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Association of air pollution exposure with low arousal threshold obstructive sleep apnea: A cross-sectional study in Taipei, Taiwan☆

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ABSTRACT

Emerging evidence witnesses the association of air pollution exposure with sleep disorders or the risk of obstructive sleep apnea (OSA); however, the results are not consistent. OSA patients with or without a low arousal threshold (LAT) have different pathology and therapeutic schemes. No study has evaluated the potential diverse effects of air pollution on the phenotypes of OSA. The current study aimed to evaluate the associations of short-term and long-term exposure to air pollution with sleep-disordered measures and OSA phenotypes. This cross-sectional study consisted of 4634 participants from a sleep center in Taipei from January 2015 to April 2019. The personal exposure to ambient $PM_{2.5}$ and NO_2 was assessed by a spatial-temporal model. Overnight polysomnography was used to measure the sleep parameters. According to a developed clinical tool, we defined the low arousal threshold (LAT) and identified the OSA patients with or without LAT. We applied a generalized linear model and multinomial logistic regression model to estimate the change of sleep measures and risk of the OSA phenotypes, respectively, associated with an interquartile range (IQR) increment of personal pollution exposure after adjusting for the essential confounders. In the single-pollutant model, we observed the associations of NO_2 with sleep-disordered measures by decreasing the total sleep time, sleep efficiency, extending the time of wake after sleep onset, and the association of NO_2 with the increased risk of LAT OSA by around 15%. The two-pollutant model with both long-term and short-term exposures confirmed the most robust associations of long-term NO_2 exposure with sleep measures. An IQR increment of NO_2 averaged over the past year (6.0 ppb) decreased 3.32 min of total sleep time and 0.85% of sleep efficiency. Mitigating exposure to air pollution may improve sleep quality and reduce the risk of LAT OSA.

1. Introduction

Obstructive sleep apnea (OSA) is a common disease of sleep-disordered breathing (SDB), with nearly one billion adults affected globally (Benjafield et al., 2019). OSA is characterized by repeated episodes of a partial or complete collapse of the upper airways during sleep and is accompanied by significant health complications, including metabolic disorders, depression, and cardiovascular diseases (Azarbarzin et al., 2019; Cadby et al., 2015; Clark et al., 2020). Sleep disorders and OSA can be identified with the implementation of overnight polysomnography by recording the brain waves, the oxygen level in the blood, heart rate, breathing, and eye and leg movements during sleep (Biernacka and Douglas, 1993; Littner, 2000).

It was estimated in a previous study (Eckert et al., 2013) that in approximately one-third of patients with OSA, respiratory events were

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Abbreviation's list

AHI	apnea-hypopnea index
CI	confidence interval
IQR	inter-quartile range
LAT	low arousal threshold
LUR	land-use regression
NO_2	nitrogen dioxide
OSA	obstructive sleep apnea
$PM_{2.5}$	particulate matter with an aerodynamic diameter less than 2.5 μm
RRR	relative risk ratio
SaO_2	arterial oxygen saturation
SE	sleep efficiency
SDB	sleep-disordered breathing
TST	total sleep time
WASO	wake after sleep onset

terminated early because of a low respiratory arousal threshold, preventing the opportunity for ventilatory drive to build up and restore pharyngeal patency during sleep. A low arousal threshold (LAT) is one of several physiologic traits involved in the pathogenesis of OSA and may be a therapeutic target; pharmacologically increasing the arousal threshold can reduce OSA severity (Eckert et al., 2014a, 2014b). In OSA patients with LAT, strategies to raise the arousal threshold could resolve OSA by preserving sleep and facilitating upper airway muscle activity (Eckert et al., 2014a, 2014b). The arousal threshold is strongly related to several markers of sleep apnea severity, including apnea-hypopnea index (AHI), nadir oxygen saturation, the fraction of hypopnea events et al. (Edwards et al., 2014). According to a developed clinical screening tool, OSA patients with LAT could be identified noninvasively (Edwards et al., 2014).

The risk factors associated with the occurrence of OSA include older age, male sex, obesity, and predisposing craniofacial abnormalities (Cistulli, 1996; Senaratna et al., 2017; Sharma et al., 2006). Emerging evidence supported the adverse influence of air pollution on sleep health and sleep quality (Cao et al., 2021; Liu et al., 2020b). Either long-term or short-term exposure to ambient air pollution may associate with sleep-disordered breathing and OSA by increasing the respiratory disturbance index (RDI), AHI, oxygen desaturation index (ODI), or decreasing the sleep duration and sleep efficiency (Billings et al., 2019; Lappharat et al., 2018; Shen et al., 2018; Weinreich et al., 2015; Zanobetti et al., 2010). However, the associations between air pollution and sleep measures may vary across the different exposure assessment methods, time of the exposure windows, seasons, and geographical areas (Clark et al., 2020). Furthermore, no studies have examined the association of ambient air pollution with the subtypes of OSA up to date.

We designed this cross-sectional study using information collected from the patients from a sleep center in Taipei, Taiwan, to evaluate the associations of traffic-related air pollution exposure with sleep-disordered measures and two types of OSA. We identified the OSA patients with or without LAT by the developed non-invasive clinical screening tool (Edwards et al., 2014). We adopted the residential exposures to $PM_{2.5}$ and NO_2 (the annual mean concentrations in 2019 for each participant) estimated from a validated land-use regression model in a recently published study to denote the spatial variation of the exposure (Z. Li et al., 2020). We then incorporated monitoring data averaged over the previous 0–1, 0–3, 0–6 days, and one month, one year, and two years before the date of the sleep center visit to represent both short-term and long-term pollution exposure for each participant. We hypothesized that exposure to traffic-related pollutants might be associated with sleep-disordered breathing and OSA.

