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Association between air pollutant exposure, body water distribution and sleep disorder indices in individuals with low-arousal-threshold obstructive sleep apnoea

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ABSTRACT

Background Air pollution may alter body water distribution, it may also be linked to low-arousal-threshold obstructive sleep apnoea (low-ArTH OSA). Here, we explored the mediation effects of air pollution on body water distribution and low-ArTH OSA manifestations.

Methods In this retrospective study, we obtained sleep centre data from healthy participants and patients with low-ArTH OSA (N=1924) in northern Taiwan. Air pollutant exposure at different time intervals (1, 3, 6 and 12 months) was estimated using the nearest station estimation method, and government air-quality data were also obtained. Regression models were used to assess the associations of estimated exposure, sleep disorder indices and body water distribution with the risk of low-ArTH OSA. Mediation analysis was performed to explore the relationships between air pollution, body water distribution and sleep disorder indices.

Results First, exposure to particulate matter (PM) with a diameter of ≤10 µm (PM_{10}) for 1 and 3 months and exposure to PM with a diameter of ≤2.5 µm ($PM_{2.5}$) for 3 months were significantly associated with the Apnoea–Hypopnoea Index (AHI), Oxygen Desaturation Index (ODI), Arousal Index (Arl) and intracellular-to-extracellular water ratio (I-E water ratio). Significant associations were observed between the risk of low-ArTH OSA and 1-month exposure to PM_{10} (OR 1.42, 95% CI 1.09 to 1.84), $PM_{2.5}$ (OR 1.33, 95% CI 1.02 to 1.74) and ozone (OR 1.27, 95% CI 1.01 to 1.6). I-E water ratio alternation caused by 1-month exposure to PM_{10} and 3-month exposure to $PM_{2.5}$ and PM_{10} had partial mediation effects on AHI and ODI.

Conclusion Air pollution can directly increase sleep disorder indices (AHI, ODI and Arl) and alter body water distribution, thus mediating the risk of low-ArTH OSA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exposure to air pollution may lead to alterations in body water distribution and exacerbate the sleep disorder indices (ie, Apnoea–Hypopnoea Index, Oxygen Desaturation Index and Arousal Index).

WHAT THIS STUDY ADDS

⇒ Air pollution (particulate matter (PM_{10}) and $PM_{2.5}$ exposure) worsens obstructive sleep apnoea (OSA) severity and alters body water distribution, affecting sleep disorder indices. One-month PM_{10}, $PM_{2.5}$ and ozone exposure mediates the risk of low-arousal-threshold (low-ArTH) OSA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Reducing exposure to air pollutants may reduce sleep disorder indices, thus decreasing the risk of low-ArTH OSA.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder affecting approximately 1 billion people globally.[1] This disorder is characterised by the partial or complete obstruction of the upper airway during sleep, which reduces oxygen delivery.[2] In approximately one-third of patients, OSA disrupts sleep continuity and limits the accumulation of respiratory stimuli that are required to restore upper airway patency and airflow during sleep.[3] This propensity to be woken prematurely in response to respiratory events is defined as low-arousal-threshold (low-ArTH) OSA.[4] Several risk factors for low-ArTH OSA have been identified, including ageing,[5] body water distribution[6] and air pollutant exposure.[7] However, whether these factors exert a synergistic effect on low-ArTH OSA manifestations requires further investigation.

OSA manifestations are evaluated through polysomnography (PSG), followed by the

measurement of sleep disorder indices—namely the Apnoea–Hypopnoea Index (AHI), Oxygen Desaturation Index (ODI) and Arousal Index (ArI). A study suggested that when screening for the risk of low-ArTH OSA, patients with OSA should fulfil at least two of these three criteria: (1) AHI<30 events/hour, (2) lowest oxygen saturation values >82.5% (measured through pulse oximetry) and (3) proportion of hypopnoea (ie, hypopnoea-to-total respiratory event) >58.3%.[8] Notably, air pollution affects the AHI, ODI, ArI and ArTH. For instance, in a review of 15 studies involving approximately 133 000 participants from 10 countries, the authors noted that air pollutants such as particulate matter (PM) with a diameter of ≤2.5 µm ($PM_{2.5}$) and 10 µm (PM_{10}), nitrogen oxide (NO) and nitrogen dioxide (NO_2) might be associated with increased mean AHI, ODI and ArI values, thereby resulting in sleep quality impairment.[9] A related study on the effects of air pollution on the central nervous system reported that air pollutant exposure may increase sleep arousal frequency, and that air pollutant exposure may be associated with low-ArTH OSA.[7] Moreover, patients with low-ArTH OSA tend to exhibit sleep arousal due to respiratory disturbances, particularly minor events such as hypopnoea rather than apnoea.[10] Several mechanisms associated with this manifestation of low-ArTH OSA, which is partially linked to air pollutant exposure, have been identified. For example, the brain circuitry involved in neural substrates and glutamatergic signalling potentially causes sleep arousal.[11] An animal study suggested that exposure to $PM_{2.5}$ interferes with the circuitry of the brain and alters its ultrastructure.[12] Moreover, neuroinflammation and increased oxidative stress in the brain may interfere with the sleep–wake cycle by inducing sleep arousal, and these physiological responses are exacerbated by air pollution.[13 14] PM and NO_2 may affect the central nervous system by altering neurotransmitter levels and breaking down protective epithelial barriers, thus disrupting sleep-regulated brain functions.[15 16] Hence, air pollutant exposure may be a risk factor for the worsening of sleep disorder indices and low-ArTH OSA; thus, further relevant investigation is required.

Air pollutant exposure may affect the balance or fluctuation of body water distribution, namely intracellular water (ICW) and extracellular water (ECW), and may thus worsen sleep disorder indices. Chronic air pollutant exposure may trigger airway mucosa inflammation and osmotic pressure changes, leading to inflammation and oedema of the proximal upper airways and thus changing the body water distribution balance and increasing sleep disorder indices.[17 18] In addition, fine particles have been reported to trigger an oxidative mechanism that increases the oxidative stress of cells and alters the water balance between intracellular and extracellular compartments.[19] Consequently, interactions may exist between air pollutants, body water distribution and OSA severity, but their relationships have yet to be comprehensively explored.

