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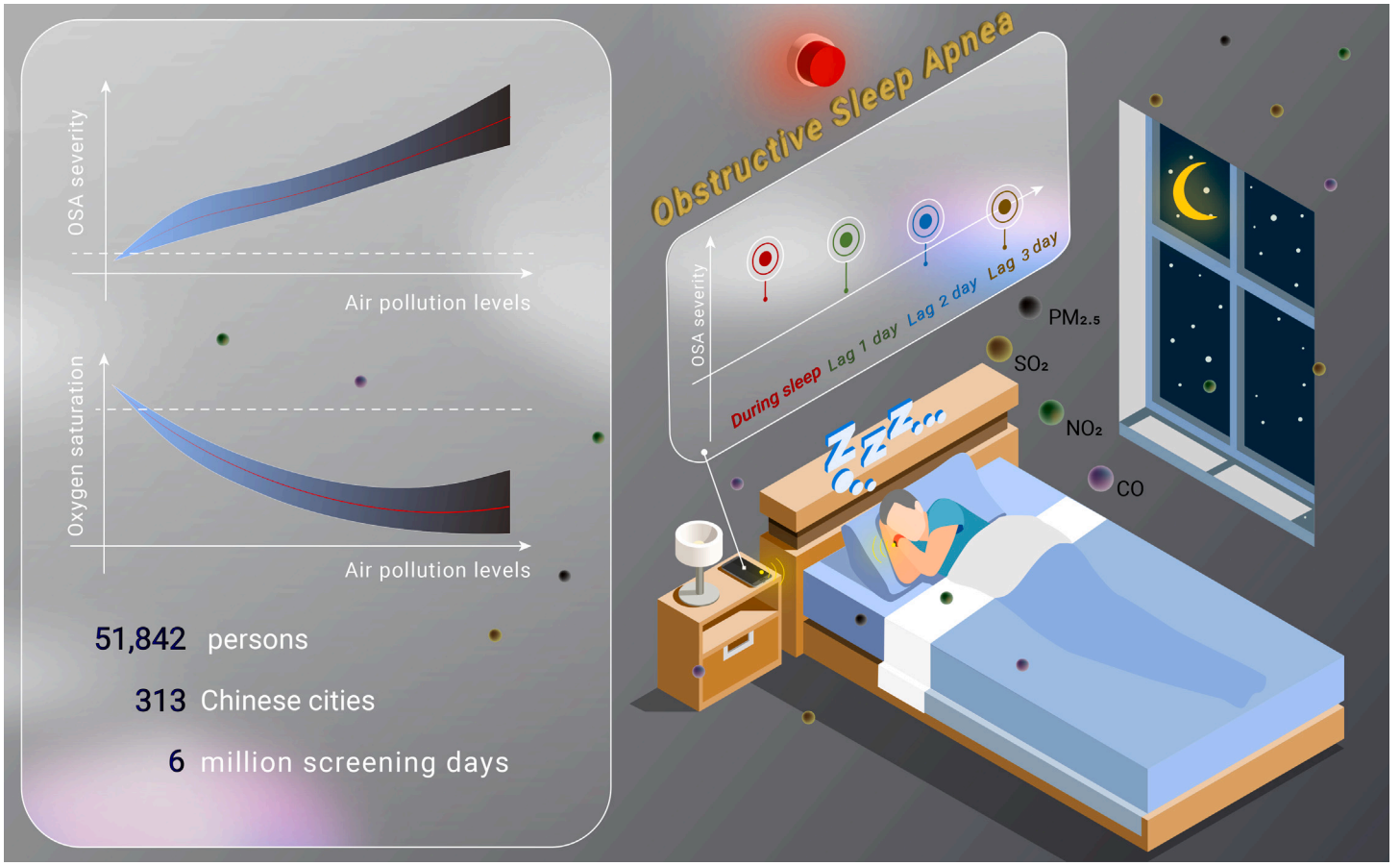
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- We analyzed the smart device-based sleep monitoring data of 6 million person-days in China.
- Short-term air pollution exposure increases obstructive sleep apnea (OSA) severity.
- The effects of air pollutants occur during the sleep period and last for 2 days.
- The exposure-response curves for air pollutants and OSA severity are almost linear.