2. Materials and methods

2.1. Study participants

This cross-sectional study consisted of 4634 participants from Taipei metropolitan area including Taipei and New Taipei City. They were recruited from the sleep center of Taipei Medical University Hospital from January 2015 to April 2019 and spatially distributed in the urban area (**Fig. 1**). The selection criteria were the sleep center visitors in the age range of 20–85 without cardiopulmonary diseases, central sleep apnea, mixed sleep apnea, etc. As alcohol and caffeine may change sleep patterns and make symptoms of some sleep disorders worse, the participants have been advised to avoid drinks or food containing alcohol or caffeine during the afternoon and evening before polysomnography. Napping in the afternoon before a sleep study is discouraged. The OSA with or without LAT for each participant was identified according to parameters measured by overnight polysomnography. Personal exposure to ambient air pollution was estimated by the spatial-temporal model. Such study protocol was approved by the joint institutional review board at the Taipei Medical University in Taipei, Taiwan (TMU-JIRB No.:N201910048). Patient consents for inclusion in the study are not necessary as the data used in the current study were retrospective data and the patients could not be identifiable.

All participants have been covered by the universal National Health Insurance and most of them have bought private insurance to fully reimburse their medical expenses for the sleep center visit (Wu et al., 2010). We used the average family income by the district level collected from the Taiwan Ministry of Finance based on the 2012 tax statistics to define the indicator of neighbourhood social-economic status (SES) for the participants according to their residential addresses (Chen et al., 2020; Chuang et al., 2022).

2.2. Polysomnography

We used in-laboratory polysomnography (Embla N7000, Medcare, Iceland) and its related analytic software (Somnologica, Medcare, Iceland) to perform overnight polysomnographic analysis (Biernacka and Douglas, 1993). American Academy of Sleep Medicine (AASM) criteria were used to score apneas, hypopneas, and arousals (Ruehland et al., 2009).

We collected the essential characteristics of all participants, including age, sex, body mass index (BMI), and neck and waist circumference, which would affect the sleep parameters of interest as previous studies observed (Liu et al., 2016; Shen et al., 2018). Sleep parameters measured by polysomnography for the current study included total sleep time (TST, min), sleep efficiency (SE, measured as the total sleep time divided by the total time in bed, %), wake after sleep onset (WASO, min), events of apnea and hypopnea per hour (AHI), and events of arousal per hour (arousal index) including spontaneous and respiratory arousal index. Arterial mean and minimum oxygen saturation (SaO_2, %) were measured by pulse oximetry.

2.3. Personal air pollution exposure

We collected ambient air pollution ($PM_{2.5}$ and NO_2) and weather data (temperature and relative humidity) between January 2013 and December 2019 from air monitoring stations operated by the Taiwan Environmental Protection Administration (EPA) Taiwan (TWEPA, 2020). Hourly monitoring data from 7 stations in Taipei and 12 stations in New Taipei City were used but excluding one national park station and two background stations, leaving 16 stations (**Fig. 1**) to compute the daily 24-hr mean concentrations of $PM_{2.5}$ and NO_2. We calculated the moving averages of lag 0–1, 0–3, 0–6, 0–30, 0–365, 0–730 days' concentrations and merged them with the polysomnography data by the date of the sleep center visit. Such moving averages represented the short-, medium-, and long-term pollution levels proceeding the sleep

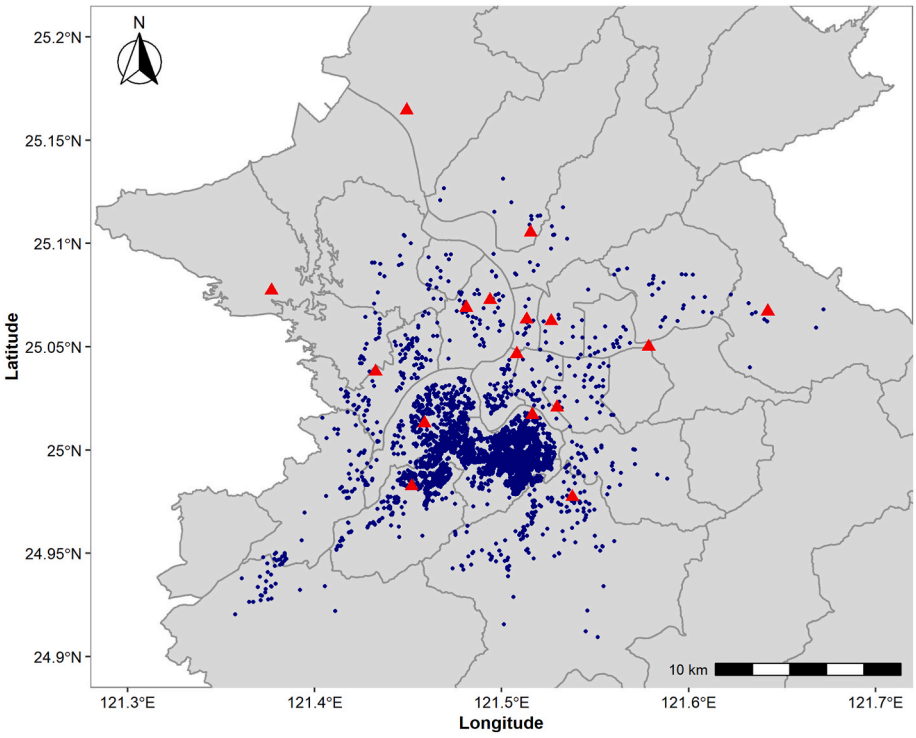

Fig. 1. The spatial distribution of the participants (dark blue dot) and the location of the air pollution monitoring stations (red triangle) in the Taipei metropolitan area.

measures, respectively, and captured the temporal variations of the ambient pollution exposure (Fang et al., 2015; Shen et al., 2018; Zanobetti et al., 2010).