Considering the necessity to further examine the associations between air pollution, body water distribution and sleep disorder indices in low-ArTH OSA, the objective of this retrospective study was to investigate the relationships among these variables. This study hypothesised that air pollutant exposure influences sleep disorder indices directly and modifies body water distribution indirectly, thereby leading to increases in the AHI, ODI and ArI. To investigate this hypothesis, we collected and analysed the data of both healthy individuals and patients with low-ArTH OSA from a sleep centre in northern Taiwan. Information regarding their residential address, body composition, body water distribution and PSG parameters was collected for examination. Using the obtained addresses, exposure volumes to various air pollutants were estimated, and the relationships between air pollution and the aforementioned variables were investigated. The potential influence of air pollution on the risk of low-ArTH OSA was also evaluated.

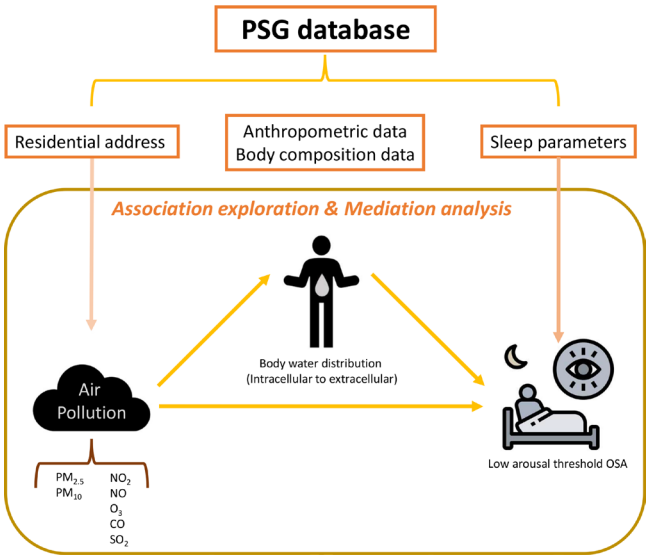

Figure 1 Workflow of data acquisition and statistical analysis of this study. This study first retrospectively accessed the PSG database to obtain the addresses, anthropometric data, body composition data and sleep parameters of patients at a sleep centre. Next, based on the obtained addresses and data from government air monitoring stations, air pollutant exposure levels were estimated. The retrieved data were subsequently subjected to further association and mediation analyses. CO, carbon oxide; NO_2, nitrogen dioxide; NO, nitrogen oxide; O_3, ozone; PM_{10}, aerodynamic diameter of <10 µm; $PM_{2.5}$, aerodynamic diameter of <2.5 µm; PSG, polysomnography; SO_2, sulfur dioxide (SO_2).

METHODS

Study population

Figure 1 presents the workflow of data acquisition and statistical analysis in this study. First, this retrospective study analysed patient data between June 2019 and December 2021 from the PSG database of the sleep centre of Shuang Ho Hospital (New Taipei City, Taiwan). Participants were included in the analysis if they (1) had

Table 1 Demographic characteristics and body composition details of the sample (N=1924)

Variable	Mean±SD	Variable	N (%)
Age (year)	46.8±13.63	Sex	
BMI (kg/m^2)	26.13±4.72	Male	1170 (60.81)
Neck circumference (cm)	36.8±3.92	Female	754 (39.19)
Waist circumference (cm)	89.62±12.19	OSA severity	
Body composition		Normal	326 (16.94)
Visceral fat level	10.85±4.86	Mild	541 (28.12)
Fat proportion (%)	28.42±8.88	Moderate	431 (22.4)
Muscle proportion (%)	17.81±4.63	Severe	626 (32.54%)
TBW (%)	49.9±5.56		
Body water distribution			
ICW (%)	58.46±2.61		
ECW (%)	41.54±2.61		
I-E water ratio	141.65±14.95		

ICW (%)=(ICW (kg)/TBW (kg))×100.
ECW (%)=(ECW (kg)/TBW (kg))×100.
I-E water ratio=(ICW/ECW)×100.
BMI, body mass index; ECW, extracellular water; ICW, intracellular water; I-E water ratio, ratio of ICW to ECW; OSA, obstructive sleep apnoea; TBW, total body water.

complete data on PSG parameters and a total recording time >6 hours, (2) were aged from 18 to 85 years, (3) had not undergone any invasive surgery or non-invasive treatment for OSA, (4) had not regularly used hypnotic or psychotropic medications, (5) had not been diagnosed as having central nervous system disorders (eg, brain tumour, stroke or major head trauma) and (6) exhibited normal AHI (<5 events/hour) or satisfied the screening criteria for low-ArTH OSA. The residential address and physical profiles (which included information on age, sex, body mass index (BMI), and neck and waist circumferences) were obtained from the clinical records of all eligible individuals.

Body composition and body water distribution

Data on body composition and body water distribution were obtained from the aforementioned medical database. Data determination was conducted using the Tanita MC-780 system (Tanita, Tokyo, Japan), and the procedures were as follows. Individuals were instructed to undergo data determination (the measurement of bioelectrical impedance) before PSG. All participants were required to fast for at least 3 hours and empty their bladders before undergoing bioelectrical impedance measurement. During data collection, patients were instructed to stand still and shoulder-width apart while holding the induction metal handles with both arms placed straight down. Next, the visceral fat level and percentages of fat, muscle and water in the whole-body scale were obtained automatically. The ECW and ICW percentages and ICW-to-ECW ratio (I-E water ratio: ICW/ECW×100) were calculated.