ARTICLE

Air pollution may increase the sleep apnea severity: A nationwide analysis of smart device-based monitoring

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Obstructive sleep apnea (OSA) can lead to sleep deprivation, accidents, and cardiovascular diseases. However, research on the short-term effects of air pollutants on OSA severity is limited and inconsistent. We conducted a novel case time series analysis using a nationwide dataset among Huawei smart device users to assess the association between air pollution and OSA severity in a population at moderate-to-severe risk of OSA. Fixed-effects regression models were used to assess the associations between air pollution and the risk of OSA exacerbation, apnea-hypopnea index (AHI), and oxygen saturation. A total of 51,842 participants who were at moderate-to-severe risk of OSA (mean age [SD]: 45.4 [11.0], 95.5% male) were included, with 6,232,056 person-days of monitoring. The associations of fine particulate matter, nitrogen dioxide, carbon monoxide, and sulfur dioxide with OSA severity could occur during the sleep period, and last for 2 days. An increase of 1 interquartile range in the moving average concentrations of air pollution during the sleep period and the 2 previous days was associated with a 1.14%–4.31% increase in the risk of OSA exacerbation, an increase in AHI by 0.05–0.17 events/h, and a decrease in oxygen saturation (%) by 0.003–0.014. The exposure-response curves were almost linear. The associations between air pollutants and OSA were consistently stronger in participants aged 45 years or older. By virtue of the smart device-based technology, this large-scale, nationwide, longitudinal study provides compelling evidence that short-term exposure to air pollution may worsen sleep apnea. Our findings highlight the significance of ongoing efforts to improve air quality in mitigating OSA severity and the relevant disease burden in an aging era.

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder characterized by repeated episodes of apnea and hypopnea during sleep, leading to reduced oxygen desaturation and sleep disruption.[1,2] It was estimated that 23.6% of Chinese adults aged 30–69 years had OSA, with nearly half of them experiencing moderate-to-severe OSA.[2] There is strong evidence linking OSA, especially moderate-to-severe OSA, to an elevated risk of accidents, neurocognitive impairment, and various cardiometabolic diseases.[3–6] Therefore, identifying the risk factors for OSA is essential in preventing the condition and reducing the resultant disease burden.

Air pollution has recently been proposed as a potential risk factor for OSA.[7] Exposure to air pollution could lead to increased inflammatory responses in the nasal or pharyngeal areas, induce neuroinflammation, and disrupt neurotransmitter levels, all of which are implicated in the etiology of OSA. Several studies suggested that even a short-term exposure to air pollution may be associated with OSA-related respiratory events, sleep quality, or sleep-related parameters, but the existing findings were quite mixed.[8–12] Previous studies generally had relatively small sample size (ranging from dozens to thousands) or used only one-night sleep monitoring, or were conducted in single centers, limiting their statistical power and the generalizability of their results. Besides, in most previous studies, air pollution data were based on daily 24-h averages, without taking into account personalized sleep time, leading to unmeasured exposure misclassification due to the discrepancies between sleep time and a calendar day.[10,12] In addition, some previous studies enrolled patients admitted to sleep centers who reported OSA-like symptoms, but overlooked individuals who were unaware of these symptoms, reducing the representativeness of the results. Furthermore, the environment in sleep centers often significantly deviated from patients' accustomed settings, potentially producing uncontrolled influences on the estimated associations between air pollution and OSA severity.[10] Most importantly, there is compelling evidence to suggest that OSA severity can vary significantly from one night to the next[13,14]; however, almost all existing findings have been derived from cross-sectional studies with only one-night monitoring, which does not capture the night-to-night variability in OSA severity and may be susceptible to potential residual confounding due to various unmeasured time-varying factors.[10,12]

A recently validated smart device-based technology for OSA screening provides a unique opportunity to collect large-scale, individual-level, longitudinal, at-home sleep monitoring data.[15] We thereby conducted a nationwide case time series study to investigate the associations between short-term exposure to various air pollutants and the risk of OSA exacerbation. We also evaluated the impacts of air pollution on continuous measures of the apnea-hypopnea index (AHI) and oxygen saturation, which are commonly used indicators of OSA severity.[16]

RESULTS

Descriptive statistics

As illustrated in Figure S1, we excluded 324 participants with less than 7 days of eligible monitoring and those residing in districts more than 50 km away from the nearest air quality monitors (n = 206), or 100 km away from the nearest meteorological stations (n = 912). We finally included a total of 51,842 participants who were at moderate-to-severe risk of OSA with 6,232,056 person-days of eligible monitoring from December 16, 2019, to October 15, 2022. These participants were distributed across 313 Chinese cities at or above the prefecture level (Figure S2). The participants had an average age of 45.4 years, with a standard deviation of 11.0 years. Of the participants, 95.5% were male, 40.1% with a history of hypertension, and 7.8% with a history of diabetes. Each participant had an average of 118 eligible monitoring days.

The characteristics of OSA-related parameters and environmental conditions are summarized in Table 1. OSA exacerbation occurred in 46.1% of all monitored person-days. In days without OSA exacerbation, the median levels of AHI and oxygen saturation were 0.93 events/h and 96.58%, respectively, while in days with OSA exacerbation, these values were 29.95 events/h and 96.39%. The average exposure levels of all air pollutants during sleep time were higher on days with OSA exacerbation compared with those without.

