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Indoor air pollution impacts cardiovascular autonomic control during sleep and the inflammatory profile

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ABSTRACT

The present study explores the modifications of cardiovascular autonomic control (CAC) during wake and sleep time and the systemic inflammatory profile associated with exposure to indoor air pollution (IAP) in a cohort of healthy subjects.

Twenty healthy volunteers were enrolled. Indoor levels of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and volatile organic compounds (VOCs) were monitored using a portable detector for 7 days. Together, a 7-day monitoring was performed through a wireless patch that continuously recorded electrocardiogram, respiratory activity and actigraphy. Indexes of CAC during wake and sleep time were derived from the biosignals: heart rate and low-frequency to high-frequency ratio (LF/HF), index of sympathovagal balance with higher values corresponding to a predominance of the sympathetic branch. Cyclic variation of heart rate index (CVHRI events/hour) during sleep, a proxy for the evaluation of sleep apnea, was assessed for each night. After the monitoring, blood samples were collected to assess the inflammatory profile. Regression and correlation analyses were performed.

A positive association between VOC exposure and the CVHRI ($\Delta\% = +0.2\%$ for 1 $\mu g/m^3$ VOCs, $p = 0.008$) was found. The CVHRI was also positively associated with LF/HF during sleep, thus higher CVHRI values corresponded to a shift of the sympathovagal balance towards a sympathetic predominance ($r = 0.52$; $p = 0.018$). NO_2 exposure was positively associated with both the pro-inflammatory biomarker TREM-1 and the anti-inflammatory biomarker IL-10 ($\Delta\% = +1.2\%$ and $\Delta\% = +2.4\%$, for 1 $\mu g/m^3$ NO_2; $p = 0.005$ and $p = 0.022$, respectively).

The study highlights a possible causal relationship between IAP exposure and higher risk of sleep apnea events, associated with impaired CAC during sleep, and a pro-inflammatory state counterbalanced by an increased anti-inflammatory response in healthy subjects. This process may be disrupted in vulnerable populations, leading to a harmful chronic pro-inflammatory profile. Thus, IAP may emerge as a critical and often neglected risk factor for the public health that can be addressed through targeted preventive interventions.

1. Introduction

A substantial portion of human exposure to air pollution may occurs indoors, especially in high-income countries where people typically spend the majority of their time in indoor settings like homes, offices, public buildings, or during commuting (Rumchev et al., 2018),

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(Goldstein et al., 2021), (Blaustein et al., 2024).

Indoor air may contain a wide variety of chemical compounds including particulate matter (PM), volatile organic compounds (VOCs) and nitrogen dioxide (NO_2). Indoor air pollutants could originate from indoor sources (such as building materials, furnishings, consumer and household products, cooking), or they may infiltrate indoor spaces from outdoor origins like vehicle emissions, or derive from chemical reactions from primary pollutants (Campagnolo et al., 2017), (Spinazzè et al., 2020), (Saraga et al., 2023), (Roberts et al., 2021). According to the latest update of the *Global Burden of Disease* study (2019), indoor air pollution was ranked 8th among the main risk factors for premature death and it was attributed to be responsible for the 4.1% of global annual deaths (Ritchie and Roser, 2013), (Bennitt et al., 2021). Potential health effects related to exposure to indoor air pollutants may be relevant, especially among vulnerable population groups (Kumar et al., 2023) with serious impact on cardiovascular morbidity and mortality (Ritchie and Roser, 2013), (Bennitt et al., 2021), (Kumar et al., 2023), (Samet et al., 2016), (Uzoigwe et al., 2013), (Tobaldini et al., 2019). However, the impact of indoor air pollution on cardiovascular health has been recently recognized. In 2021, the World Heart Federation, the American College of Cardiology, the American Heart Association and the European Society of Cardiology published a joint opinion in order to raise awareness among health care providers on the importance of intervention strategies on air quality, especially the indoor one, for cardiovascular benefits (Brauer et al., 2021). Furthermore, this position paper calls for further research on the detrimental connection between cardiovascular disease and air quality. Actually, the pathophysiological mechanisms underlying the impact of indoor air pollution on public health remain insufficiently explored.

