



Association of short-term ozone and temperature with sleep disordered breathing

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ABSTRACT Scarce evidence suggests that ambient air pollution and temperature might play a role in incidence and severity of sleep disordered breathing (SDB). We investigated the association of short-term exposure to fine particulate matter (particles with a 50% cut-off aerodynamic diameter of 10 µm (PM₁₀)), ozone and temperature with SDB in the general population.

Between 2006 and 2008, 1773 participants (aged 50–80 years) of the Heinz Nixdorf Recall study underwent screening for SDB, as defined by the apnoea–hypopnoea index (AHI). We assessed daily exposure to PM₁₀, ozone, temperature and humidity. We used multiple linear regression to estimate associations of daily PM₁₀, ozone levels and temperature on the day of screening, adjusting for relative humidity, season, age, sex, body mass index, education, smoking habits, alcohol consumption and physical activity.

In the study population, the mean±SD AHI was 11.2±11.4 events·h⁻¹. Over all seasons, an interquartile range increase in temperature (8.6°C) and ozone (39.5 µg·m⁻³) was associated with a 10.2% (95% CI 1.2–20.0%) and 10.1% (95% CI 2.0–18.9%) increase in AHI, respectively. Associations for temperature were stronger in summer, yielding a 32.4% (95% CI 0.0–75.3%) increase in AHI per 8.6°C (p-value for season–temperature interaction 0.08). We observed that AHI was not associated with PM₁₀.

This study suggests that short-term variations in ozone concentration and temperature are associated with SDB.



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In middle-aged to elderly subjects SDB is associated with short-term ozone concentration and temperature <http://ow.ly/O7lLt>

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Introduction

Sleep disordered breathing (SDB) is a highly prevalent disorder among middle-aged and elderly adults, characterised by recurrent irregularities of respiration during sleep [1]. Severe untreated SDB increases the risk of fatal and nonfatal cardiovascular events compared with healthy controls [2]. Similarly, ambient air pollution has been associated with adverse effects on cardiovascular morbidity and mortality [3].

In numerous studies it has been shown that both SDB and air pollution are linked to hypertension [4, 5], diabetes [6, 7], coronary heart disease (CHD) and stroke [8–11]. Moreover, SDB and air pollution are associated with subclinical atherosclerosis as determined by carotid intima-media thickness and coronary artery calcium [12–15].

It has been suggested that air pollution may have an impact on the incidence and severity of SDB. However, findings are scarce and conflicting. So far, only the Sleep Heart Health Study (SHHS) analysed the relationship between SDB and air pollution particulate matter (particles with a 50% cut-off aerodynamic diameter of 10 µm (PM₁₀)) in a community-based population consisting of 3030 participants [16]. The authors observed that short-term PM₁₀ levels were associated with the apnoea–hypopnoea index (AHI) during summer, but not winter. Furthermore, elevated temperature was related to increased AHI during all seasons. Conversely, in a recent Brazilian retrospective analysis of 7523 patients admitted to a sleep laboratory due to suspected sleep disorders, it was found that decreased temperature was associated with increased AHI [17]. Additionally, as opposed to the SHHS, no association was observed between short-term PM₁₀ concentrations and AHI. The Brazilian study also investigated the role of short-term ozone levels in relation to the AHI; however, no association was found.

The aim of this analysis was to investigate the association of short-term exposure to PM₁₀, ozone and temperature with SDB in a middle-aged to elderly population.