Regression results

Associations of air pollutants with OSA exacerbation, AHI, and oxygen saturation at different lag days are summarized in Figure 1. Overall, we found significant associations of $PM_{2.5}$, $PM_{2.5\text{-}10}$, NO_2, CO, and SO_2 with an increased risk of OSA exacerbation, elevated AHI levels, and decreased oxygen saturation levels, but the magnitudes of associations varied depending on the specific air pollutants, the outcomes studied, and the lag periods considered. The associations of

Table 1. The median (P25, P75) of AHI, oxygen saturation, and environmental conditions for days with OSA exacerbation and days without OSA exacerbation, respectively

Indicators	Person-days without OSA exacerbation (N = 3,357,709)	Person-days with OSA exacerbation (N = 2,874,347)
AHI (events/h)	0.93 (0.58, 1.23)	29.95 (22.64, 37.95)
Oxygen saturation (%)	96.58 (96.11, 97.01)	96.39 (95.95, 96.79)
$PM_{2.5}$ ($\mu g/m^3$)[a]	23.12 (14.22, 37.67)	24.00 (14.78, 39.12)
$PM_{2.5-10}$ ($\mu g/m^3$)[a]	18.88 (10.56, 32.00)	19.44 (10.73, 33.11)
NO_2 ($\mu g/m^3$)[a]	23.89 (15.33, 38.14)	24.50 (15.67, 39.11)
CO (mg/m^3)[a]	0.62 (0.47, 0.81)	0.63 (0.48, 0.82)
SO_2 ($\mu g/m^3$)[a]	6.09 (4.22, 8.78)	6.20 (4.33, 9.00)
Temperature (°C)[b]	19.05 (10.60, 25.29)	18.33 (10.16, 24.88)
Relative humidity (%)[b]	70.68 (58.40, 79.83)	70.66 (58.33, 79.85)

AHI, obstructive sleep apnea; CO, carbon monoxide; NO_2, nitrogen dioxide; OSA, obstructive sleep apnea; P25, 25th percentile; P75, 75th percentile; $PM_{2.5}$, fine particulate matter; $PM_{2.5-10}$, coarse particulate matter; SO_2, sulfur dioxide.
[a]Air pollution levels from the hour of falling to sleep to the hour of waking up.
[b]weather conditions in 3 moving days before falling to sleep.

most air pollutants could occur during the sleep period and last for 2 days. We therefore used the moving average concentrations of air pollution during sleep time and 2 previous days as the main lag in subsequent analyses.

For OSA exacerbation and AHI, air pollutants, with the exception of $PM_{2.5-10}$, exhibited associations during the sleep period, and these associations were generally less pronounced in the subsequent days. An IQR increase in air pollutant concentrations was associated with increases of 1.14%–4.31% in risk of OSA exacerbation and increases of 0.05–0.17 events/h in AHI. In the case of oxygen saturation, all pollutants showed immediate associations during the sleep period. Exposures during 1 day before sleep showed stronger associations compared with other lag times for most air pollutants. An IQR increase in air pollutant concentrations was associated with decreases of 0.003–0.014 in oxygen saturation (%).

Figures 2, 3, and 4 illustrate the exposure-response curves for the associations of air pollutants with OSA exacerbation, AHI, and oxygen saturation. For $PM_{2.5}$, NO_2, CO, and SO_2, the curves are almost linear, with higher concentrations consistently leading to an increase in the risk of OSA exacerbation and AHI levels, and a decrease in oxygen saturation levels. In the case of $PM_{2.5-10}$, the curves are largely non-significant in its association with OSA exacerbation and AHI. However, when examining its association with oxygen saturation, the curves exhibit a decline at lower concentrations, followed by a plateau at higher concentrations.

Subgroup analyses indicated that the associations of $PM_{2.5}$, NO_2 and SO_2 with OSA exacerbation and AHI were significantly stronger in participants aged 45 years or older. There were no statistically significant between-group differences based on sex, body mass index, sleep duration, or a history of hypertension and diabetes (Figures S3–S5).

In the sensitivity analysis, the main estimates of $PM_{2.5}$ were stable when using alternative data from the exposure model (Figures S6 and S7).

DISCUSSION

By virtue of individual-level, longitudinal, at-home sleep monitoring data from smart devices, we obtained the largest dataset to date and provided robust and coherent epidemiological evidence that short-term exposure to air pollution could significantly increase the severity of OSA, including the elevated risk of OSA exacerbation, higher AHI level, and lower oxygen saturation. The impacts of air pollution exposures on OSA exacerbation and AHI were most pronounced during the sleep period. Middle-aged and elderly participants were more susceptible to these air pollution-related impacts.