Evidence from studies on outdoor air pollution exposure has suggested a potential link with several major cardiovascular risk factors, including a shift of the cardiovascular autonomic control towards a sympathetic predominance, alterations of sleep and a chronic low-grade systemic inflammation (Fiordelisi et al., 2017), (Li et al., 2017), (Niu et al., 2020), (Tobaldini et al., 2018), (Tripathy et al., 2021), (Tsai et al., 2019), (Zhou et al., 2023), (Macchi et al., 2023). However, a direct evaluation of exposure to indoor air pollutants and its impact on these risk mechanisms has not been conducted so far. Thus, the present study aims to explore the modifications of cardiovascular autonomic control during both wakefulness and sleep, as well as the systemic inflammatory profile, associated with exposure to indoor air pollution in a cohort of healthy subjects.

2. Material and methods

2.1. Population of the study

From December 2022 to October 2023, 20 healthy volunteers were enrolled. They had no chronic pathologies and were not under acute or chronic pharmacological treatment. The exclusion criteria were absence of stable sinus rhythm on the electrocardiogram (ECG) (e.g., pacemaker rhythm, atrial fibrillation, extrasystole supra/ventricular), history of surgery in the last 12 months, recent infectious events (<3 months), performance of agonistic physical activity, state of pregnancy and breastfeeding, denial of providing an informed consent. All volunteers were living and working within the Milan metropolitan area, Italy. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the local Ethics Committee "Comitato Etico—Milano Area 2", Milan, Italy (approval code 933_2022bis).

2.2. Study design and procedures

A cross-sectional study was performed. During the screening visit, the study was illustrated to the participants and the informed consent form was collected. Then, each subject underwent a 7-day monitoring session, at the end of which a standardized evaluation was performed.

Specifically, once the screening visit was completed, the participants wore a validated patch monitor (RootiRX; Rooti Labs, Taipei, Taiwan) for the 7-day ECG and actigraphy monitoring (250Hz sampling rate) (Karaoğuz et al., 2019). At the same time, they were given a plug-and-play device for indoor monitoring of air pollutants (AirAssure™ 8144-6 Indoor Air Quality Monitor; TSI, Shoreview, MN, USA). More in detail, this direct-reading device was used to measure continuously (i.e., 1-min resolution) $PM_{2.5}$ (i.e., particulate matter with aerodynamic diameter $\leq$2.5 μm), VOCs and NO_2 indoor concentrations. Participants were instructed on the positioning of the monitor, which was to be placed in the living room of their residences, away from windows, air conditioners and sources of combustion, to obtain representative levels of indoor average exposures. The monitor was left in place for 7 days. A time-activity diary was provided to collect information regarding all in-house activities during the 7-day monitoring (e.g., how many hours were spent indoors; cooking habits; smoke; etc.). Smoking status of each participant was defined as follows: i) smoker, participant who has smoked 100 cigarettes in his/her lifetime and who currently smokes cigarettes; ii) non-smoker, participant who has never smoked, or who has smoked less than 100 cigarettes in his/her lifetime; iii) former smoker, participant who has smoked at least 100 cigarettes in his/her lifetime but who had quit smoking at the time of the interview. The participants were also asked if they smoked e-cigarettes. Furthermore, an ad-hoc questionnaire was administered regarding housing characteristics, such as number of people living in the apartment, smoking habits of each individual if more than one cohabitant, place chosen for smoking (at the window, on the balcony, apartment's room), type of hob (gas or induction), heating type, presence of domestic animals.

At the end of the 7 days of monitoring, healthy volunteers were asked to return to the laboratory for the evaluation session. A blood sample was then withdrawn for the subsequent analysis of systemic inflammatory biomarkers and the Pittsburgh Sleep Quality Index (PSQI) was administered for the evaluation of subjective quality of sleep (Curcio et al., 2013).