Sleep profile-PSG parameter

Three recording systems were used to perform PSG at the sleep centre of Shuang Ho Hospital, including the Embla N7000 (ResMed, San Diego, California, USA), Embletta MPR (Natus Medical, Pleasanton, California, USA), and Nox-A1 (Nox Medical, Alpharetta, Georgia, USA). Two types of scoring interface, including RemLogic software (V.3.41; Embla Systems, Thornton, Colorado, USA) and Noxturnal system (V.6.2.2; Nox Medical), were employed corresponding to the various PSG hardware systems. The procedures for scoring physiological signals in PSG were all conducted by a certificated PSG technologist in accordance with the American Academy of Sleep Medicine manual published in 2017.[20] Specifically, apnoea (≥90% reduction in the signals of an oronasal thermistor), hypopnoea (≥30% reduction in the signals of nasal prong pressure combined with ≥3% oxygen desaturation or with occurring arousal) and the frequency of oxygen desaturation (≥3% oxygen desaturation) were scored. The PSG technologists scored intervals that comprised alterations in brainwave signals (≥3 s) with high-frequency patterns that did not spindle (alpha wave: 8–12 Hz, theta wave: 4–8 Hz, high-frequency: >16 Hz) and that were preceded by stable sleep (≥10 s) as arousal events. Next, the AHI and the ArI were calculated accordingly, and OSA severity was defined as follows: none, AHI<5 events/hour; mild, AHI: 5–15 events/hour; moderate, AHI=15–30 events/hour and severe, AHI≥30 events/hour.[21] To reduce the individual scoring bias, another technologist was requested to examine the scoring outcomes independently, and the varying parts were extracted for discussions to reach a scoring consensus.

Table 2 Sleep parameters on polysomnography of all participants (N=1924)

Categorical variable	Mean±SD
Sleep architecture	
Sleep efficiency (%)	76.76±12.8
Wake (% of SPT)	16.57±11.53
NREM (% of SPT)	71.3±10.27
REM (% of SPT)	12.1±6.1
WASO (min)	55.85±39.49
TST (min)	281.32±47.54
Sleep quality index (events/hour)	
ODI	18.43±20.61
Snoring index	198.35±220.59
ArI	18.08±10.94
Low-ArTH criteria	
AHI (events/hour)	23.88±21.04
minSpO$_2$ (%)	86.16±7.25
F-hypopnoea (%)	89.07±13.41

ODI=the cumulative frequency of desaturation episodes (≥3%) occurring per hour.
F-hypopnoea=hypopnoea events/(hypopnoea events+apnoea events).
AHI, Apnoea–Hypopnoea Index; ArI, Arousal Index; ArTH, arousal threshold; F-hypopnoea, fraction of hypopnoea; minSpO$_2$, minimum values in oxygen saturation as measured using pulse oximetry; NREM, non-rapid eye movement; ODI, Oxygen Desaturation Index; REM, rapid eye movement; SPT, sleep period of time; TST, total sleep time; WASO, wake time after sleep onset.

Estimation of air pollutant exposure level

This retrospective study acquired hourly monitoring data on air pullulation levels, temperature, humidity and rainfall from 16 air quality stations subsidised and organised by Taiwan Environmental Protection Administration (19 stations, excluding 1 national park station and 2 background stations). The air pollutants included PM$_{10}$, PM$_{2.5}$, carbon monoxide (CO), NO, NO$_2$, sulfur dioxide (SO$_2$) and ozone (O$_3$). All the exposure data for the participants were calculated backward from the time of visiting the sleep centre. This study used an adjusted form of a previously reported estimation approach for air pollutant exposure values, which were determined using the data from the nearest station.[22] Specifically, in this method, we employed the data obtained from air pollution monitoring stations situated within a 3 km radius of the homes of the participants; these stations were considered to be neighbouring stations. Next, as shown in online supplemental figure S1, weights were assigned to these selected stations based on the distances between the stations and the participants' homes; then, the weighted average of daily exposure levels was computed. Online supplemental figure S2 provides a comparison of PM$_{10}$ and PM$_{2.5}$ exposure outcomes obtained from two methods: the original nearest station estimation method and the revised method with reference data from the neighbouring stations. The distance was restricted, so that the nearest station was selected, thereby causing imprecise estimates. This study calculated the mean from 1, 3, 6 and 12 months prior to the date of PSG for determining the short-term, medium-term and long-term exposure, respectively.

Statistical analysis

To explore the associations between air pollution, body water distribution, arousal response and OSA severity, multiple linear regression models were employed. To determine the risk of low-ArTH from air pollutant exposure, this study classified the individuals into two groups, namely healthy and low-ArTH OSA groups, on the basis of the aforementioned criteria using clinical screening variables.[8] Multivariable logistic regression models were employed to investigate mean air pollutant exposure between the healthy (AHI<5 events/hour) and low-ArTH groups. The effects of air pollutants on sleep parameters were analysed using the unit of the IQR alterations for individual pollutant exposure. The level of significance was set to p<0.05. SPSS (V.20.0; IBM) was used for all statistical analyses.

RESULTS

Description of basic characteristics, PSG parameters and exposure level to air pollutants of the recruited population

The demographic characteristics of participants (N=1924) are summarised in table 1, and their PSG parameters are presented in table 2. The mean age and BMI of participants were 46.8 years and 26.13 kg/m^2, respectively, and 60.81% of them were men. Regarding body water distribution, ECW% versus ICW% was 41.54%–58.46%, and the mean derived I-E water ratio was 141.65 (SD: 14.95). Regarding OSA severity, we recorded 326 participants with low OSA severity (16.94%), 541 with mild OSA (28.12%), 431 with moderate OSA (22.4%) and 626 with severe OSA (32.54%). Participants exhibited mean sleep efficiency of 76.76%, ODI of 18.43 events/hour, and ArI of 18.08 events/hour. Regarding the low-ArTH screening criteria, the means of AHI, minSpO2, and F-hypopnoea were 23.88 events/hour, 86.16% and 89.07%, respectively.

Table 3 details the exposure level to air pollutants presented as medians with IQRs. The medians of 1-month, 3-month, 6-month and 12-month exposure were similar, whereas the IQRs indicated a relative decreasing pattern over time.