Previous studies have provided limited and inconsistent insights into the short-term associations between air pollutants and OSA, AHI, and oxygen saturation. In the Sleep Heart Health Study consisting of 3,030 participants who underwent a single-night polysomnography screening, short-term impacts of PM_{10} were found in summer but not in other seasons, for the increases in the percentage of sleep time at <90% oxygen saturation and the respiratory disturbance index (the ratio of the count of all apnea and hypopnea events to the total sleep time).[8] Conversely, in the Heinz Nixdorf Recall study, which included 1,773 participants undergoing screening for sleep-disordered breathing, investigators did not find a statistically significant association between PM_{10} and AHI across all seasons.[12] Similarly, in a retrospective study by Cassol et al., involving correlation analyses with one-night in-laboratory data from 7,523 patients suspected to having sleep disorders, AHI was not found to be correlated with PM_{10} and SO_2 but did show a significant correlation with CO.[17] In a recent cross-sectional study among 4,634 adults who were admitted to sleep centers for the polysomnography diagnostic test, short-term $PM_{2.5}$ exposure was not associated with OSA, AHI, and oxygen desaturation, while NO_2 exposure showed a significant association with elevated AHI and oxygen desaturation index (defined as the number of episodes of oxygen desaturation per hour of sleep) in patients with an AHI of <15, and increased odds of mild OSA.[10] The inconsistent findings in previous studies might be attributed to differences in study design, sample size, population characteristics, exposure assessment, and exposure windows that were evaluated. For example, the use of one-night sleep monitoring could result in apparent bias in relation to time-varying confounders (eg, seasonality).

Our findings on the associations of air pollution with OSA severity are biologically plausible in the following aspects. First, air pollution could induce immediate nasal or pharyngeal inflammatory responses, subsequently increasing upper airway resistance and diminishing airway patency.[18,19] These biological reactions might in turn result in reductions in lung ventilation and perfusion and exacerbation in hypoxia associated with OSA. Second, some studies have reported that air pollutants may translocate into brain through the olfactory nerve and penetrate the central nervous system,[20] resulting in elevated neuroinflammation and altered neurotransmitter levels.[21,22] The abovementioned changes might impact the areas of brain that regulate sleep and ventilation, further contributing to the exacerbation of OSA symptoms.[23] Third, the frequent reductions in ventilation associated with air pollution exposure during sleep can result in OSA patients receiving less air, ultimately leading to a decrease in oxygen saturation.

We found that the associations of air pollution with OSA severity were more pronounced in middle-aged and elderly people. Aging, a major risk factor for OSA,[24] is associated with the deterioration of upper airway muscle tone and a more easily collapsible airway due to the age-related loss of collagen.[25,26] These structural changes in older patients could substantially reduce airway flow during sleep and play key roles in the pathophysiology of OSA in this age group.[27] In addition, aging is associated with the decreased airway immunity and deteriorated mucociliary clearance, which might facilitate the retention of air pollutants and the release of proinflammatory cytokines in the upper airway. The nasal or pharyngeal inflammatory responses can further reduce the airflow.[19]

Our study has several notable strengths. First, we obtained an ultra-large, nationwide database (more than 6 million person-days of sleep monitoring), providing ample statistical power to detect even subtle effects of air pollution. Second, in comparison with previous studies conducted among patients admitted to sleep centers, the current real-world study collected sleep monitoring data at home, enhancing the generalizability of our findings. Third, in contrast to most previous studies with a single-night measurement using a cross-sectional design, this nationwide longitudinal study utilized intensively repeated measures (an average of 118 eligible screening days per participant), so that our dataset could provide ample variations in both air pollutant concentrations and OSA-related parameters, and thus allow for comprehensive explorations on a stable and full-range exposure-response relationship. Fourth, for the first time, we applied a case time series design to adjust for both time-invariant and time-varying confounders that were not adequately addressed in previous studies. Finally, we matched air pollution exposure levels according to the individualized sleep time at an hourly resolution, thereby avoiding temporal exposure misclassification that was widespread in previous studies.