2.3. 7-Day ECG and actigraphy monitoring data analysis

The ECG and actigraphy biosignals acquired from 7-day monitoring via patch devices were processed by AI (Rooti Labs, Taipei City, Taiwan) to obtain indexes of cardiovascular autonomic control during wakefulness and sleep. In particular, the average heart rate (HR) during sleep and wakefulness was assessed for each participant. An index of sympathovagal balance was derived through the analysis of heart rate variability in the frequency domain, i.e. the ratio between the relative power of the low-frequency band (LF, range 0.04–0.15 Hz) to relative power of the high-frequency band (HF, 0.15–0.4 Hz), or LF/HF index. Higher values of LF/HF correspond to a predominance of the sympathetic branch (Shaffer et al., 2014). As regards the sleep period, the average value of cyclic variation of heart rate index (CVHRI n° events/hour) over the 7 days was obtained. The cyclic variation of heart rate is a characteristic pattern of heart rate variability represented by bradycardia during apnoea and transient tachycardia during apnoea cessation for individual apnoeic episodes (Hayano and Yuda, 2021). The cyclic variation of heart rate (CVHR) detection was performed through an autocorrelated wave detection algorithm with adaptive threshold (Hayano et al., 2011a). Valid CVHR events were defined as at least 3 consecutive cycles of increase in heart rate (>6 beats/min) lasting for 10–120 s (Hsu et al.). The CVHR index (CVHRI) was then calculated as the mean number of CVHR events per hour of sleep. The CHVRI closely correlated with the apnoea–hypopnoea index (AHI), which is one of the most widely used parameters in the clinical field for the investigation of sleep-disordered breathing (Hsu et al.), (Hayano et al., 2011b). In particular, data on both subjects referred for diagnostic sleep studies and general population demonstrated that the CVHRI performed well in identifying patients with a AHI $\geq$15 per hour, with a predetermined

CVHRI threshold of ≥15 per hour (sensitivity from 83% to 88% and specificity from 88% to 97%) (Hayano et al., 2011a), (Hayano et al., 2013). The benefit of evaluating the CVHRI by the use of a patch ECG Holter monitor is linked to the less invasiveness and greater comfort for the recorded subject compared to the performance of a classic polysomnography (Penzel et al., 2020). Therefore, the evaluation can be continued for several nights and with results more in line with the natural condition of the subject thanks to the reduction of instrumentation interference with sleep.

2.4. Indoor air quality monitoring data analysis

Daily mean indoor concentrations of $PM_{2.5}$, VOCs and NO_2 were obtained from AirAssure™ 8144-6 Indoor Air Quality Monitor for each enrolled subject. To improve data quality, comparative sessions between all the PM direct-reading monitors and a gravimetric gold standard instrument for $PM_{2.5}$ (Harvard Impactor MS&T Area Sampler Diagnostic and Engineering, Inc., Harrison, ME, USA, named here as "HI" - Harvard Impactor) were performed periodically in a reference indoor environment. In a nutshell, inter-comparison tests (lasting 6 h per session) allowed to obtain a ratio between results of $PM_{2.5}$ concentrations through the gravimetric method (mean ± standard deviation = 18.7 ± 9.2 μg/m^3) and through direct-reading monitors (9.2 ± 5.2 μg/m^3). These correction factors (2.37 ± 0.51) were then provided, to be applied a posteriori on $PM_{2.5}$ data obtained through each of the direct-reading instruments (Ródenas García et al., 2022), (Spinazzè et al., 2022). HI worked at a flow rate of 10 L/min to collect PM on 37-mm polytetrafluoroethylene filters. Mass concentrations were determined by performing gravimetric analysis following a standardised procedure (EN 12341:2014). Briefly, the filter was conditioned in a controlled environment (temperature, 20 ± 1 °C; relative humidity, 50 ± 5%) for a minimum of 24 h and subsequently weighed before and after the sampling using a microbalance (Gibertini Micro 1000, Novate, Milan, Italy). Quality assurance/quality control details on this procedure can be found in previous studies (Borghi et al., 2017), (Rovelli et al., 2017), (Spinazzé et al., 2017). For each subject, the average daily exposure to $PM_{2.5}$, VOCs and NO_2 were obtained by averaging the exposure values in 24 h for the 7 days of monitoring.

2.5. Outdoor air pollution data analysis

Daily mean outdoor exposures to $PM_{2.5}$ and NO_2 were obtained as daily concentrations from the fixed stations of the regional monitoring service (*Agenzia regionale per la protezione dell'ambiente ARPA Lombardia* https://www.arpalombardia.it/Pages/Aria/qualita-aria.aspx). For each subject, the average daily exposures to $PM_{2.5}$ and NO_2 were obtained by averaging the exposure values in 24 h from the data collected at the station closest to the home and the one closest to the work address.

2.6. Plasma biomarkers analysis

During the evaluation session, all patients underwent venous blood sampling for the assessment of systemic inflammatory markers. Fasting blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 1200 g for 15 min at room temperature to obtain platelet-free plasma, rapidly frozen and stored at −20 °C.