Associations between air pollution and sleep disorder indices

This study analysed the associations between air pollutant levels at different time scales and different sleep disorder indices. The findings are summarised in table 4 (in the form of per one unit of increment in IQR and 95% CI). We observed that the IQRs of PM$_{10}$ and PM$_{2.5}$ for both

Table 3 Exposure values to air pollution and background conditions of the sample

Categorical variables	Median (IQR)			
	1 month	3 months	6 months	12 months
Air pollutant				
PM_{10} (μg/m^3)	24.03 (3.4)	23.45 (2.69)	24.12 (2.13)	24.97 (1.75)
$PM_{2.5}$ (μg/m^3)	12.75 (2.41)	12.41 (1.68)	12.61 (1.45)	13.03 (0.66)
CO (ppm)	0.44 (0.07)	0.43 (0.06)	0.43 (0.05)	0.44 (0.02)
NO (ppb)	4.47 (0.85)	4.55 (0.72)	4.47 (0.43)	4.52 (0.29)
NO_2 (ppb)	14.94 (2.07)	14.96 (2.21)	14.7 (1.6)	15.22 (1.15)
SO_2 (ppb)	1.86 (0.21)	1.89 (0.24)	1.89 (0.21)	1.94 (0.22)
O_3 (ppb)	29.28 (3.99)	29.16 (2.95)	28.75 (1.42)	28.91 (0.55)
Background	Mean (SD)			
Ambient temperature (°C)	23.32 (4.49)	23.44 (4.31)	23.9 (3.04)	24.07 (0.33)
Relative humidity (%)	73.21 (4.24)	73.27 (3.75)	73.08 (2.6)	72.86 (1.48)

Date are expressed as median (IQR).
CO, carbon monoxide; NO_2, nitrogen dioxide; NO, nitrogen oxide; O_3, ozone; PM_{10}, particulate matter with an aerodynamic diameter of≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; SO_2, sulfur dioxide.

1-month and 3-month exposure were significantly associated with AHI values (p<0.01). The short-term exposure IQRs of CO, NO_2 and O_3 were positively associated with AHI values (p<0.05). The association patterns of ODI were identical to those of AHI. Significant associations were observed between ArI and PM_{10}, $PM_{2.5}$ and O_3 in the short and medium term (p<0.05).

Associations between air pollution and body water distribution

This study then analysed the associations between air pollutant levels and the body water distribution of participants. The obtained outcomes are presented in table 5 (per one unit of increment in IQR and 95% CI). Total body water (TBW) was positively associated with the IQRs of PM_{10} and NO_2 in both the short and medium term, whereas $PM_{2.5}$ was only associated with the medium-term IQRs (p<0.05). PM_{10} was associated with the I-E water ratio in the short term, whereas both PM_{10} and $PM_{2.5}$ were associated with the I-E water ratio in the medium term. The associations between exposure to air pollutants and body water distribution were similar to those with the sleep disorder indices; specifically, the associations were only observed in the short (1 month) and medium term (3 months).

Associations between PM exposure and sleep disorder indices considering the effects of body water distribution

Significant associations were found between 1 month PM_{10} exposure, 3-month PM exposure, sleep disorder indices and the I-E water ratio. Therefore, the synergistic associations between PM exposure and sleep disorder indices were further analysed considering the effects of body water distribution. As presented in table 6, the results revealed that an IQR increase in 1-month PM_{10} exposure was positively associated with increases of 4.24, 3.91 and 1.44 events/hour in the AHI, ODI and ArI values, respectively (95% CIs 2.82 to 5.66, 2.51 to 5.31 and 0.56 to 2.32 events/hour, respectively; all p<0.01). Moreover, an IQR increase in 3-month PM_{10} exposure was positively associated with increases of 2.06, 2.01 and 1.06 events/hour in the AHI, ODI and ArI values, respectively (95% CIs 0.69 to 3.43, 0.67 to 3.35 and 0.22 to 1.89 events/hour; p<0.01, p<0.01 and p<0.05, respectively). Similarly, an IQR increase in 3-month $PM_{2.5}$ exposure was positively associated with increases of 2.57, 2.43 and 1.07 events/hour in the AHI, ODI and ArI values, respectively (95% CIs 0.98 to 4.15, 0.88 to 3.99 and 0.11 to 2.04 events/hour; p<0.01, p<0.01 and p<0.05, respectively). Moreover, significant associations were observed between 1-month $PM_{2.5}$ exposure and sleep disorder indices in the analysis considering body water distribution (ie, the I-E water ratio). However, the difference when examining the associations of 1-month $PM_{2.5}$ exposure with the I-E water ratio was nonsignificant (table 5). Therefore, only 1-month PM_{10} exposure and 3-month PM_{10} and $PM_{2.5}$ exposure were included in the mediation analysis.

Mediation analysis of associations between air pollution, body water distribution and sleep disorder index

Next, we investigated the associations between air pollution, body water distribution and OSA severity using mediation analysis (figure 2). This analysis included PM_{10} (short and medium term), $PM_{2.5}$ (short term), I-E water ratio, AHI and ODI because they demonstrated significant associations after adjustment for age, sex and BMI; for fine PM exposure, ambient temperature and humidity were further adjusted for. The indirect (mediated) effects of PM_{10} (short and medium term) and $PM_{2.5}$ (short term) on the I-E water ratio (path 1) were positive

Table 4 Associations between the sleep disorder indices and an IQR alteration in exposure to short-term, medium-term and long-term air pollution