Residential exposure to air pollution has been assessed by a validated land-use regression (LUR) model to represent each participant's annual mean exposure at his or her address in 2019 (Z. Li et al., 2020). In brief, the LUR models were developed with the supervised forward linear regression approach, using $PM_{2.5}$ and NO_2 measured from the fixed-site stations as the dependent variables and population density, road network, land-use type, normalized difference vegetation index, meteorology, and elevation as predictor variables. These LUR-model-based air pollution exposure estimates captured the spatial variability in exposure for participants in a sleep cohort (Z. Li et al., 2020). We used such estimates divided by the annual mean pollutant level of the Taipei metropolitan area in 2019 to denote the spatial variations of the personal exposure level for the participants in this study, assuming that the identified predictors of LUR (population density, road network, land-use type, vegetation index, and elevation et al.) for $PM_{2.5}$ and NO_2 were not significantly changed in the past five years (the study period of 2015–2019). We then incorporated the spatial variations by multiplying the up-mentioned moving averages to estimate the personal exposure of each participant, taking both spatial and temporal variation into account simultaneously (Yang et al., 2018).

Personal ambient temperature and relative humidity (RH) exposure were estimated from the nearest air monitoring station according to the residential address of each participant (Shen et al., 2018).

2.4. Statistical analysis

TST in minutes, SE in percentiles (%), and WSAO in minutes were treated as continuous variables. TST and SE approximately exhibited normal distribution. WASO showed a positively skewed distribution and was log-transformed after adding 1 before fitting the model. We used a generalized linear regression model to estimate the absolute change of TST and SE and the percent change of WASO associated with an interquartile range (IQR) increment of personal pollution exposure.

According to a developed clinical tool, we identified the low arousal threshold (LAT) as with at least two of the following conditions: 1) AHI $<$30 events per hour; 2) minimum $SaO_2 > 82.5\%$; and 3) the fractions of hypopnea events $>$58.3% (Edwards et al., 2014). The participants were then further categorized into three groups: non-OSA patients (AHI$<$5/hr), OSA patients with LAT (AHI $\geq$ 5/hr and LAT $= 1$), and OSA patients without LAT (AHI $\geq$ 5/hr and LAT $= 0$). We fit a multinomial logistic regression model to estimate the relative risk ratio (RRR) of OSA with or without LAT associated with an IQR increment of personal pollution exposure, compared with non-OSA patients.

To control for potential confounders, we included several covariates in the model for adjustment. We adjusted for the essential characteristics of each participant, such as age, sex, BMI, neck, and waist circumference, which may affect the sleep parameters of interest in this study. We adjusted for the neighbourhood SES by including a three-level indicator (low, medium, and high) in the model using the tertiles of the family income as the cut-off points. Because we recruited the patients from the sleep center for around five years, both sleep measures and pollutant exposures exhibited seasonality and long-term trends (Cassol et al., 2012; Cheng et al., 2019). We, therefore, included a natural spline with 3 degrees of freedom (*df*) per year for the date of the sleep center visit to control the effect of seasonality and possible long-term trends (Qiu et al., 2020). We also included the natural splines with 5 *df* for mean temperature and RH exposure at lag0-6 in the model to adjust for the potential non-linear effects of weather conditions in the past week (Shen et al., 2018). We included the personal exposures of proceeding 0–1, 0–3, 0–6, 0–30, 0–365, 0–730 lag days into the model one at a time to assess the associations with both short-term and long-term exposure to $PM_{2.5}$ and NO_2.

We conducted two-pollutant models as the sensitivity analysis to test the robustness of the associations of $PM_{2.5}$ and NO_2 with sleep measures and the risk of two OSA subtypes while controlling the confounding from each other. We also followed Zanobetti's approach by including both the 365-day moving averages of $PM_{2.5}$ and NO_2 (long-term effects)

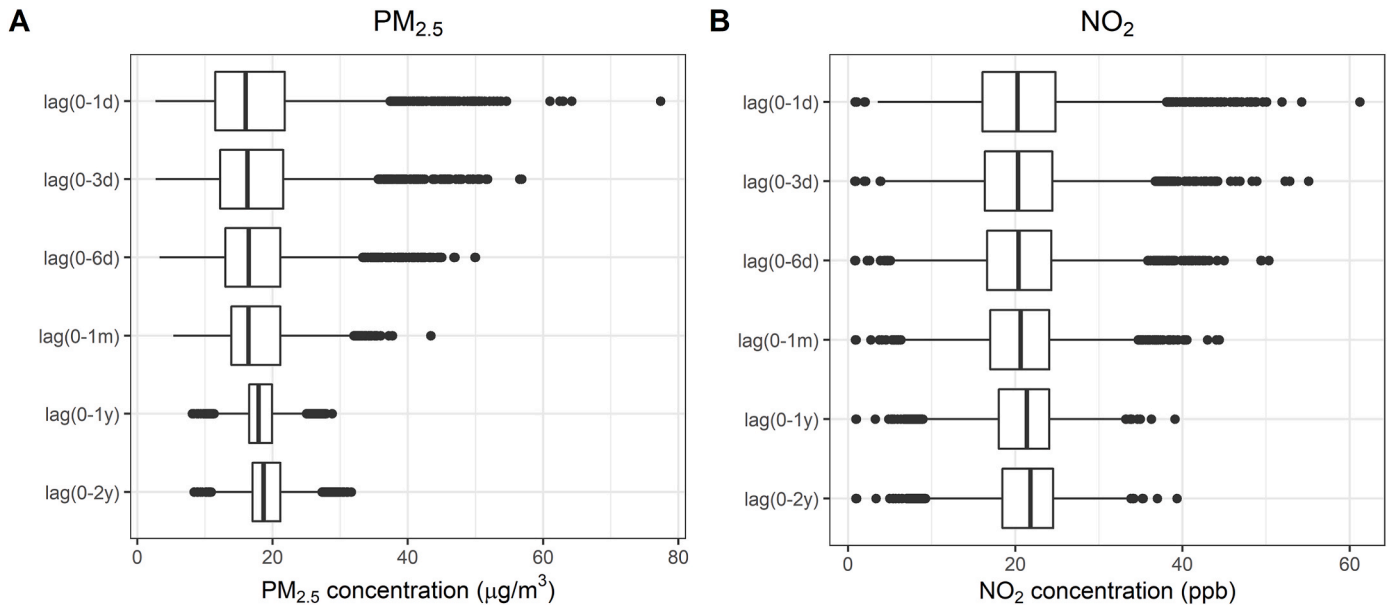

Fig. 2. Distribution of the personal exposure to both short-term and long-term traffic-related air pollution ('d' for day, 'm' for month, and 'y' for year).