To quantify plasma concentrations of interferon (IFN)-γ, Interleukin (IL)-10, IL-6, Tumor necrosis factor (TNF)-α, soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) and brain derived neurotrophic factor (BDNF), Human Simple Plex assays (ProteinSimple, CA, USA) on Ella device (Ella System, Bio-techne, Minneapolis, MN, USA) were performed (Dysinger et al., 2017). Instrument calibration was executed using the in-cartridge factory standard curve and plasma samples were measured with a dilution according to the manufacturer's instructions (ProteinSimple, CA, USA). A single well was used for each sample, as triplicate assays are performed automatically in the Simple Plex microfluidic platform.

2.7. Self-reported sleep quality assessment

The subjective sleep quality was assessed through the questionnaire PSQI. It is possible to calculate a global score where higher scores indicate greater sleep quality impairment. A global score higher than 5 is considered as an indicator of relevant sleep disturbances (Curcio et al., 2013).

2.8. Statistical analysis

Data were analysed using SPSS Statistics V.27 (IBM, Armonk, New York, USA). The Shapiro-Wilk test was performed to evaluate the normal distribution of the data. Results were expressed as absolute frequency, relative frequency, means and standard deviation (SD) if variable was normally distributed or median and interquartile range (IQR) if variable was not normally distributed. Differences in exposure to indoor air pollutants were assessed between groups for: i) outdoor $PM_{2.5}$ and NO_2 levels higher than the 24-h exposure threshold recommended by WHO, iii) presence of a resident at home who occasionally smokes by the window, iv) presence of gas hob. The Student's t-test or Mann–Whitney *U* test for independent samples according to the data distribution was used. Linear regression models were performed and adjustments were made for the smoking status of participants, as it could be a confounding factor affecting CAC and the inflammatory profile. Dependent variables were log-transformed (base *e*) to achieve normality of models' residuals. Effects of exposure to indoor air pollutants were thus expressed as Δ%, which corresponded to (exp(β)–1) × 100, with a 95% confidence interval (CI), and represented the percentage increase in dependent variables for 1 μg/m^3 increase in indoor air pollutants. A p value < 0.05 was considered statistically significant. All the graphs were created with SigmaPlot 12.5 (Grafiti LLC, Inpixon, California, USA).

3. Results

3.1. Population

Twenty healthy volunteers were enrolled in this study. All enrolment criteria for healthy subjects were met. Nine subjects, out of 20, were enrolled during the winter season, typically the season with the highest concentration of environmental air pollutants in Europe and characterised by a higher percentage of time spent indoor, while the other 11 volunteers were enrolled in summer and autumn, when indoor and outdoor pollutant are expected to be lower. The mean age of the recruited population was 27 years old (range: from 25 to 32 years old), 50% were smokers and 65% female. None of the participants used or had used e-cigarettes. Fifty percent reported a poor sleep quality through the PSQI. These characteristics are listed in Table 1.

3.2. Outdoor and indoor air pollution exposure

According to data reported in Table 1, 14 participants (70%) were exposed to daily outdoor $PM_{2.5}$ levels higher than the 24-h air quality guideline (AQG) level recommended by WHO (>15 μg/m3) (Organization, 2021). Furthermore, 9 participants (45%) were exposed to daily outdoor NO_2 concentrations higher than the 24-h AQG level recommended by WHO (>25 μg/m^3) (Organization, 2021).

Regarding the characteristics that influence exposure to indoor air pollutants, 11 subjects (55%) reported smoking or having a cohabitant who occasionally smokes by the window. All the participants had radiators as heating system and none of them had combustion stoves or fireplaces. Only 3 participants had domestic animals. The gas hob was present in 13 (65%) homes, while 7 (35%) were equipped with an induction hob. Table 1 shows the average 24-h exposures to the main indoor air pollutants obtained from direct monitoring over 7 days.

Table 1
Characteristics of participants and domestic environment. Outdoor and indoor daily average exposure levels to air pollutants. Results are expressed by absolute and relative frequencies, means and standard deviation (SD) if the variable is normally distributed or median and interquartile range (IQR) if the variable is not normally distributed. Abbreviations: PSQI, Pittsburgh Sleep Quality Index; $PM_{2.5}$, fine particulate matter; VOCs, volatile organic compounds; NO_2, nitrogen dioxide.