Some limitations should be also acknowledged. First, the consumer-led approach for OSA screening could attenuate the population representativeness of our results. Second, this study is inherently observational in nature, making it challenging to establish a causal relationship between air pollution and OSA severity. Third, exposure misclassifications are inevitable, because all environmental data were measured based on nearby fixed-site monitoring rather than personal measurements. However, ambient monitoring data have been widely

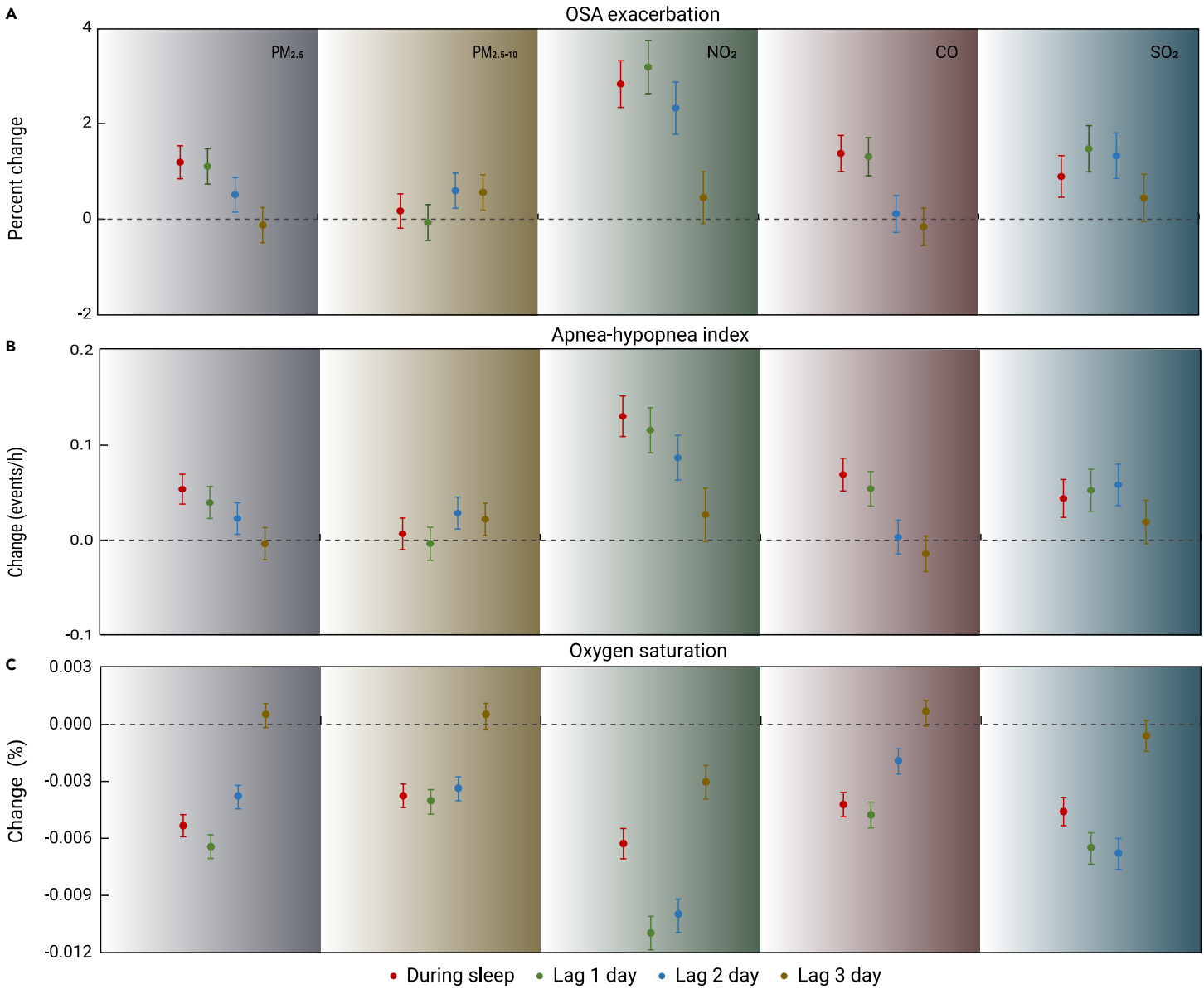

Figure 1. Estimated percent changes (and 95% confidence intervals) in risk of obstructive sleep apnea exacerbation (A) Absolute changes (and 95% confidence intervals) in apnea-hypopnea index (B) and oxygen saturation (C) per interquartile range increase in air pollutant concentrations across various lag periods. $PM_{2.5}$, fine particulate matter; $PM_{2.5-10}$, coarse particulate matter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide; OSA, obstructive sleep apnea. Note: During sleep means the duration from the hour of falling in sleep to the hour of waking up.

used in epidemiological studies investigating the short-term effects of air pollution, and such surrogates have been validated to only bias the effect estimates downward.[28] Fourth, we did not account for factors like indoor air pollutants, long-term exposure to air pollution, noise, and socioeconomic characteristics. These factors are unlikely to introduce significant bias into our results because they tend to remain relatively stable over days, weeks, even months for the same participants, and can be automatically controlled in the self-control design. However, the absence of these data restricts our ability to further explore their potential effect modifications. Finally, OSA risk and severity were measured using smart devices without clinical confirmation, thus diagnostic errors are also inevitable. Nevertheless, we could reasonably assume that these errors were rare, occurred randomly, and were not closely related to variations in air pollution, so our results would be not substantially biased.

