through PPAR delta pathways based on Tox21 screening. Insulin resistance is a major disease phenotype in type 2 diabetes mellitus (T2DM) (Olefsky and Saltiel, 2000), and emerging evidence suggests that sleep disorders are highly prevalent among individuals with T2DM (Khalil et al., 2020). Our mediation analysis provided support for this hypothesis by showing that HSD11B1 mediates the association between PFOA and sleep duration. HSD11B1 can control local glucocorticoid levels by catalyzing the intracellular reduction of inactive cortisone to active cortisol, a ligand activating glucocorticoid receptor, and is thus important for glucose metabolism, T2DM, and obesity (Chapman et al., 2013; do Nascimento et al., 2015). The exact roles of PPAR γ and HSD11B1 in the association between PFAS and sleep deserve further mechanistic studies.

Both CTD and Tox21 did not indicate direct neurotoxicity of PFAS. In CTD, PFDA and PFOA did not show an inferred association with sleep disorders through genes such as CHRNA4 and SLC6A3, which are primarily related to neuronal function or neurotransmitters (Díaz-Otero et al., 2008; Dyck et al., 2005; Greenwood et al., 2012). Similarly, Tox21 indicated that PFAS did not exhibit neurotoxicity through assays targeting acetylcholine esterase (AChE) receptors, which are crucial for various brain functions, including memory, attention, and learning (Li et al., 2022). However, direct toxicity (i.e., acting as an agonist or antagonist for neurotransmitter receptors) may not be necessary for PFAS to impact brain health. In addition, Tox21 also did not test any other neurotransmitter receptors including hypothetical targets such as dopamine and glutamate receptors.

Since PFAS may cross BBB (Cao and Ng, 2021), PFAS can induce oxidative stress, which is supported by CTD pathway enrichment analysis, in the brain or induce neuroinflammation which can damage neurons leading to neurological outcomes like poor sleep health. Our mediation analysis showed that CTSB proteins mediated some of the total effects between PFOS and sleep disturbance. CTSB is a lysosomal protease and experiment evidence suggests that CTSB can increase oxidative stress, neuroinflammation, and neuronal apoptosis and is related to multiple neurological disorders (Ni et al., 2022; Pišlar and Kos, 2014). Inhibition of CTSB expression may be a new candidate for drug discovery to mitigate the impact of PFAS on sleep.

Our study had several strengths. First, our novel framework provided plausible biological mechanisms that would justify the associations between PFAS and sleep. Our study was the first study include omics biomarkers and computational toxicology approaches to understand the mechanisms of PFAS-associated sleep problems. In addition, our mediation was informed by computational toxicology analysis which limited the possibility of chance findings/false positive results. Our PFAS data were measured in two time point as well as sleep durations which

Fig. 6. Toxicity of selected PFAS by cell type labeled with assay target.
*Each point represents individual assay and is labeled with its assay target **Activity level is measured using the point-of-departure method to describe the toxicity of the PFAS (value range of log10(M)*(-1))

allowed for two cross-sectional analyses and longitudinal analysis of PFAS on sleep. Our study had well characterized covariates that minimized the risk of confounding as well as residual confounding due to misclassified confounders. Selection bias was less like since participant characteristics were fairly similar between those who were lost and those who remained in the cohort. Lastly, our study filled the gap on PFAS and sleep research by focusing on young adults while previous studies focused on infants, children, pregnant women and mid-life adults as shown in Supplemental Table 25.

Our study had some limitations. First, in our association study, our study's sample size is limited and therefore, we might not capture the association between some PFAS and sleep outcomes. Our results should be interpreted with caution and further studies with larger sample sizes are needed to confirm our findings. However, Figs. 2 to 4 suggest that the overall effect estimates are largely consistent across all PFAS and all sleep outcomes, which increased the validity of our statistically significant findings. Second, since our study population was young adults with a history of overweight or obesity, there might be a limit on the generalizability of our results. However, it is important to understand the effect of chemical pollutants in susceptible populations as the effect may be more evident in subpopulations due to effect measure modification. Third, our sleep outcomes were self-reported and thus are prone to misclassification. It is important to point out that previous studies suggest some comparability between subjective and objective measures of sleep and self-perceived sleep measurements may also reflect the quality of their sleep than subjective measures (Cudney et al., 2022; O'Sullivan et al., 2023). Since study participants did not know their level of chemical exposure nor did the study itself reveal the hypothesis of the association between chemical pollutants and sleep when they reported their sleep outcomes, the potential misclassification is likely to be non-differential and thus bias our results towards the null. In addition, we could have residual confounding due to misclassification of potential confounders (i.e., self-reported physical activity) and uncontrolled confounding by other socioeconomic status variables such as family income. However, we controlled for a similar set of potential confounders as previous studies (Guo et al., 2023; Huang et al., 2022). In addition, cigarette smoking and alcohol drinking were used as binary variables (ever/never) due to small sample size and therefore, misclassification was possible, leading to either under or overestimation of the effect. We also did not control for indoor environment both at dorm/apartment and/or at parent's house including shared bedroom, workload of school, lighting which are highly correlated with sleep behaviors. However, these activities would less likely influence PFAS levels in blood, which would not confound the associations. Lastly, we did not adjust for co-exposure to other environmental pollutants such as noise, PM2.5 which would confound our observed associations. For example, air pollution is an important risk factor for shorter sleep duration and worse sleep quality (Liu et al., 2020). Higher PFAS levels