Table 1
The essential characteristics, sleep measures, and environmental exposures at lag0 for the patients from the sleep center, Taipei metropolitan area.

	All patients (N = 4634)	Non-OSA (N = 1063)	OSA (N = 3571)	LAT OSA (N = 2222)	OSA without LAT (N = 1349)	P-value [a]
Basic characteristics						
Age (yrs)	49.6 (13.6)	45.4 (13.9)	50.9 (13.2)	51.6 (13.4)	49.7 (12.8)	<0.01
Sex: Male (N (%))	3075 (66.4)	441 (41.5)	2634 (73.8)	1527 (68.7)	1107 (82.1)	<0.01
BMI (kg/m^2)	26.7 (4.9)	23.3 (3.3)	27.7 (4.8)	26.7 (4.4)	29.4 (5.1)	<0.01
Neck (cm)	37.5 (4.2)	34.3 (3.4)	38.4 (4.0)	37.6 (3.7)	39.9 (4.0)	<0.01
Waist (cm)	91.0 (13.1)	80.2 (10.0)	98.8 (12.2)	91.4 (11.2)	98.8 (12.3)	<0.01
Neighbourhood SES [b]						0.07
Low	779 (16.8)	193 (18.2)	586 (16.4)	345 (15.5)	241 (17.9)	
Medium	2545 (54.9)	583 (54.8)	1962 (54.9)	1256 (56.5)	706 (52.3)	
High	1310 (28.3)	287 (27.0)	1023 (28.6)	621 (27.9)	402 (29.8)	
Sleep measures						
Total Sleep Time (hr)	4.6 (1.1)	4.6 (1.1)	4.6 (1.0)	4.5 (1.1)	4.7 (0.9)	<0.01
Sleep Efficiency (%)	75.8 (17.1)	75.7 (18.2)	75.9 (16.7)	74.6 (17.6)	77.9 (15.0)	<0.01
Wake after sleep onset (min) [c]	49.5 (25.5, 86.0)	42.0 (20.5, 84.5)	51.5 (26.5, 86.5)	52.5 (26.5, 90.0)	49.0 (27.0, 81.0)	0.03
AHI (events/hr) [c]	18.2 (5.9, 40.7)	1.5 (0.4, 3.1)	26.4 (13.5, 48.9)	16.8 (10.3, 25.8)	53.8 (39.4, 72.5)	<0.01
Arousal Index (events/hr) [c]	19.7 (12.2, 31.5)	12.8 (8.3, 18.7)	22.6 (14.4, 35.3)	18.8 (12.5, 27.5)	33.3 (21.0, 52.0)	<0.01
Respiratory Arousal Index [c]	4.6 (1.2, 13.4)	0.3 (0, 0.9)	7.3 (3.2, 17.3)	4.4 (2.3, 8.3)	19.1 (9.9, 35.0)	<0.01
Spontaneous Arousal Index [c]	5.2 (0, 10.9)	6.8 (0, 12.8)	4.8 (0, 10.2)	6.7 (0, 12.7)	2.3 (0, 6.4)	<0.01
Mean SaO_2 (%)	95.6 (2.3)	97.2 (1.1)	95.2 (2.3)	95.9 (1.4)	94.0 (3.0)	<0.01
Environmental factors						
$PM_{2.5}$ (μg/m^3)	17.4 (9.3)	17.4 (9.5)	17.4 (9.2)	17.1 (9.2)	17.8 (9.3)	0.20
NO_2 (ppb)	20.8 (7.8)	20.7 (7.8)	20.8 (7.7)	20.8 (7.8)	20.9 (7.6)	0.61
Temperature (°C)	24.2 (5.5)	24.1 (5.5)	24.2 (5.5)	24.2 (5.4)	24.3 (5.5)	0.35
Relative Humidity (%)	71.6 (9.2)	71.5 (9.0)	71.7 (9.2)	71.8 (9.2)	71.5 (9.2)	0.79

Abbreviations: BMI, body mass index; SES, social-economic status; AHI, apnea-hypopnea index; SaO_2, arterial oxygen saturation; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; OSA, obstructive sleep apnea; LAT, low arousal threshold.

[a] P-values are obtained from one-way ANOVA for continuous variables and Chi-square test for categorical variables for comparison among Non-OSA, LAT OSA, and OSA without LAT groups.

[b] The neighbourhood SES was identified by the family income in the district level and categorized into low, medium, and high group using the tertiles as the cut-offs.

[c] These variables are skewed distributed, described as median (25th,75th percentiles), and logarithm transformation in the test. Other variables are approximately normally distributed and described as mean (standard deviation).

and the differences between the daily measures of these two predictors and their 365-day average (short-term effects) in the two-pollutant model to test the effects of long-term and short-term exposures simultaneously (Zanobetti et al., 2010).

The effect estimates are presented as the absolute change in TST and SE or percent change in WASO, or relative risk ratio (RRR) of OSA with or without LAT compared with non-OSA, along with the 95% confidence interval (CI) associated with an IQR increment in personal pollution exposure. All analyses were conducted within the R statistical environment version 3.5.3 using the packages "mgcv" and "nnet" to fit a generalized linear model and multinomial logistic regression, respectively (R Core Team, 2019).