Categorical variables	Beta coefficient (95% CI)			
	1 month	3 months	6 months	12 months
AHI (events/hour)				
PM_{10} (μg/m^3)	4.33 (2.91 to 5.75)**	2.16 (0.79 to 3.53)**	.62 (–0.48 to 1.73)	0.67 (–0.56 to 1.9)
$PM_{2.5}$ (μg/m^3)	4.48 (3.02 to 5.93)**	2.67 (1.09 to 4.25)**	0.18 (–1.3 to 1.65)	–0.79 (–1.9 to 0.32)
CO (ppm)	2.22 (0.93 to 3.52)**	1.21 (–0.3 to 2.72)	–0.21 (–1.42 to 1.01)	0.38 (–0.34 to 1.11)
NO (ppb)	0.53 (–0.17 to 1.22)	0.3 (–0.3 to 0.9)	0.12 (–0.37 to 0.62)	0.14 (–0.33 to 0.61)
NO_2 (ppb)	2.4 (1.07 to 3.73)**	1.29 (–0.26 to 2.84)	0.16 (–1.19 to 1.5)	0.03 (–0.94 to 1.01)
SO_2 (ppb)	–0.36 (–1.08 to 0.36)	0.38 (–0.52 to 1.28)	0.18 (–0.75 to 1.11)	0.16 (–0.86 to 1.17)
O_3 (ppb)	1.66 (0.43 to 2.88)*	0.52 (–0.58 to 1.61)	0.71 (–0.43 to 1.84)	0.1 (–0.73 to 0.92)
ODI (events/hour)				
PM_{10} (μg/m^3)	4.01 (2.62 to 5.41)**	2.12 (0.78 to 3.46)**	0.7 (–0.39 to 1.78)	1.02 (–0.19 to 2.22)
$PM_{2.5}$ (μg/m^3)	4.21 (2.78 to 5.64)**	2.55 (0.99 to 4.1)**	0.27 (–1.18 to 1.72)	–0.69 (–1.78 to 0.4)
CO (ppm)	2.4 (1.13 to 3.67)**	1.31 (–0.17 to 2.79)	–0.04 (–1.23 to 1.15)	0.27 (–0.44 to 0.98)
NO (ppb)	0.61 (–0.07 to 1.29)	0.3 (–0.29 to 0.88)	0.16 (–0.33 to 0.64)	0.25 (–0.21 to 0.71)
NO_2 (ppb)	2.48 (1.17 to 3.78)**	1.32 (–0.2 to 2.85)	0.24 (–1.08 to 1.57)	0.18 (–0.78 to 1.14)
SO_2 (ppb)	–0.35 (–1.06 to 0.36)	0.51 (–0.38 to 1.39)	0.34 (–0.57 to 1.25)	0.34 (–0.66 to 1.34)
O_3 (ppb)	1.44 (0.24 to 2.64)*	0.32 (–0.76 to 1.4)	0.85 (–0.26 to 1.96)	0.06 (–0.75 to 0.87)
ArI (events/hour)				
PM_{10} (μg/m^3)	1.48 (0.6 to 2.36)**	1.09 (0.26 to 1.93)*	0.35 (–0.32 to 1.02)	–0.55 (–1.29 to 0.19)
$PM_{2.5}$ (μg/m^3)	1.63 (0.73 to 2.53)**	1.11 (0.14 to 2.07)*	–0.1 (–0.99 to 0.8)	–0.17 (–0.84 to 0.49)
CO (ppm)	0.5 (–0.3 to 1.3)	0.58 (–0.34 to 1.5)	–0.25 (–0.99 to 0.48)	–0.08 (–0.51 to 0.36)
NO (ppb)	0.23 (–0.2 to 0.65)	0.16 (–0.2 to 0.53)	–0.08 (–0.38 to 0.23)	–0.26 (–0.54 to 0.03)
NO_2 (ppb)	0.99 (0.17 to 1.81)*	1.06 (0.11 to 2.01)*	0.17 (–0.65 to 0.99)	–0.23 (–0.82 to 0.36)
SO_2 (ppb)	–0.27 (–0.72 to 0.17)	–0.36 (–0.91 to 0.19)	–0.44 (–1.01 to 0.12)	–0.5 (–1.11 to 0.12)
O_3 (ppb)	–0.31 (–1.06 to 0.45)	0.36 (–0.31 to 1.03)	0.62 (–0.07 to 1.31)	–0.04 (–0.54 to 0.46)

Multivariable linear regression models were adjusted for age, sex, body mass index, temperature and relative humidity.
*p<0.05, **p<0.01.
AHI, Apnoea–Hypopnoea Index; ArI, Arousal Index; CO, carbon monoxide; NO_2, nitrogen dioxide; NO, nitrogen oxide; O_3, ozone; ODI, Oxygen Desaturation Index; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; SO_2, sulfur dioxide.

and significant, as indicated by the regression coefficients (p<0.05). Next, the total effect (mediated and direct) of short-term exposure to PM_{10} and medium-term exposure to PM_{10} on AHI (regression coefficients of 4.33 and 2.16) and on ODI (4.01 and 2.12) were positive and significant, respectively (path 3). For the total effect (mediated and direct) of medium-term exposure to $PM_{2.5}$, the regression coefficients were 2.67 for AHI and 2.55 for ODI. After considering the indirect (mediated) effects between air pollutants and the I-E water ratio on AHI or ODI (path 3*), the partial mediation effects were determined. In mediation analysis, the associations of other air pollutants with ArI was nonsignificant.

Associations between air pollution and the risk of low-ArTH OSA

To explore the associations between air pollution and the risk of low-ArTH OSA, we compared the exposure levels to various air pollutants between healthy participants and patients with low-ArTH OSA using logistic regression (ORs)). As summarised in table 7, we observed that short-term PM_{10}, $PM_{2.5}$ and O_3 exposure was significantly associated with an elevated OR of low-ArTH OSA incidence. In particular, an IQR increment in PM_{10}, $PM_{2.5}$ and O_3 exposure was associated with an increased OR of 1.42, 1.33 and 1.27, respectively (95% CIs 1.09 to 1.84, 1.02 to 1.74 and 1.01 to 1.6, respectively).

DISCUSSION

Sleep disorder indices are associated with air pollution and body water distribution. However, the relationships between them and the effects of air pollution on arousal require further investigation. Thus, this study collected data regarding PSG, body composition and estimated exposure levels to various air pollutants and investigated

Table 5 Associations between the body water distribution and an IQR alteration in exposure to short-term, medium-term and long-term air pollution