In conclusion, this nationwide case time series study provides compelling evidence that short-term exposure to air pollution could increase OSA severity. These associations between air pollution and OSA severity could occur during the sleep period and last for 2 days. Our findings highlight the importance of reducing air pollution exposures to mitigate OSA severity and relevant disease burden in an aging era. This study also suggests that continuous sleep screening by virtue of "smart technology" is a promising and feasible approach for OSA patients, especially for those residing in areas with high air pollution levels.

MATERIALS AND METHODS

Study design

This study used data from the pre-mobile atrial fibrillation app (mAFA) II registry, established to screen the users' atrial fibrillation status by the photoplethysmography (PPG)-based Huawei smart devices (Huawei Technologies Co.). Users can freely download this application from the Huawei Appstore, and it can provide both sleep apnea screening and atrial fibrillation screening. We recruited users who were aged 18 or older, residing in mainland China, possessing compatible smart devices, and providing electronic informed consent. The study received approval from the Central Medical Ethic Committee of Chinese People's Liberation Army General Hospital (S2017-105-02). This study adheres to the principles of the Declaration of Helsinki. Patients with moderate-to-severe OSA are more likely to experience excessive sleeplessness, and various comorbid conditions compared with those with mild OSA. We only included participants identified as having a risk of moderate-to-severe OSA through this application from December 16, 2019, to October 15, 2022. We did not consider individuals with mild OSA because of the limited clinical relevance and the substantial computational burden in relation to the much larger sample size. Participants were classified as having moderate-to-severe OSA risk if, in any 2-week period, they had at least 5 days

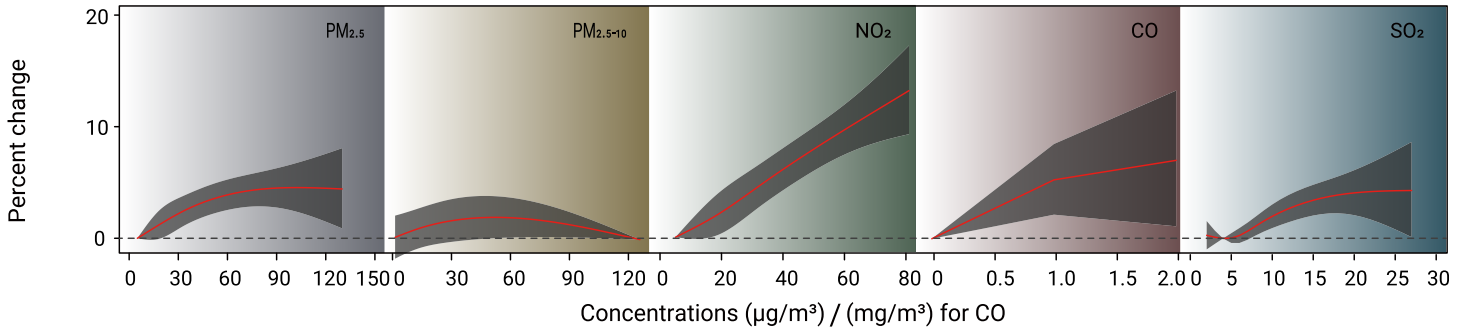

Figure 2. Exposure-response curves for the association between air pollutant levels during sleep time and 2 days before and the onset of obstructive sleep apnea exacerbation
Solid lines = percent change in relative risk of obstructive sleep apnea exacerbation; shaded areas = 95% confidence intervals. $PM_{2.5}$, fine particulate matter; $PM_{2.5–10}$, coarse particulate matter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide.

of monitoring and ≥80% of monitoring measurements showed an AHI >15 events per hour during sleep. An eligible monitoring day was defined as having a duration of 4–12 h of sleep monitoring. Participants with less than 7 eligible monitoring days were further excluded to reduce the influences of having too few monitoring days.

We applied a novel case time series design to analyze the longitudinal data, which combines elements of traditional time series method with self-matched methods like the case-crossover approach.[29] This approach allows for flexible control of time-varying confounders within a longitudinal structure, and automatically addresses time-invariant confounders through a self-controlled structure.

Health data

Sleep-related data were collected using the Huawei smartwatch GT2, capable of capturing PPG signals through an optical heart rate sensor and wrist pulse oximeter. Sleep apnea was evaluated based on pulse rate variability and blood oxygen saturation, which were estimated and extracted from the PPG signals during sleep using a machine learning algorithm. A hypopnea or apnea event was identified when PPG-based respiratory waveforms were reduced by 30% or 90%, respectively. AHI was calculated as the total number of hypopnea and apnea events per hour during sleep. In this study, we additionally defined a binary variable of OSA exacerbation, classifying an AHI ≥5 as indicative of OSA exacerbation. Previous studies have demonstrated that compared with the gold-standard technique (polysomnography), the present PPG-based technique (used by smart devices) has high levels of sensitivity and specificity in OSA screening.[15,30–32] In the present study, a total of 1,628 participants who had been identified as having a moderate-to-severe OSA risk via smartwatches received the gold-standard testing in hospitals; and 92% of the participants were ultimately diagnosed, indicating a high accuracy of our screening technique.