Characteristic	N° of subjects (percentage), Mean ± SD, Median [IQR]
Enrolment Season	
Winter	9 (45%)
Summer and Autumn	11 (55%)
Age	27 ± 2
Sex (N° of female)	13 (65%)
Poor sleep quality (PSQI score>5)	10 (50%)
Smoking status	
Smoker	10 (50%)
Non-smoker	10 (50%)
Former smoker	0 (0%)
E-cigarette user	0 (0%)
Household inhabitant	
Single inhabitant	6 (30%)
Two inhabitants	12 (60%)
Three inhabitants	1 (5%)
Four inhabitants	1 (5%)
Indoor smoking or smoking by window	11 (55%)
Heating system	
Radiators	20 (100%)
Combustion stove	0 (0%)
Fireplace	0 (0%)
Type of hob	
Gas	13 (65%)
Induction	7 (35%)
Households with domestic animals	3 (15%)
Exposure to outdoor air pollutants	
$PM_{2.5}$ 24h average exposure (μg/m³)	19.1 [12.5–29.4]
NO_2 24h average exposure (μg/m³)	24.3 [19.8–39.8]
$PM_{2.5}$ > 15 μg/m3 (WHO 24-h AQG)	14 (70%)
NO_2 > 25 μg/m3 (WHO 24-h AQG)	9 (45%)
Exposure to indoor air pollutants	
$PM_{2.5}$ 24h average exposure (μg/m³)	18.0 [10.8–35.5]
NO_2 24h average exposure (μg/m³)	16.7 ± 3.6
VOC 24h average exposure (μg/m³)	795 ± 395

Average daily values of indoor exposure to $PM_{2.5}$ were significantly higher in subjects enrolled during days characterized by above-AQG outdoor $PM_{2.5}$ (>15 μg/m³) (Table 2, p = 0.019), whereas average daily values of indoor exposure to NO_2 were not influenced by outdoor NO_2 (Table 2, p = 0.820). The levels of indoor air pollutants were not influenced by the presence of smokers and the type of hob.

3.3. Relationship between indoor air pollution exposure and CAC

Table 3 shows the average values relating to cardiovascular autonomic control obtained from the 7-day monitoring of overall healthy participants. For HR and LF/HF, both the average values over 24 h and the average values during wakefulness and sleep were reported. As regards the CVHRI index, only one subject reported a value greater than the cut-off of 15 events/hour, suggestive of higher risk of sleep apnoea.

Linear regression analysis adjusted for smoking habits of the participants highlighted a significant positive association between average daily exposures to VOCs and the CVHRI (Δ% = +0.2%, 95% CI [0.01–0.3%]; p = 0.008). Higher levels of daily exposure to VOCs corresponded to greater number of cyclic variations in heart rate. The CVHRI was also found to be positively associated with the average value of LF/HF during sleep, therefore higher CVHRI values corresponded to a shift in the sympathovagal balance towards a sympathetic predominance during sleep (see Fig. 1; r = 0.52; p = 0.018). The other pollutants did not show effects on cardiovascular autonomic control.

Table 2
Analysis of average daily indoor exposures to air pollutants based on the main sources. Results are expressed by means and standard deviation (SD), if the variable is normally distributed, or median and interquartile range (IQR), if the variable is not normally distributed. Abbreviations: PM2.5, fine particulate matter; VOCs, volatile organic compounds; NO2, nitrogen dioxide; AQG, air quality guideline.

Groups	Mean ± SD, Median [IQR]	p
$PM_{2.5}$ (μg/m³)		
Outdoor concentration below AQG (≤15 μg/m³)	6.8 [6.1–21.7]	0.019
Outdoor concentration above AQG (>15 μg/m³)	27.5 [14.9–62.6]	
Absence of smokers	19.9 [10.3–36.8]	0.939
Presence of smokers	16.2 [7.1–56.2]	
Induction hob	16.0 [11.2–39.3]	0.874
Gas hob	19.9 [6.8–55.0]	
NO_2 (μg/m³)		
Outdoor concentration below AQG (≤25 μg/m³)	11.8 [2.3–21.6]	0.820
Outdoor concentration above AQG (>25 μg/m³)	18.2 [0.8–31.2]	
Absence of smokers	18.9 ± 21.0	0.588
Presence of smokers	14.8 ± 11.6	
Induction hob	11.0 ± 11.2	0.258
Gas hob	19.7 ± 17.9	
VOCs (μg/m³)		
Absence of indoor smokers	645 ± 288	0.107
Presence of indoor smokers	635 ± 406	
Induction hob	598 ± 217	0.102
Gas hob	902 ± 434	

Table 3
Cardiovascular autonomic control during 24 h, wakefulness and sleep. Abbreviations: HR, heart rate; LF/HF, low frequency to high frequency ratio; CVHRI, cyclic variation of heart rate index.