Categorical variables	Beta coefficient (95% CI)			
	1 month	3 months	6 months	12 months
TBW (%)				
PM_{10} (μg/m^3)	0.33 (0.01 to 0.65)*	0.45 (0.14 to 0.76)**	0.25 (–0.0 to 0.49)	0.19 (–0.08 to 0.47)
$PM_{2.5}$ (μg/m^3)	0.21 (–0.12 to 0.54)	0.43 (0.07 to 0.79)*	0.26 (–0.07 to 0.59)	–0.03 (–0.28 to 0.22)
CO (ppm)	0.15 (–0.14 to 0.45)	0.2 (–0.14 to 0.54)	0.11 (–0.16 to 0.39)	–0.03 (–0.19 to 0.13)
NO (ppb)	0.09 (–0.07 to 0.25)	0.02 (–0.11 to 0.16)	0.01 (–0.1 to 0.12)	–0.03 (–0.13 to 0.08)
NO_2 (ppb)	0.35 (0.05 to 0.65)*	0.38 (0.04 to 0.73)*	0.25 (–0.06 to 0.55)	–0.03 (–0.25 to 0.19)
SO_2 (ppb)	0.05 (–0.11 to 0.21)	0.15 (–0.05 to 0.36)	0.15 (–0.06 to 0.36)	0.17 (–0.05 to 0.4)
O_3 (ppb)	–0.04 (–0.31 to 0.24)	0.11 (–0.14 to 0.36)	–0.05 (–0.31 to –0.21)	0.04 (–0.15 to 0.22)
I-E water ratio				
PM_{10} (μg/m^3)	1.13 (0.22 to 2.04)*	1.18 (0.3 to 2.06)*	0.56 (–0.15 to 1.26)	0.48 (–0.31 to 1.26)
$PM_{2.5}$ (μg/m^3)	0.88 (–0.06 to 1.82)	1.2 (0.19 to 2.22)*	0.66 (–0.29 to 1.6)	–0.07 (–0.78 to 0.63)
CO (ppm)	0.36 (–0.46 to 1.19)	0.47 (–0.5 to 1.44)	0.2 (–0.57 to 0.98)	–0.12 (–0.58 to 0.33)
NO (ppb)	0.13 (–0.32 to 0.57)	0.01 (–0.38 to 0.39)	–0.01 (–0.33 to 0.3)	–0.09 (–0.39 to 0.21)
NO_2 (ppb)	0.86 (0.01 to 1.71)	0.86 (–0.14 to 1.85)	0.46 (–0.4 to 1.33)	–0.15 (–0.77 to 0.47)
SO_2 (ppb)	0.09 (–0.37 to 0.55)	0.24 (–0.33 to 0.82)	0.14 (–0.46 to 0.73)	0.26 (–0.38 to 0.91)
O_3 (ppb)	0.34 (–0.44 to 1.12)	0.25 (–0.45 to 0.96)	0.16 (–0.57 to 0.88)	0.07 (–0.45 to 0.6)

Multivariable linear regression models were adjusted for age, sex, body mass index, temperature and relative humidity; calculation of I-E water ratio: ICW/ECW×100.
*p<0.05; **p<0.01.
CO, carbon monoxide; I-E water ratio, ratio of intracellular water to extracellular water; NO, nitrogen oxide; NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; SO_2, sulfur dioxide; TBW, total body water.

their relationships using multivariable linear regression models and mediation analysis. Moreover, the associations between air pollution and the risk of low-ArTH OSA were explored.

In this study, we estimated the long-term exposure levels of $PM_{2.5}$ and PM_{10} to be 13.03 and 24.97 μg/m^3, respectively, both of which were higher than their annual means in the 2021 air quality guidelines of the WHO (5 and 15 μg/m^3, respectively).[23] Here, we proposed a revised method where we used data from stations in the proximity of the participants' homes by limiting the maximum distance of the stations rather than using data only from the nearest stations.[24] The supplemental results suggested that this revised approach offers a more precise approximation to the actual data than methods that solely reference the air pollution readings of the nearest station. The proposed approach may enhance data reliability by reducing potential estimation errors that occur when relying on only one information source. For instance, if the nearest station is at a considerable distance, the obtained results may be less reliable.

In this study, 1-month PM_{10}, $PM_{2.5}$, CO, NO_2 and O_3 exposure was significantly associated with increased AHI and ODI values. Similar outcomes have also been observed for the 3-month exposure to PM_{10} and $PM_{2.5}$. Pertaining to the arousal response, exposure to PM_{10}, $PM_{2.5}$ and NO_2 in the 1-month and 3-month was positively and significantly associated with ArI values. Consequently, air pollution potentially affects the physiology of both the respiratory and central nervous systems. Specifically, exposure to air pollutants is associated with inflammatory responses in the upper and lower respiratory tract, which may increase airway resistance and thereby aggravate OSA severity.[25] Fine particles and gaseous pollutants (eg, NO_2) may also irritate the respiratory system and cause oedema in the nasopharyngeal and oropharyngeal tracts and subsequent airway narrowing, thereby increasing sleep disorder indices.[26] A study examined the relationships between sleep variables from PSG data and mean PM_{10} exposure levels in winter (December and January) and summer (June and July).[27] Its results demonstrated the AHI values were higher in winter than in summer, aligning with increased PM_{10} levels. Various reasons could account for these observed relationships. Air pollution may also mediate the development of an inflammatory response and may cause the bronchial physiology to become unstable, which has been identified as a risk factor for OSA.[28 29] PM may accumulate in the lower respiratory tract and induce inflammation and an oxidative response, possibly increasing oxidative stress, overwhelming the antioxidant defence and increasing hypoxaemia risk.[30] Consistent with the current findings,

Table 6 Associations between sleep disorder indices and IQR variations for 1-month and 3-month exposure to fine PM considering the effects of body water distribution

Variable	Beta coefficient (95% CI)
1-month exposure to PM_{10} (μg/m^3)	
AHI (events/hour)	4.24 (2.82 to 5.66)**
ODI (events/hour)	3.91 (2.51 to 5.31)**
ArI (events/hour)	1.44 (0.56 to 2.32)**
1-month exposure to $PM_{2.5}$ (μg/m^3)	
AHI (events/hour)	4.40 (2.95 to 5.86)**
ODI (events/hour)	4.13 (2.70 to 5.56)**
ArI (events/hour)	1.61 (0.71 to 2.51)**
3-month exposure to PM_{10} (μg/m^3)	
AHI (events/hour)	2.06 (0.69 to 3.43)**
ODI (events/hour)	2.01 (0.67 to 3.35)**
ArI (events/hour)	1.06 (0.22 to 1.89)*
3-month exposure to $PM_{2.5}$ (μg/m^3)	
AHI (events/hour)	2.57 (0.98 to 4.15)**
ODI (events/hour)	2.43 (0.88 to 3.99)**
ArI (events/hour)	1.07 (0.11 to 2.04)*

Multivariable linear regression models were adjusted for age, sex, body mass index, temperature and relative humidity.
Unit of outcome (ie, sleep disorder indices) was subjected to Box-Cox transformation.
*p<0.05; **p<0.01.
AHI, Apnoea–Hypopnoea Index; ArI, Arousal Index; ODI, Oxygen Desaturation Index; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm.