may be associated with higher air pollution due to common industrial activities. We might overestimate the effect of PFAS on sleep. There is a need to assess the co-occurrence pattern between PFAS and other environmental factors.

There are also limitations in data mining in toxicological databases. As we briefly mentioned, there could be possible publication bias. There are large discrepancies in the number of existing publications across the selected chemicals. For example, PFOA, with references of 466 studies, is the most studied across all selected PFAS compared to PFDA with references of 138 studies. The lack of studies could either indicate a lack of positive findings or a lack of general interest in studying certain chemicals. In addition, only four chemicals are screened for toxicity in Tox21 and the cell lines available in Tox21 are mostly liver, kidney, and cancer cells, which further limits its ability to infer the neurotoxic effect of PFAS, and available assays for testing neurotoxicity are only targeting AChE receptors. It is therefore not recommended to make inferences on the neurotoxicity of PFAS using Tox21 results. However, combining evidence from two toxicological databases as well as epidemiological evidence may help with strengthening the results from either an association or computational toxicology approach.

Our mediation analysis is informed by both the association study and computational toxicology analysis, which greatly strengthened the hypothesis testing and inferential power. However, the mediation analysis also has several limitations. We did not have the same set of proteins measured between baseline and follow-up which limits the analysis conducted among baseline participants and may explain why we did not observe any proteins mediating the association between PFDA and sleep duration at baseline. Lastly, our mediation analysis was conducted cross-sectionally, and we are not able to tell the exact temporal relationship among PFAS, proteins, and sleep outcomes. PFAS may influence sleep first and then lead to disrupted protein levels in the study participants. Future studies need to consider this temporal relationship between sleep and disrupted protein levels.

Sleep is crucial for brain function and thus improving sleep health can help to reduce future risks of mood-related disorders, neurodevelopmental problems, and neurodegeneration. Understanding the association between PFAS and sleep health may lead to new insight into the mechanisms of how PFAS influences neuronal function in the human brain. Our study has identified several individual PFAS for their associations with poor sleep health and several potential molecular mechanisms through computational toxicology analysis confirmed using mediation analysis with proteomics data. Future large-scale epidemiological studies and mechanistic studies are needed to confirm our findings. In addition, sleep health of young children might be more vulnerable to chemical pollutants like PFAS due to higher dose of PFAS per body weight and developing body and defense system (Rappazzo et al., 2017) and therefore, future studies should consider studying the impact of PFAS in different age groups including younger children.

CRediT authorship contribution statement

Shiwen Li: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Jesse A. Goodrich:** Writing – review & editing, Data curation. **Jiawen Carmen Chen:** Writing – review & editing, Data curation. **Elizabeth Costello:** Writing – review & editing, Data curation. **Emily Beglarian:** Writing – review & editing. **Jiawen Liao:** Writing – review & editing, Data curation. **Tanya L. Alderete:** Writing – review & editing, Data curation. **Damaskini Valvi:** Writing – review & editing, Data curation. **Brittney O. Baumert:** Writing – review & editing, Data curation. **Sarah Rock:** Writing – review & editing, Data curation. **Sandrah P. Eckel:** Writing – review & editing, Methodology. **Rob McConnell:** Writing – review & editing. **Frank D. Gilliland:** Writing – review & editing. **Zhanghua Chen:** Writing – review & editing, Data curation. **David V. Conti:** Writing – review & editing, Methodology. **Lida Chatzi:** Writing – review & editing, Supervision, Methodology. **Max Aung:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data are not publicly available due to them containing information that could compromise research participant privacy or consent.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.envadv.2024.100585.

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