Environmental data

Hourly concentrations of criteria air pollutants during the study period were obtained from China's National Urban Air Quality Real-time Publishing Platform. We evaluated fine particulate matter ($PM_{2.5}$), coarse particulate matter ($PM_{2.5-10}$, that is PM_{10} minus $PM_{2.5}$), nitrogen dioxide (NO_2), carbon monoxide (CO), and sulfur dioxide (SO_2). We did not evaluate ozone as its concentrations during nighttime, especially indoors, were considerably lower than the established "safe" thresholds.[33] Meteorological data including temperature and relative humidity were collected from the National Oceanic and Atmospheric Administration. All environmental exposure data were matched to the nearest monitoring stations at the district level for privacy reasons. To reduce exposure measurement errors, participants located more than 50 km from the nearest air pollution monitoring station and more than 100 km from the nearest meteorological monitoring station were excluded. The top and bottom 0.1% of hourly concentrations for air pollutants were trimmed to reduce the potential impact of outliers on the analyses. The exposure levels of air pollutants during sleep period were calculated as the mean concentrations from the hour of falling asleep to the hour of waking up. The exposure levels on days before sleep were calculated as the mean concentrations for every 24 h before the time of falling asleep, briefed as lag 1 day, 2 days, etc. To allow for the sensitivity analysis using exposure models, we matched daily $PM_{2.5}$ data with the model developed by the project of Tracking Air Pollution in China (TAP, a spatial resolution of 10 × 10 km, http://tapdata.org.cn).[34–36] We did not conduct similar sensitivity analyses for other air pollutants because there were no publicly available exposure models that could cover the entire study period.

Statistical analyses

The case time series design splits the follow-up period into daily time series for each case, yielding a set of multiple case-specific time series. Fixed-effects regression models were used to estimate the association between air pollution and the risk of OSA exacerbation, AHI, and oxygen saturation. In main models, we incorporated the subject/year/month strata intercept to control for the individual-level variations, as well as the yearly and monthly variations. We also included natural splines of day (with 8 degrees of freedom [*df*] per year) to control for seasonal and long-term trends, natural cubic splines of 3-day moving average of temperature and humidity (with 6 *df*) to adjust for their potentially lagged and nonlinear confounding effects, a categorical variable of the day of the week, and a binary variable of public holidays. In order to investigate the potential lagged associations of air pollution, we evaluated the associations across various lag days, including the sleep period and the 3 days preceding the hour of falling asleep. We first fitted nonlinear models using natural cubic splines with 3 *df* for air pollution variables to examine the shape of exposure-response curves. If a nonlinear relationship was observed, we would report the effect estimates by comparing the extreme air pollution levels (ie, the 99th percentile) to the reference concentrations. In the case of a linear relationship, we would present the effect estimates as per interquartile range (IQR) increase of air pollutant concentrations. For OSA exacerbation, the estimated relative risk was transformed into the percentage change in risk associated with each IQR increase in air pollutants, which was calculated using the following formula: $(e^{\beta \times IQR} - 1) \times 100\%$.[37] For AHI and oxygen saturation, the absolute changes were presented.