3. Results

Fig. 1 shows the spatial distribution of the participants and the location of the sixteen air pollution monitoring stations in the Taipei metropolitan area. The distribution of the personal exposure to both

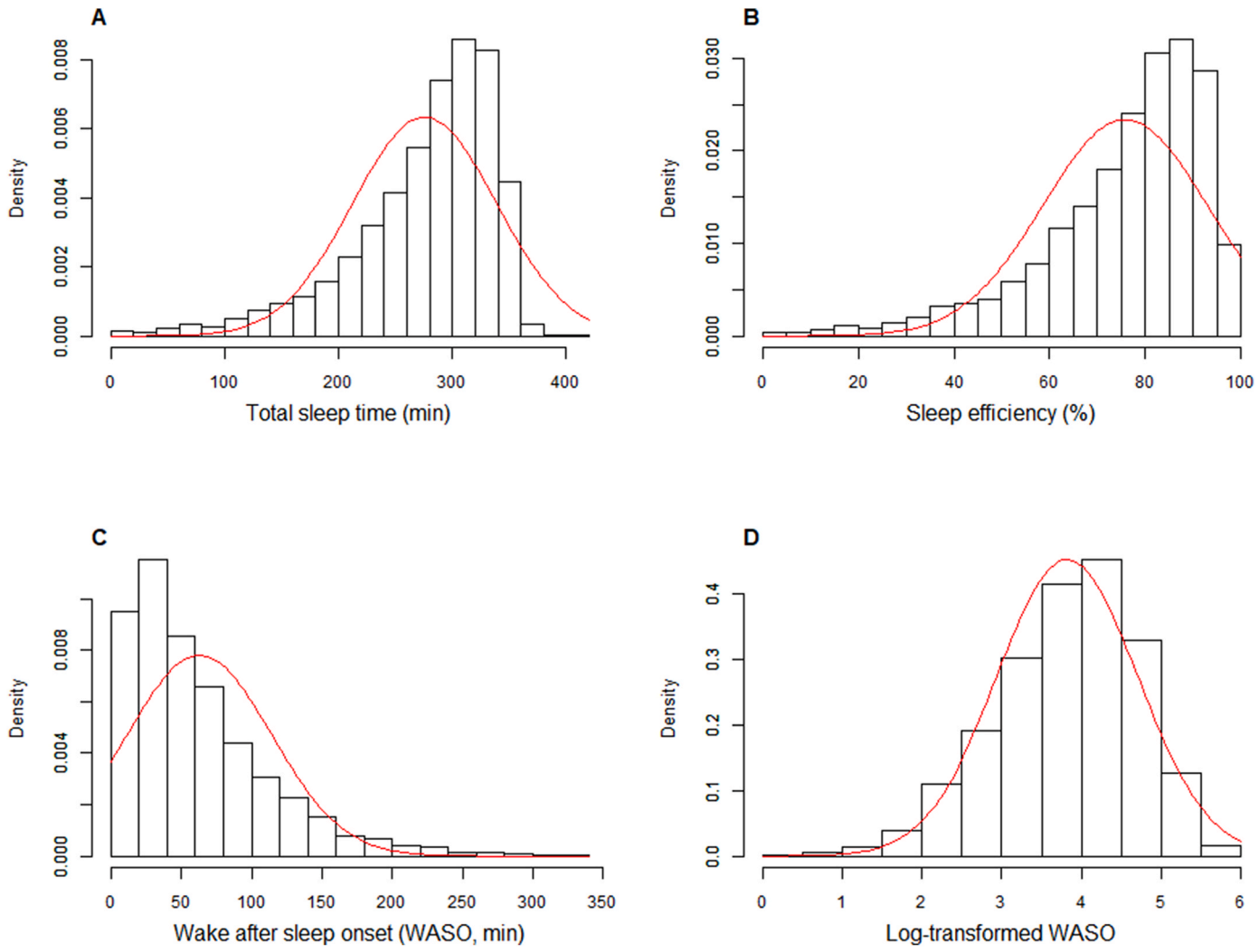

Fig. 3. Distribution of the total sleep time, sleep efficiency and wake after sleep onset.

short-term and long-term $PM_{2.5}$ and NO_2 is shown in Fig. 2, with the IQR presented as the width of the boxplot.

Among the 4634 sleep-disordered participants, 1063 were non-OSA patients, 2222 were LAT OSA, and 1349 were OSA without LAT. Compared with non-OSA, OSA patients had significant older age, higher BMI, more oversized neck and waist circumference, and a higher prevalence of men (Table 1). OSA without LAT patients tended to be in the higher neighbourhood SES than LAT OSA and non-OSA ($p = 0.07$). WASO is an indicator of sleep fragments; longer WASO time indicates more sleep interruptions. OSA without LAT (or with high arousal threshold) tended to have more severe OSA characterized by a higher AHI, lower oxygen saturation, more respiratory arousals, and fewer spontaneous arousals, which is consistent with the clinical observations and in the previous studies (Edwards et al., 2014). In contrast, the LAT OSA patients had the lowest total sleep time and sleep efficiency but the longest WASO time and a relatively higher spontaneous arousal index (Table 1). Environmental exposures including $PM_{2.5}$, NO_2, ambient temperature, and RH on the same day of the sleep center visit were statistically non-significant differences among the three patient groups.

Fig. 3 shows the distribution of the sleep measures. WASO exhibited a positively skewed distribution, and it turned to normal distribution after log transformation. We found the associations between pollution exposures and the sleep measures (Table 2). In single-pollutant models, an IQR increment of $PM_{2.5}$ averaged over the past two years (4.1 $\mu g/m^3$) decreased 3.1 min of total sleep time and 0.9% of sleep efficiency, but only with borderline significant. Meanwhile, an IQR increment of NO_2 averaged over the past year (6.0 ppb) decreased 3.5 min of total sleep time, 1% of sleep efficiency, and increased 3.5% of WASO. Further adjusting the confounding from each other in two-pollutant models showed that the effects of $PM_{2.5}$ decreased to null while the effects of medium- and long-term effects of NO_2 changed slightly and kept statistically significant on total sleep time and sleep efficiency (Table 2).

Short- and medium-term exposure to NO_2 was associated with the increased risk of LAT OSA in the single-pollutant model (Table 3). Compared with non-OSA patients, the excess risk of LAT OSA was 15% (2%, 31%) per IQR increment of NO_2 at lag (0-6d) (7.7 ppb). Such effect estimate changed to 21% (5%, 39%) with further adjustment for $PM_{2.5}$ at the same lags. But we did not find the statistically significant associations of NO_2 with the increased relative risk of non-LAT OSA (RRR≈1.08–1.13, $P > 0.05$). We also did not find any associations of $PM_{2.5}$ with OSA (with or without LAT).