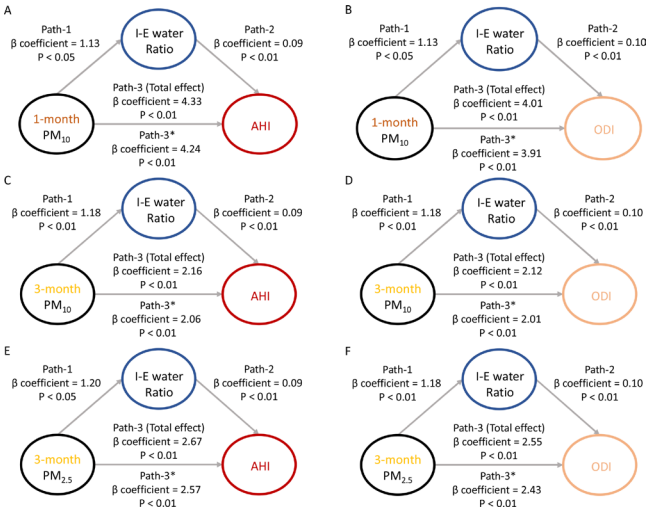

Figure 2 Mediation analysis of air pollutants between the I-E water ratio and sleep disorder indices. Mediation analysis of I-E water between PM with a 1-month and 3-month PM_{10} or $PM_{2.5}$ exposure and sleep disorder indices (AHI and ODI). The beta coefficients of the adjusted linear regression models and derived p values are presented in the path diagram. The outcomes demonstrated that I-E water ratio partially mediates the effects of 1-month PM_{10}, 3-month PM_{10} and 3-month $PM_{2.5}$ exposure on the AHI and ODI values. All four requirements or a mediation effect were satisfied: path-1, path-2, path-3 and path-3* were statistically significant. Note: path-1, path-3 and path-3*: adjusted for age, sex, body mass index, temperature and relative humidity; path-2: adjusted for age, sex and body mass index. AHI, Apnoea–Hypopnoea Index; I-E water ratio, the ratio of intracellular water to extracellular water; ODI, Oxygen Desaturation Index; PM_{10}, aerodynamic diameter of <10 μm; $PM_{2.5}$, aerodynamic diameter of <2.5 μm.

a study reported positive associations between air pollution and worsened OSA severity, as follows: $PM_{2.5}$–AHI, NO_2–ArI and NO_2–AHI.[31] Another multiethnic study observed that higher annual exposure concentrations of NO_2 (10 ppb) and $PM_{2.5}$ (5 μg/m^3) were associated with an increased risk of OSA incidence.[32] Public awareness regarding the effects of air pollutant exposure on sleep disorder indices should be increased.

Regarding the effects of air pollution on the alterations of body water distribution, we determined that 1-month PM_{10} and 3-month PM_{10} and $PM_{2.5}$ exposure was associated with increased TBW and I-E water ratio after adjustment for age, sex and BMI. Although no direct evidence or mechanisms support that air pollution may increase water retention, particularly for ICW, some explanations may account for these observations. Specifically, following exposure to air pollutants, the defence mechanisms of the epithelium and mucosa in the respiratory system are deactivated, including excessive inflammation in cells and reduced barrier function.[33] A study investigated the molecular mechanisms in the cell membrane of airway epithelial cells and the results indicated that PM exposure might affect the permeability of these cells, leading to tissue swelling.[34] These physiological responses to air pollutants may indirectly contribute to the alteration of the water ratio between the intracellular and extracellular compartments. Exposure to fine particles may also exacerbate oxidative stress in the intracellular environment, resulting in inflammation and oedema.[35] Another possible explanation is the osmotic pressure changes in the cell membrane caused by air pollution. Studies have reported that the organic components of $PM_{2.5}$ may contribute to cell cycle dysregulation as well as several other responses (ie, elevated osmotic pressure and exacerbation of cell inflammation).[36] Additionally, the toxic effects of fine particle exposure may increase the vascular permeability of endothelial cells and may further cause cell swelling because of the excess fluid in the intracellular environment.[37] On the basis of the association of the 1-month and 3-month $PM_{2.5}$ and PM_{10} exposure with the I-E water ratio of body water distribution and sleep disorder indices, we performed mediation analysis to examine their interactions and their partial mediation effects. To the best of our knowledge, this study may be the first to explore these mediation effects. No study has reported similar results or indicated the mechanisms

Table 7 Associations (ORs) of IQR alterations in exposure to short-term, medium-term and long-term air pollution between the healthy and OSA with low-ArTH groups

Categorical variables	OR (95% CI)			
	1 month	3 months	6 months	12 months
PM_{10} (μg/m^3)	1.42 (1.09 to 1.84)*	1.31 (0.99 to 1.72)	1.02 (0.83 to 1.26)	0.92 (0.74 to 1.15)
$PM_{2.5}$ (μg/m^3)	1.33 (1.02 to 1.74)*	1.36 (1.0 to 1.84)	1.03 (0.78 to 1.36)	1.03 (0.85 to 1.26)
CO (ppm)	1.06 (0.85 to 1.33)	1.1 (0.84 to 1.44)	1.02 (0.83 to 1.26)	1.13 (0.99 to 1.29)
NO (ppb)	1.04 (0.93 to 1.18)	1.09 (0.97 to 1.21)	1.07 (0.98 to 1.17)	1.04 (0.96 to 1.13)
NO_2 (ppb)	1.16 (0.92 to 1.48)	1.24 (0.94 to 1.65)	1.17 (0.92 to 1.49)	0.95 (0.79 to 1.13)
SO_2 (ppb)	1.1 (0.97 to 1.25)	1.05 (0.89 to 1.24)	1.04 (0.88 to 1.24)	1.05 (0.88 to 1.26)
O_3 (ppb)	1.27 (1.01 to 1.6)*	0.96 (0.79 to 1.17)	0.89 (0.72 to 1.09)	0.94 (0.82 to 1.09)

*Multivariable linear regression models were adjusted for age, sex, body mass index, temperature and relative humidity. p<0.05.
*p<0.05.
CO, carbon monoxide; low-ArTH, low-arousal-threshold; NO, nitrogen oxide; NO_2, nitrogen dioxide; O_3, ozone; OSA, obstructive sleep apnoea; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; SO_2, sulfur dioxide.

of these synergistic effects. However, these underlying mechanisms may explain how fine particles directly aggravate OSA severity and increase the I-E water ratio of body water, which may indirectly and further aggravate OSA severity. Taken together, the results indicate that air pollution may alter the distribution and volume of body water by affecting cell physiology.