Materials and methods

Study population

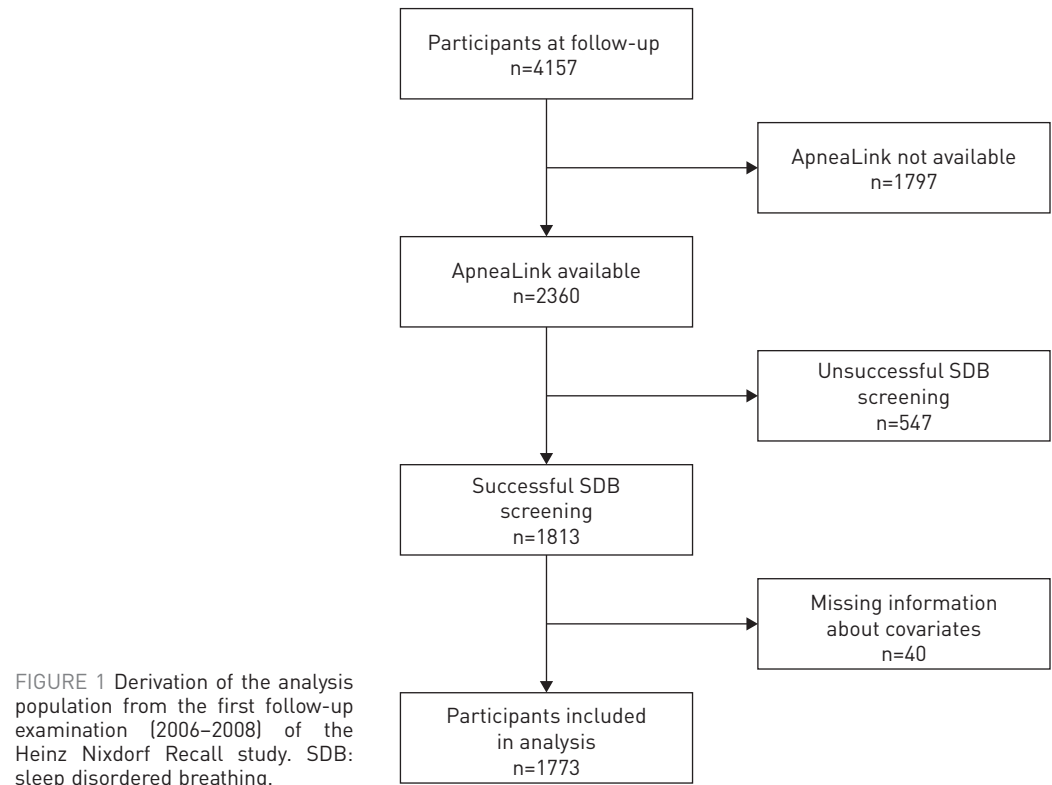
Participants of the Heinz Nixdorf Recall (Risk factors, Evaluation of coronary CALcium and Lifestyle) (HNR) study were randomly selected from mandatory city registries in Essen, Bochum and Mülheim (Germany) and invited to participate in the study as previously reported [18]. The study is a population-based cohort study on the predictive value of modern stratification techniques for cardiac events. Physician- or self-referral was not allowed, in order to avoid selection bias. A total of 4814 subjects aged 45–75 years (50% females) were included between 2000 and 2003. All participants provided written informed consent and the study was approved by the ethical committee at the University Essen, Germany. At baseline (2000–2003) and first follow-up (2006–2008), in-depth clinical and laboratory examinations were performed. Lifestyle and risk factor assessment was performed using standardised physician-conducted interviews and self-administered questionnaires.

Assessment of SDB

Between May 2006 and September 2008, screening for SDB with an ApneaLink (ResMed, Sydney, Australia) was performed during the follow-up visit 5 years after baseline at the age of 50–80 years (figure 1). As availability of screening devices was limited, an ApneaLink was handed out consecutively to 2360 participants at random. In order to determine AHI, linearised nasal flow was measured using ApneaLink. The device is a single-channel screening tool for SDB. It consists of a nasal cannula attached to a small case that houses a pressure transducer. The device is held in place by a belt worn around the chest. The participants agreed to wear the device for one night. They were instructed by the staff of the HNR study centre and were provided with an instruction sheet for use at home. Participants were asked to send the devices back to the study centre on the morning after the screening night.