Further sensitivity analysis with both long-term and short-term exposure to $PM_{2.5}$ and NO_2 included in two-pollutant models simultaneously confirmed the most robust associations of long-term NO_2 exposure with sleep measures (Table 4). An IQR increment of NO_2 averaged over the past year (6.0 ppb) decreased 3.32 (0.45, 6.18) minutes of total sleep time and 0.85% (0.08%, 1.63%) of sleep efficiency.

Table 2
Effect estimates (95% CI) on sleep measures associated with an IQR increment of personal pollution exposure in single- and two-pollutant models by lags[a].

Pollution exposures [b]	Total Sleep Time (min) (Abs. change)	Sleep Efficiency (%) (Abs. Change)	Wake After Sleep Onset (min) (% change)
$PM_{2.5}$ (μg/m^3) (Single-plt model)			
Lag(0-1d) (IQR = 10.3)	−1.02 (−3.55, 1.52)	−0.29 (−0.98, 0.39)	−1.40 (−4.74, 2.05)
Lag(0-3d) (IQR = 9.3)	−1.40 (−4.22, 1.43)	−0.40 (−1.16, 0.37)	−0.52 (−4.27, 3.27)
Lag(0-6d) (IQR = 8.1)	−1.98 (−5.00, 1.05)	−0.60 (−1.42, 0.21)	1.06 (−3.01, 5.30)
Lag(0-1m) (IQR = 7.2)	−2.03 (−6.59, 2.53)	−0.57 (−1.80, 0.66)	4.52 (−1.75, 11.2)
Lag(0-1y) (IQR = 3.4)	−2.62 (−5.70, 0.46)	−0.79 (−1.63, 0.04)	2.31 (−1.88, 6.68)
Lag(0-2y) (IQR = 4.1)	−3.05 (−6.56, 0.46)	−0.92 (−1.87, 0.03)	2.74 (−2.05, 7.76)
NO_2 (ppb) (Single-plt model)			
Lag(0-1d) (IQR = 8.8)	−1.58 (−3.98, 0.83)	−0.48 (−1.13, 0.17)	0.97 (−2.27, 4.32)
Lag(0-3d) (IQR = 8.1)	−2.19 (−4.65, 0.28)	−0.64 (−1.30, 0.03)	1.80 (−1.55, 5.27)
Lag(0-6d) (IQR = 7.7)	**−2.66 (-5.23, -0.09)**	**−0.78 (-1.48, -0.08)**	2.80 (−0.73, 6.46)
Lag(0-1m) (IQR = 7.1)	**−3.26 (-6.00, -0.52)**	**−0.91 (-1.66, -0.17)**	3.75 (−0.04, 7.68)
Lag(0-1y) (IQR = 6.0)	**−3.52 (-5.98, -1.05)**	**−0.95 (-1.62, -0.29)**	**3.57 (0.16, 7.10)**
Lag(0-2y) (IQR = 6.1)	**−3.51 (-5.95, -1.07)**	**−0.95 (-1.61, -0.29)**	**3.54 (0.17, 7.03)**
NO_2 adjusted for $PM_{2.5}$ at the same lags (Two-plt model)			
Lag(0-1d) (IQR = 8.8)	−1.47 (−4.26, 1.33)	−0.46 (−1.22, 0.29)	2.25 (−1.56, 6.21)
Lag(0-3d) (IQR = 8.1)	−2.12 (−5.00, 0.76)	−0.63 (−1.41, 0.15)	2.80 (−1.14, 6.90)
Lag(0-6d) (IQR = 7.7)	−2.42 (−5.38, 0.53)	−0.70 (−1.49, 0.10)	3.11 (−0.94, 7.34)
Lag(0-1m) (IQR = 7.1)	**−3.47 (-6.59, -0.35)**	**−0.97 (-1.81, -0.13)**	3.11 (−1.11, 7.63)
Lag(0-1y) (IQR = 6.0)	**−3.30 (-6.17, -0.44)**	**−0.85 (-1.62, -0.07)**	3.54 (−0.41, 7.65)
Lag(0-2y) (IQR = 6.1)	**−3.28 (-6.11, -0.45)**	**−0.84 (-1.61, -0.08)**	3.46 (−0.44, 7.52)

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; IQR, inter-quartile range; CI, confidence interval.

[a] Generalized linear regression model was used while adjusting for the long-term trend, seasonality, weather conditions, essential characteristics of participants (age, sex, BMI, neck and waist circumference), and neighbourhood SES.

[b] 'd' for day, 'm' for month, and 'y' for year.

Table 3
Relative risk ratio (95% CI) of OSA with or without LAT associated with an IQR increment of personal pollution exposure by lags, compared with non-OSA patients[a].