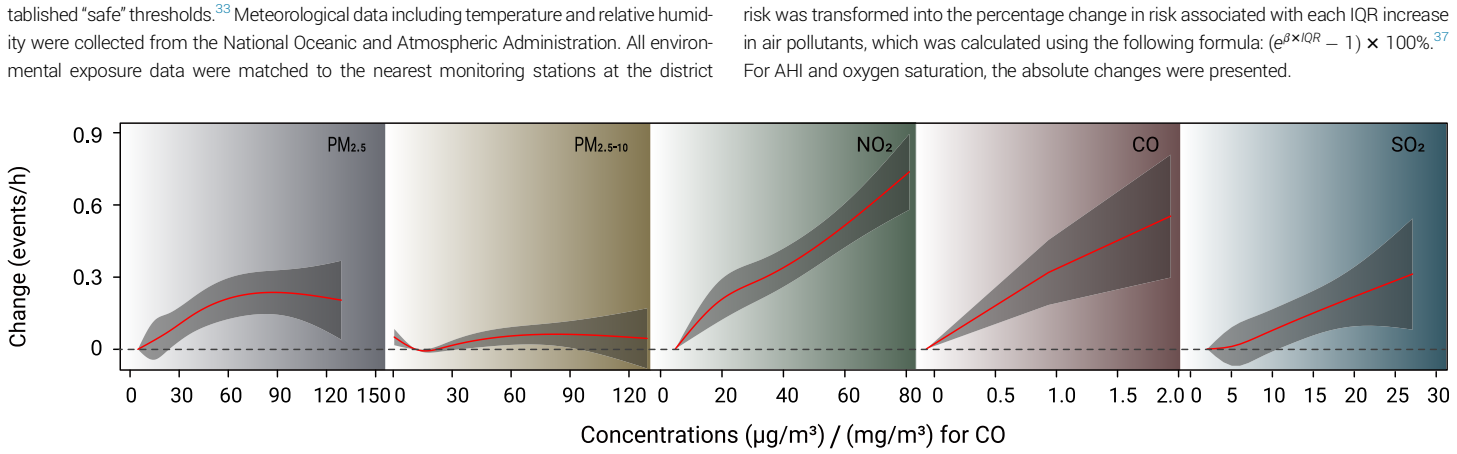

Figure 3. Exposure-response curves for the association between air pollutant levels during sleep time and 2 days before and apnea-hypopnea index Solid lines = change of apnea-hypopnea index; shaded areas = 95% confidence intervals. Abbreviations: $PM_{2.5}$, fine particulate matter; $PM_{2.5–10}$, coarse particulate matter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide.

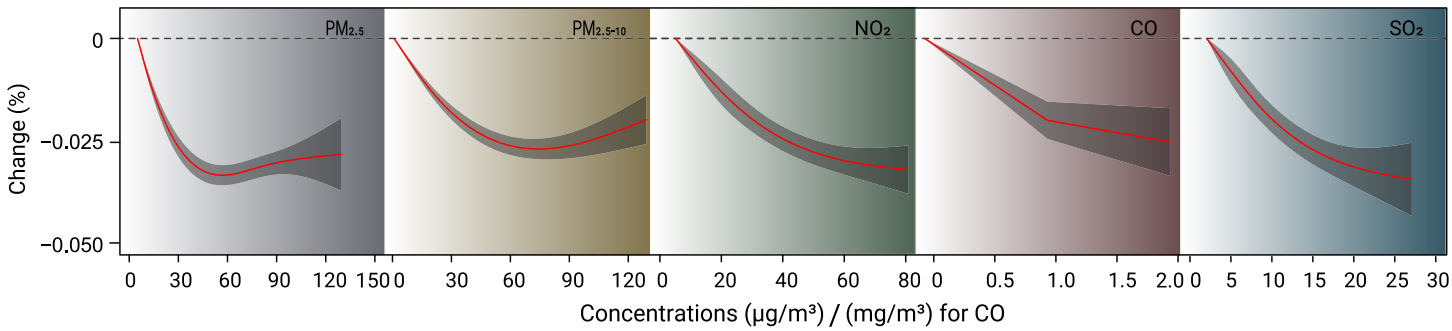

Figure 4. Exposure-response curves for the association between air pollutant levels during sleep time and 2 days before and levels of oxygen saturation Solid lines = change of oxygen saturation levels; shaded areas = 95% confidence intervals. $PM_{2.5}$, fine particulate matter; $PM_{2.5-10}$, coarse particulate matter; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide.

To examine potential effect heterogeneity, we did subgroup analyses by age (<45 and ≥ 45 years), sex, body mass index (<24 and ≥ 24 kg/m^2), and sleep duration (<7 h and ≥ 7 h), as well as history of hypertension and diabetes. The statistical significance of differences in effects between subgroups was tested using the following formula: $(Q_1 - Q_2) \pm 1.96\sqrt{Se_1{}^2 + Se_2{}^2}$, where Q1 and Q_2 indicate the estimates for each subgroup, and Se_1 and Se_2 represent their respective standard errors.[38] The p values for between-group difference tests were calculated based on the 95% CIs mentioned above.

To assess the robustness of the results, we did sensitivity analyses for $PM_{2.5}$ by using daily data from an exposure model instead of relying on measurements obtained from nearby air quality monitors.

All statistical analyses were performed with R (version 4.1.2) using the "gnm" package. All statistical tests are two-sided and p values less than 0.05 were considered to be statistically significant.

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AUTHOR CONTRIBUTIONS

Y.G., H.K., and R.C. are joint corresponding authors and contributed equally to conceptualization, project administration, funding acquisition, resources, supervision, and writing - review & editing. Q.Z. contributed to data curation, formal analysis, investigation, writing-original draft, and writing - review & editing. H.W., X.Z., A.L., and C.L. contributed to software, methodology, validation, and writing - review & editing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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