ApneaLink has been validated in numerous studies for the screening of sleep apnoea [19, 20]. Several studies have compared ApneaLink to the gold standard of polysomnography (PSG). These studies reported a high diagnostic accuracy, defined by sensitivity (73.1–94.4%) and specificity (84.7–94.6%). Default

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settings of the screening device were used for the definitions of apnoea and hypopnoea. An apnoea was defined as a decrease in airflow by $>80\%$ of baseline for ≥ 10 s; a hypopnoea was defined as a decrease in airflow by $50\text{--}80\%$ of baseline for ≥ 10 s.

Automated analyses of duration and number of hypopnoeas and apnoeas (with ApneaLink firmware version 2.97 and scoring software version 5.13) were verified by investigators experienced with the technique and who were blinded to other clinical data. Recordings with obvious artefacts or short recording time (<2 h) were disregarded. Recordings could not be evaluated in 547 participants due to technical problems like power failure, poor recording quality or recording periods. No attempt was made to repeat failed ApneaLink recordings. A total of 1773 participants could be included in the present analysis.

Exposure assessment

The study area ($\sim 20 \times 30$ km) consists of the three adjacent cities of Mülheim, Essen and Bochum in the densely populated Ruhr area. Daily means (lag 0) as well as moving averages for lag 0–1 day and lag 0–2 days for temperature, ozone (8-h mean), relative humidity and PM₁₀ representing the citywide background concentration of pollutants were received from the North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection (Landesamt für Natur, Umwelt und Verbraucherschutz (LANUV) NRW, Essen, Germany). Temperature and relative humidity were measured at three background monitoring stations, PM₁₀ concentrations were measured at two and ozone levels at four monitoring stations. Overall means from these background monitoring stations were calculated for each day and used as exposure values.

Covariates

All covariates were assessed in a standardised way and either measured at the study centre (blood pressure, blood glucose, height and weight, *etc.*) or assessed in a standardised interview (medication, history of and current diseases, interventions, *etc.*) or assessed with a self-administered questionnaire (lifestyle variables). Blood pressure was determined from the mean value of the second and third of three measurements taken ≥ 3 min apart (Omron 705-CP monitor; OMRON, Mannheim, Germany) and classified according to threshold values from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [21]. Hypertension was defined as blood pressure $>140/90$ mmHg or use of antihypertensive medication. Body mass index (BMI) was calculated

from standardised measurements of height and weight. Participants were considered diabetic if they reported a physician diagnosis of diabetes or were taking anti-diabetic medication or had a random glucose $>200 \text{ mg-dL}^{-1}$ or a fasting glucose $>125 \text{ mg-dL}^{-1}$. Stroke was defined as a self-reported history of an ischaemic or haemorrhagic event. Congestive heart failure (CHF) was defined as history of heart failure that was diagnosed by any physician any time prior to the interview. CHD was defined as a self-reported history of a myocardial infarction or implantation of a coronary stent or angioplasty or bypass surgery. Smoking history was categorised as 1) current smoker, 2) former smoker, defined as smoking cessation >1 year ago, and 3) never-smoker. Amount of alcohol intake was calculated from type and number of drinks per week and given as g-week^{-1} . No physical activity was defined as no regular engagement in sports. Social status was assessed on the basis of years of schooling (<10 , 11–13, 14–18 or >18 years). Current medication was categorised according to the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization).