Pollution exposure [b]	Non-OSA (N = 1063)	OSA (N = 3571)	OSA with LAT (N = 2222)	OSA without LAT (N = 1349)
$PM_{2.5}$ (μg/m^3 (Single-plt model)				
Lag(0-1d) (IQR = 10.3)	1.00	1.02 (0.91, 1.15)	1.01 (0.89, 1.14)	1.06 (0.92, 1.21)
Lag(0-3d) (IQR = 9.3)	1.00	1.06 (0.92, 1.21)	1.05 (0.91, 1.20)	1.08 (0.93, 1.26)
Lag(0-6d) (IQR = 8.1)	1.00	1.01 (0.88, 1.17)	1.00 (0.87, 1.15)	1.05 (0.89, 1.23)
Lag(0-1m) (IQR = 7.2)	1.00	1.14 (0.92, 1.41)	1.15 (0.94, 1.40)	1.12 (0.89, 1.41)
Lag(0-1y) (IQR = 3.4)	1.00	1.06 (0.92, 1.23)	1.09 (0.94, 1.25)	1.01 (0.85, 1.18)
Lag(0-2y) (IQR = 4.1)	1.00	1.07 (0.91, 1.26)	1.10 (0.94, 1.28)	1.00 (0.84, 1.20)
NO_2 (ppb) (Single-plt model)				
Lag(0-1d) (IQR = 8.8)	1.00	**1.13 (1.01, 1.27)**	**1.14 (1.01, 1.28)**	1.11 (0.97, 1.27)
Lag(0-3d) (IQR = 8.1)	1.00	**1.13 (1.01, 1.27)**	**1.15 (1.02, 1.29)**	1.10 (0.96, 1.26)
Lag(0-6d) (IQR = 7.7)	1.00	**1.14 (1.01, 1.29)**	**1.15 (1.02, 1.31)**	1.11 (0.96, 1.29)
Lag(0-1m) (IQR = 7.1)	1.00	**1.14 (1.00, 1.30)**	**1.14 (1.00, 1.30)**	1.13 (0.97, 1.32)
Lag(0-1y) (IQR = 6.0)	1.00	1.11 (0.99, 1.24)	1.11 (0.99, 1.25)	1.09 (0.95, 1.25)
Lag(0-2y) (IQR = 6.1)	1.00	1.11 (0.99, 1.24)	1.11 (0.99, 1.25)	1.09 (0.95, 1.25)
NO_2 adjusted for $PM_{2.5}$ at the same lags (Two-plt model)				
Lag(0-1d) (IQR = 8.8)	1.00	**1.17 (1.02, 1.33)**	**1.19 (1.04, 1.36)**	1.11 (0.95, 1.30)
Lag(0-3d) (IQR = 8.1)	1.00	**1.15 (1.00, 1.31)**	**1.17 (1.02, 1.34)**	1.08 (0.92, 1.26)
Lag(0-6d) (IQR = 7.7)	1.00	**1.18 (1.03, 1.36)**	**1.21 (1.05, 1.39)**	1.12 (0.95, 1.32)
Lag(0-1m) (IQR = 7.1)	1.00	1.13 (0.97, 1.31)	1.13 (0.97, 1.31)	1.13 (0.95, 1.34)
Lag(0-1y) (IQR = 6.0)	1.00	1.11 (0.97, 1.27)	1.10 (0.96, 1.27)	1.12 (0.96, 1.32)
Lag(0-2y) (IQR = 6.1)	1.00	1.11 (0.97, 1.27)	1.10 (0.96, 1.26)	1.12 (0.96, 1.31)

Abbreviations: OSA, obstructive sleep apnea; LAT, low arousal threshold; IQR, inter-quartile range; CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide.

[a] Multinomial logistic regression model was applied while adjusting for the long-term trend, seasonality, weather conditions, essential characteristics of participants (age, sex, BMI, neck and waist circumference), and neighbourhood SES.

[b] 'd' for day, 'm' for month, and 'y' for year.

4. Discussion

In the current study, we observed 47.9% of patients from the sleep center with LAT OSA. In these individuals, waking up prematurely is predicted to contribute to their OSA by disrupting sleep continuity and limiting the opportunity for adequate upper airway muscle recruitment to restore airflow during sleep (Eckert et al., 2013). Therefore, we observed the shorter total sleep time, sleep efficiency, and longer WASO time in OSA patients with LAT. We demonstrated that traffic-related air pollutants, $PM_{2.5}$ and NO_2, were associated with decreased total sleep time, sleep efficiency, longer WASO, which was consistent with some previous studies (Fang et al., 2015; L. Li et al., 2020; W. Li et al., 2020; Zanobetti et al., 2010). In a US multicentre Sleep Heart Health Study, the sleep efficiency was decreased by 1.2% for an IQR increment of short-term exposure to PM_{10} (14.5 μg/m^3) in summer (Zanobetti et al., 2010). In a cross-sectional analysis in the UK Biobank study, every 10 μg/m^3 increase of $PM_{2.5}$ reduced sleep duration by 0.14 (95% CI: 0.10–0.18) hours (L. Li et al., 2020). Although some studies have examined the associations of air pollution with the increased AHI (Lappharat et al., 2018; Shen et al., 2018; Weinreich et al., 2015) or the risk of OSA (Billings et al., 2019), the results are not consistent (Clark et al., 2020) and no study has evaluated the influence of air pollutants on the phenotypes of OSA up to date. We observed the most robust associations of long-term NO_2 exposure with sleep measures by 3 min reduction of total sleep time and around a 1% decrease in sleep efficiency. The effect magnitude is small but comparable to previous studies (L. Li et al., 2020; Zanobetti et al., 2010), and its clinical relevance may not be ignored due to the universality of the pollution exposure. In some specific individuals (LAT OSA patients without severe anatomic abnormalities), the LAT may contribute to their OSA pathogenesis, and increasing the arousal threshold is the therapeutic target (Eckert et al., 2014b, 2014a, 2013). Our study also observed the robust association of

Table 4
Associations (95% CI) of both long-term and short-term exposure to $PM_{2.5}$ and NO_2 with sleep measures and OSA phenotypes in two-pollutant models[a].

Exposures	Sleep measures			OSA phenotypes	
	Total Sleep Time (min) (Abs. change)	Sleep Efficiency (%) (Abs. Change)	Wake After Sleep Onset (min) (% change)	OSA with LAT vs. Non-OSA (RRR)	OSA without LAT vs. Non-OSA (RRR)
Long-term $PM_{2.5}$ (IQR = 3.4 μg/m^3)	−0.50 (−4.08, 3.07)	−0.25 (−1.22, 0.72)	0.08 (−4.66, 5.06)	1.02 (0.87, 1.20)	0.93 (0.77, 1.13)
Short-term $PM_{2.5}$ (IQR = 11.3 μg/m^3)	1.84 (−1.20, 4.87)	0.46 (−0.36, 1.28)	0.48 (−3.58, 4.70)	1.03 (0.89, 1.19)	0.93 (0.79, 1.10)
Long-term NO_2 (IQR = 6.0 ppb)	**−3.32 (-6.18, -0.45)**	**−0.85 (-1.63, -0.08)**	3.55 (−0.40, 7.66)	1.10 (0.96, 1.27)	1.12 (0.96, 1.32)
Short-term NO_2 (IQR = 6.4 ppb)	−2.35 (−4.84, 0.14)	−0.53 (−1.20, 0.15)	1.97 (−1.42, 5.48)	0.96 (0.85, 1.08)	1.02 (0.89, 1.17)

Abbreviations: OSA, obstructive sleep apnea; LAT, low arousal threshold; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2, nitrogen dioxide; IQR, inter-quartile range; RRR, relative risk ratio; CI, confidence interval.