This study highlighted a significant relationship of 1-month PM_{10} and $PM_{2.5}$ exposure with an increase in ArI. Additionally, exposure to air pollutants (ie, $PM_{2.5}$, PM_{10} and O_3) was strongly associated with an elevated risk of low-ArTH OSA, suggesting that the aforementioned pollutants are risk factors for low-ArTH OSA. Although the mechanism underlying the specific association between air pollution and the declined ArTH remains unclear, some reasons may account for these findings. Specifically, the ArTH is influenced by the interactions of both the respiratory and central nervous systems. This threshold can be considered as the action point for generating an arousal response when experiencing airway occlusion. Therefore, abnormalities in both the respiratory and central nervous systems may be responsible for the impaired ArTH, which may result in awakening in patients with OSA because of the arousal responses induced by slight hypoxia stimuli.[38] In addition, PM and O_3 exposure may impair respiratory and central nervous system function by causing inflammation, cell swelling and systemic oedema.[39 40] For example, PM exposure may mediate toxicological mechanisms, causing neuroinflammation in the central nervous system and indirectly increasing sleep arousal frequency.[41] A comprehensive review revealed that elevated levels of PM exposure, even for short durations (ie, a few hours to days), can result in unstable brain haemodynamics.[42] A study suggested that short-term PM exposure damaged neurons, thus negatively affecting the central nervous system.[43] Another study noted positive associations between monthly short-term exposure to fine PM and ArI[44]; this result corroborated the current results. An animal model study indicated that PM might reach the central nervous system indirectly through the peripheral system, eventually increasing the permeability of the blood–brain barrier after PM exposure for 4–24 hours.[45] Another study proposed that short-term (1–3 months) exposure to PM results in metal and inflammatory biomarker accumulation in rat brains.[46] These physiological disturbances within the central nervous system may lead to heightened sleep arousal or disrupted sleep patterns. These potential underlying mechanisms and the related outcomes indicate that PM exposure provokes sleep arousal responses, affecting the central nervous system and thus increasing sleep arousal frequency and the risk of low-ArTH OSA. Nevertheless, further research verifying the cause-and-effect relationship between short-term PM exposure and its adverse influence on the central nervous system, which may affect the ArTH, is warranted.

This study has some limitations. Indoor and outdoor air quality may differ, and we did not measure indoor pollution. Relatedly, air pollution levels estimated based on residential addresses might not reflect the actual exposure accurately. In terms of modelling, we did not identify the effects of short-term $PM_{2.5}$ exposure on sleep-disordered measurements by using a single-pollutant model. Using air pollution measurements for each patient may improve the air pollutant exposure accuracy and enable the detailed evaluation of short-term relationships between pollution and sleep disorders. Regarding the social demography perspective of this study, self-payment at the sleep centre may have led to sampling bias. Our sample may not be representative of the general population. The socioeconomic status or lifestyle habits of participants were not obtained, which this may have may affected OSA manifestations or severity and may have resulted in potential residual confounding.[47 48] Data on psychosocial stressors, which may also confound the associations between air pollution

and OSA, were also missing, such as noise, medication and continuous positive airway pressure therapy. Further questionnaire surveys should collect this information for future research.

CONCLUSION

This study observed that air pollution, including 1-month exposure to $PM_{2.5}$, PM_{10}, CO, NO_2 and O_3 and 3-month exposure to $PM_{2.5}$ and PM_{10}, was significantly associated with increased AHI and ODI values. Both 1-month and 3-month exposure to $PM_{2.5}$, PM_{10} and NO_2 was significantly associated with increased ArI values. Significant associations were observed between the I-E water ratio, 1-month and 3-month PM_{10} exposure, and 1-month $PM_{2.5}$ exposure. Next, sleep disorder indices and 1-month and 3 month PM exposure exhibited significant associations even in the context of the effects of I-E water ratio. Similarly, 1-month and 3-month PM_{10} and 1-month $PM_{2.5}$ exposure had mediation effects on the I-E water ratio, which in turn partially worsened sleep disorder indices by increasing the AHI and ODI values. Moreover, 1-month PM_{10}, $PM_{2.5}$ and O_3 exposure was significantly associated with the risk of low-ArTH OSA.

Taken together, these results suggest that air pollutant exposure directly worsens sleep disorder indices and influences body water distribution, thereby indirectly increasing AHI and ODI values. Furthermore, PM_{10}, $PM_{2.5}$ and O_3 exposure may impact the central nervous system, increasing arousal response frequency and thus potentially increasing the risk of low-ArTH OSA. Therefore, mitigating air pollutant exposure may improve sleep disorder indices and reduce the risk of low-ArTH OSA.

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Contributors C-YT, ML and H-TH carried out the findings analysis and drafted the main manuscript text. W-HH and Y-CK performed data curation and investigation. AM validated the results. K-YL and J-HK led the project administration and offered opinions. P-HF, C-HT and K-YC made suggestions to conceptualise the project. H-CL and C-JW provided feedback and adjustment. W-TL conceptualised the project, review and editing the manuscript. Additionally, W-TL is responsible for the overall content.

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Data availability statement Data are available on reasonable request. All the data of this study were collected at the Sleep Center of Taipei Medical University–Shuang Ho Hospital (New Taipei City, Taiwan) between June 2019 and December 2021. Because our data set contains personal information, it is not available in online supplement file. For access to the data set or relevant documents, please contact the corresponding author.

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