Cardiovascular index	Mean ± SD, Median [IQR]
HR during 24 h (bpm)	77 ± 6
HR during wake time (bpm)	86 ± 7
HR during sleep time (bpm)	65 ± 6
LF/HF during 24 h	2.49 [2.18–2.90]
LF/HF during wake time	2.57 [2.40–3.36]
LF/HF during sleep time	2.15 ± 0.56
CVHRI events/h	5.0 [3.0–6.0]

3.4. Relationship between indoor air pollution exposure and systemic inflammation

At the end of the 7-day monitoring, blood samples were collected to assess the inflammatory profile. Table 4 shows the mean values of the main systemic inflammatory biomarkers related to the entire cohort.

Linear regression analysis adjusted for smoking habits of the participants highlighted a significant positive association between daily exposure values to NO_2 and the pro-inflammatory biomarker sTREM-1 (Δ% = +1.2%, 95% CI [0.4–1.9%]; p = 0.005). Moreover, daily exposure values to NO_2 were also positively associated with the anti-inflammatory biomarker IL-10 (Δ% = +2.4%, 95% CI [0.4–4.4%]; p = 0.022). Thus, higher levels of indoor exposure to NO_2 were associated with both higher levels of a pro-inflammatory biomarker and of anti-inflammatory biomarker, as shown in Fig. 2. The other pollutants did

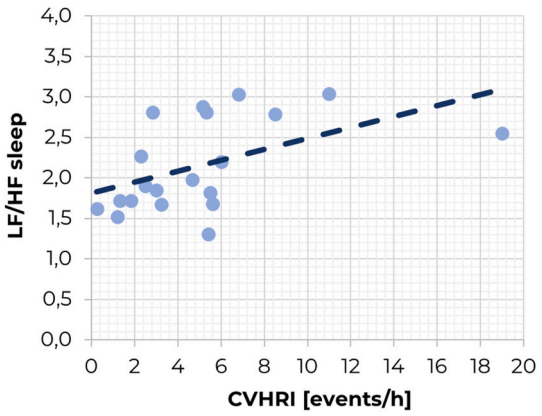

Fig. 1. Association between the number of cyclic variation in heart rate, index of sleep apnea risk, and the LF/HF index during sleep, index of the sympathovagal balance.

Table 4
Mean values of systemic pro- and anti-inflammatory biomarkers. Abbreviations: IFN-γ, interferon-γ; IL-10, Interleukin-10; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-α; sTREM-1, soluble Triggering Receptor Expressed on Myeloid Cells-1; BDNF, brain derived neurotrophic factor.

Inflammatory biomarker	Mean ± SD, Median [IQR] pg/mL
IFN-ϒ	0.55 [0.38–0.99]
IL-6	1.09 [0.78–1.35]
TNF-α	7.22 ± 1.20
IL-10	1.09 [0.78–1.35]
BDNF	9813 ± 6016
sTREM-1	230 [205–285]

not show effects on systemic inflammatory profile.

4. Discussion

The aim of the study was to explore the association between indoor air pollution exposure, the state of cardiovascular autonomic control during wake and sleep time and systemic inflammatory profile.

Our major findings are: i) a positive association between VOC exposure and CVHRI during sleep, which is related to a shift of the sympathovagal balance towards a sympathetic predominance; ii) a positive association between NO_2 daily exposure and both sTREM-1 and IL-10, a pro-inflammatory and anti-inflammatory biomarker respectively.

The study results indicate that daily indoor levels of $PM_{2.5}$, NO_2, and VOCs generally align with those observed in previous research on indoor air pollutants in urban areas (Cibella et al., 2015), (Cattaneo et al., 2011), (Kozielska et al., 2020).