[a] Both the 365-day moving averages of $PM_{2.5}$ and NO_2 (long-term effects) and the differences between the daily measures of these two predictors and their 365-day average (short-term effects) were included in the model simultaneously, with adjustment for the temporal trend, weather conditions, essential characteristics of participants, and neighbourhood SES.

short-term NO_2 with a 21% excess risk of LAT OSA, suggesting that an increased arousal threshold might probably reduce the susceptibility to air pollution exposure and benefit this subtype of OSA patients.

Potential mechanisms underlying air pollution exposure on sleep disorders have been summarized in recent systematic reviews, including the pollutants' effects on the physiology of the respiratory system and regulation of the central nervous system, and share similar mechanisms of air pollution with chronic diseases (Cao et al., 2021; Liu et al., 2020a). Exposures to air pollutants are related to the respiratory tract and systemic inflammation, chronic rhinosinusitis, and promote the proliferation of olfactory barriers, and pharyngeal inflammatory responses (Lawrence et al., 2018). The fine particles and gaseous pollutants (e.g., NO_2) may reach the lower respiratory system, induce the formation of secondary oxidation products and oxidative stress, and further reduce the vital capacity of elevating airway resistance, increase upper airway obstruction, and worsen the hypoxia (Zanobetti et al., 2010). The ultrafine particles and nitrogen oxides may also penetrate the central nervous system by changing the levels of neurotransmitters, and the breakdown of protective epithelial barriers, thus disrupting the brain function of sleep regulation (Brockmeyer and D'Angiulli, 2016; Oberdörster et al., 2004). It has been demonstrated that air pollutants could alter serotonin levels, one of the essential neurochemicals regulating the sleep-wake cycles (Chuang et al., 2018). However, the mechanism underlying the specific association between NO_2 and LAT OSA remains unclear. Environmental factors, including air pollution, may cause the increment of spontaneous arousals, leading to LAT OSA with a shorter duration of the apnea and hypopnea events and less hypoxemia. (Butler et al., 2019). Meanwhile, non-LAT OSA has more severe AHI and possibly longer duration of OSA-associated hypoxia, oxidative stress, and chronic inflammation, which may mask the effects of air pollution. Further toxicological studies are required to explore the mechanism underlying the associations of air pollution with the two types of OSA.

There are two main strengths in the current study. Firstly, we used the sleep laboratory-based polysomnography test to diagnose OSA, which is assumed as a gold standard, and a comprehensive examination to identify the OSA with LAT departure from other OSA patients (Biernacka and Douglas, 1993; Edwards et al., 2014). The two phenotypes of OSA have different therapeutic schemes, and our study demonstrated their different susceptibility to air pollution exposure. We suggested that increasing the arousal threshold in treating the LAT OSA patients might also mitigate the effect of traffic-related pollution. Second, we incorporated the spatial variation of the residential exposures to $PM_{2.5}$ and NO_2 estimated from a validated land-use regression model (Z. Li et al., 2020) with the temporal variation of ambient pollution level to quantify the personal exposure for each participant. The spatial-temporal modeling approach allows for spatial and temporal variations of pollution levels with less bias, arguably one of the most robust methods (Keller et al., 2015) than the previous studies using the nearest fixed air monitoring stations to ascertain the pollution exposure level (Cassol et al., 2012; Cheng et al., 2019; Liu et al., 2016; Shen et al., 2018; Weinreich et al., 2015; Zanobetti et al., 2010). The relatively more accurate personal exposure assessment enables us to find the robust associations of traffic-related pollutants with sleep-disordered measures and the association of NO_2 with the risk of LAT OSA.

Meanwhile, some limitations should be noted. Firstly, indoor air quality may be different from outdoor, and we did not measure the indoor pollution level. Using the participants' residential addresses to ascertain air pollution exposure levels may not adequately capture their actual exposure. In the current study, we could not identify the effect of short-term exposure to $PM_{2.5}$ on the sleep-disordered measures in the single-pollutant model. Future research of a panel study design with personal air pollution measurements will capture the personal exposure more accurately and be better to evaluate the short-term effect of pollution on sleep disorders. Secondly, the participants should self-pay the medical expenses for the sleep center visit and polysomnographic analysis, which may not be a representative sample of the general population. Furthermore, the neighbourhood SES was identified at the district level. We didn't collect the information on individual-level SES and lifestyle factors such as tobacco smoking and alcohol drinking, which may also influent the etiology of OSA (Kolla et al., 2018; Krishnan et al., 2014) and induce the potential residual confounding. Unmeasured psychosocial stresses such as noise, medication, and continuous positive airway pressure therapy might also confound the associations between air pollution and sleep disorders. Further questionnaire surveys should collect this personal information for adjustment in the future study.

5. Conclusion

We demonstrated the association of traffic-related air pollution with sleep disorder measures by decreasing the sleep duration and efficiency with more sleep disruption and increasing the risk of OSA with LAT. Mitigating exposure to air pollution may improve sleep quality and reduce the risk of OSA.

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Data availability statements

The data underlying this article are available in the article.

Credit author statement

Hong Qiu: Methodology, Formal analysis, Writing – original draft.

Wen-Te Liu: Resources, Conceptualization, Writing – review & editing. Shang-Yang Lin: Validation, Investigation. Zhi-Yuan Li: Methodology, Data curation. Yan-Su He: Data curation. Steve Hung-Lam Yim: Funding acquisition. Eliza Lai-Yi Wong: Writing – review & editing. Hsiao-Chi Chuang: Conceptualization, Writing – review & editing. Kin-Fai Ho: Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

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.

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