Concerning the relationship between domestic air pollutants and sleep, poor indoor air quality has been linked to lower sleep efficiency (Liao et al., 2019), an increased risk of developing sleep apnoea (Billings et al., 2019), as well as a greater severity of the disorder in patients suffering from sleep apnoea (Lappharat et al.), (Qiu et al., 2022). One study focusing on children demonstrated improvements in sleep quality and respiratory symptoms following interventions such as substituting polluting stoves with improved alternatives (Accinelli et al., 2014). However, indoor pollutant levels were directly monitored only in the studies of Liao et al. and Lappharat et al. (Liao et al., 2019), (Lappharat et al.), while spatiotemporal models were used in others (Billings et al., 2019), (Qiu et al., 2022). Additionally, most studies primarily focused on PM and NO_2 levels, neglecting the assessment of VOCs, which however are significant indoor air pollutants.

VOCs, including common solvents like benzene, toluene, chloroform, and aldehydes, originate from various sources such as building materials, paints, cleaning agents, flooring, carpets, pressed wood, air fresheners, cosmetics, deodorants, gas and wood burning stoves, and tobacco smoke (Tsai, 2019). These compounds are implicated in cardiovascular alterations resulting from indoor air pollution. Only a few studies have shown that both short-term and 24-h exposure to VOCs can disrupt cardiovascular autonomic control, leading to reduced heart rate variability and suppression of the parasympathetic autonomic component in healthy individuals (Mizukoshi et al., 2010), (Ji et al., 2023). This alteration poses a risk factor for adverse cardiovascular events (Thayer and Lane, 2007). Our findings are consistent with these observations, as we found that higher levels of VOC exposure over 24 h were associated with an elevated CVHRI.

The CVHRI, characterized by bradycardia during apnoea and transient tachycardia during apnoea cessation, serves as a proxy for evaluating sleep apnoea events (Hayano and Yuda, 2021). Our results indicate that CVHRI was linked with a sympathetic predominance during sleep, suggesting a possible connection between indoor VOC exposure and the alteration of cardiovascular autonomic control during sleep in healthy individuals.

Regarding the effects of air pollution on the inflammatory profile, both short- and long-term exposures to ambient NO_2 were associated with increased levels of systemic pro-inflammatory biomarkers (Xu et al., 2022), (Liu et al., 2022). However, once again, there is a lack of studies that evaluate this relationship through direct detection of indoor NO_2 levels. Notably, significant indoor sources of NO_2 include tobacco smoke and various combustion devices like stoves, water heaters, and fireplaces, particularly if not properly maintained. Our results highlighted a positive association between indoor exposure to NO_2 and sTREM-1 in healthy subjects. TREM-1 is a receptor expressed on innate

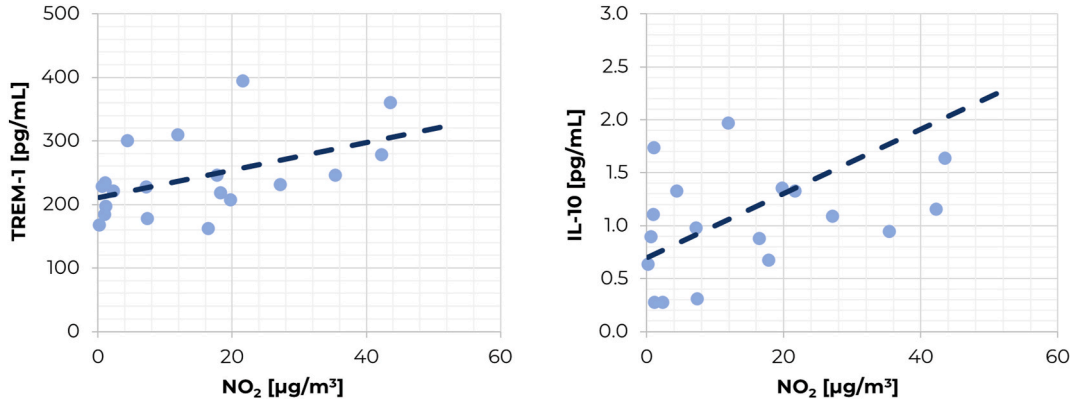

Fig. 2. Association between the daily exposure values to NO2 and the concentration of TREM-1, a pro-inflammatory biomarker, and IL-10, an anti-inflammatory biomarker.

immune cells that amplifies inflammatory responses upon activation (Tammaro et al., 2017). Its soluble form, detected in serum, may stem from the cleavage of membrane-bound receptors (Gómez-Piña et al., 2007). Elevated levels of soluble TREM-1 have been associated with adverse clinical outcomes in both infectious and non-infectious diseases (Tammaro et al., 2017), (de Oliveira et al., 2022). Additionally, we found that indoor NO_2 exposure was associated with increased levels of IL-10, an essential anti-inflammatory cytokine that regulates immune response progression with suppressive effects. Both in vitro studies and research on children residing in highly polluted areas have demonstrated heightened expression and secretion of IL-10 in response to air pollution exposure (Calderón-Garcidueñas et al., 2009), (Gruzieva et al., 2017), (Saito et al., 2002), (Dobreva et al., 2015). Thus, indoor NO_2 exposure could be linked to a systemic pro-inflammatory state, which could be balanced by increased systemic anti-inflammatory activity in healthy individuals. However, this equilibrium may be disrupted in vulnerable populations, such as those with acute or chronic diseases or the elderly, leading to a chronic pro-inflammatory state.

Both murine and human exposure models have demonstrated that inhaled air pollutants trigger the production of reactive oxygen species upon contact with lung cells (Goossens et al., 2021), (Hulin et al., 2012), (Wang et al., 2014). Induction of oxidative stress can lead to cellular damage and activate pro-inflammatory signaling cascades, both locally and systemically (Hulin et al., 2012). These responses can ultimately contribute to respiratory disturbances. Specifically, the pro-inflammatory and edematous condition of the airways may exacerbate restriction and obstruction of normal airflow, potentially leading to respiratory alterations, including sleep breathing disorders (Hulin et al., 2012), (Liu et al., 2020). Finally, since the autonomic nervous system function is extremely integrated and linked by bidirectional relationships with other systems, air pollution-induced changes in the airways, stimulation of baro- and chemo-reflexes, induction of systemic inflammatory responses, and sleep breathing disorders can collectively affect cardiovascular autonomic control (Bellocchi et al., 2022), (Perez et al., 2015), (Tobaldini et al., 2013). Therefore, these various stimuli may lead to sympathetic predominance, which, if prolonged, determines a harmful pathophysiological substrate for the development of cardiovascular diseases (Thayer et al., 2010).

Future studies on air pollution will have to integrate all these aspects, thus considering the phenomenon in its complexity and evaluating the interplay between airway inflammation, alterations in cardiovascular autonomic control, and systemic inflammatory profile. Additionally, it will be valuable to investigate these relationships within vulnerable populations, such as patients suffering from sleep disorders, respiratory or cardiovascular diseases.

5. Conclusion

Our findings suggest that exposure to indoor air pollutants, specifically to VOCs and NO_2, is associated a heightened risk of sleep apnoea events, characterized by altered cardiovascular autonomic control with a sympathetic predominance. Furthermore, our study unveils a positive association between indoor NO_2 exposure and systemic inflammatory biomarkers, suggesting a multifaceted interaction among inflammation, alterations in cardiovascular autonomic control, and sleep. Further investigations on the pathophysiological mechanisms linked to indoor air pollution exposure could provide new insights into the progression of chronic diseases, especially cardiovascular conditions. Thus, both from our current findings and future research, indoor air pollution may emerge as a critical and often neglected cardiovascular risk factor that can be addressed through targeted preventive interventions. By implementing measures to improve indoor air quality, such as replacing pollutant sources, enhancing indoor material quality, and employing air purifiers, there exists the potential to improve the health status of inhabitants, especially of vulnerable populations.

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Angelica Carandina: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giacomo Fanti:** Writing – original draft, Validation, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Alessio Carminati:** Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Michele Baroni:** Project administration, Investigation. **Greta Salafia:** Writing – original draft, Methodology, Formal analysis. **Beatrice Arosio:** Writing – review & editing, Data curation. **Chiara Macchi:** Writing – review & editing. **Massimiliano Ruscica:** Writing – review & editing. **Marco Vicenzi:** Writing – review & editing, Supervision. **Stefano Carugo:** Writing – review & editing, Supervision. **Francesca Borghi:** Writing – review & editing, Software, Methodology. **Andrea Spinazzè:** Writing – review & editing, Supervision, Investigation. **Domenico Maria Cavallo:** Writing – review & editing, Supervision. **Eleonora Tobaldini:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Nicola Montano:** Writing – review & editing, Supervision, Resources. **Matteo Bonzini:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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