Statistical analysis

Analyses were performed on a subgroup ($n=1773$) of the study population for whom the outcome measure AHI and information on all covariates were available. To normalise the distribution of residuals, AHI+1 was log transformed. Spearman correlation coefficient was used to examine the correlation between daily temperature and daily air pollutant levels. Logistic regression models were applied to investigate the association of the exposure to PM₁₀, ozone and temperature at the day of screening with SDB severity (no sleep apnoea (AHI $<5 \text{ events-h}^{-1}$), mild sleep apnoea (AHI 5–14 events-h^{-1}), moderate sleep apnoea (AHI 15–29 events-h^{-1}) and severe sleep apnoea (AHI $\geq 30 \text{ events-h}^{-1}$)), adjusting for relative humidity, season, age, sex, BMI, education, smoking habits, alcohol consumption and physical activity. Furthermore, we used linear regression models to analyse the association of the exposure to PM₁₀, ozone and temperature at the day of screening with the natural logarithm of AHI+1, adjusting for relative humidity, season, age, sex, BMI, education, smoking habits, alcohol consumption and physical activity. In an extended model we also adjusted for hypertension, diabetes, CHF, CHD and stroke. In multi-exposure models we included PM₁₀, ozone and temperature simultaneously. Linearity of effect estimates was checked with both splines and polynomials. All analyses were conducted for the complete study period and stratified by meteorological seasons. We also tested interaction by comparing summer *versus* all other three seasons with multiplicative interaction terms (summer \times exposure). Effect estimates are presented per interquartile range (IQR) of the respective exposure. Statistical analysis was performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA) and R (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 denoted the presence of a statistically significant difference.

Sample size

A formal sample size calculation is not applicable in this study, since the number of participants is already fixed. We therefore only present an estimate of the necessary sample size to detect a given difference in means of AHI. Given a study population with a ratio of exposed to unexposed subjects of 1:3 (*i.e.* highest quartile of exposure *versus* rest), a mean and standard deviation of the end-point of interest $\ln(\text{AHI}+1)$ of 2.1 events-h^{-1} and 0.9 events-h^{-1} , respectively, an alpha of 0.05 with a two-sided test and a power of 80%, a 10% difference in means of $\ln(\text{AHI}+1)$ can be detected in an unconfounded analysis with 193 exposed and 579 unexposed subjects. The resulting number of subjects (772) is well under the available 1773 subjects in this study.

Results

Higher ozone levels were generally found in spring and summer, whereas PM₁₀ levels were similarly distributed during all seasons. Maximum ozone levels exceeded the threshold for public information ($>180 \mu\text{g}\cdot\text{m}^{-3}$ during 1 h) three times during the study period. Daily ozone and temperature were moderately to highly correlated, as were daily ozone and relative humidity (table 1).

We included 1773 participants for whom data on AHI and all covariates were available (table 2). Mean and median AHI were 11.2 events-h^{-1} and 7 events-h^{-1} , respectively, with a highly skewed distribution, and (AHI+1) was therefore log transformed for analysis. SDB, defined by AHI $\geq 15 \text{ events-h}^{-1}$, was observed in 23.5% of the study population.

In general, in the analysis of the complete study period, elevations in daily mean temperature, 8-h mean ozone and PM₁₀ on the day of SDB screening were not associated with SDB severity groups, whereas elevations in daily mean temperature and 8-h mean ozone were associated with increases in AHI (figure 2). In models adjusted for short-term relative humidity, short-term PM₁₀, age, sex and lifestyle, an IQR increase in temperature (8.6°C) and ozone (39.5 $\mu\text{g}\cdot\text{m}^{-3}$) was associated with a 10.2% (95% CI 1.2–20.0%) and 10.1% (95% CI 2.0–18.9%) increase in AHI, respectively. Adjustment for comorbidities did not change

TABLE 1 Daily exposure (lag 0) for 1773 participants of the Heinz Nixdorf Recall study at the first follow-up examination[#]

Daily exposure	Mean±SD	Median	Minimum	Quartile 1	Quartile 3	Maximum	Correlation [¶]		
							O ₃	PM ₁₀	Relative humidity
Temperature °C	13.1±6.2	13.7	−3.7	8.3	17.9	28.6	0.64	0.05	−0.42
O ₃ µg·m ^{−3}	62.2±33.4	57.5	2.3	40.0	79.5	190.5		0.01	−0.64
PM ₁₀ µg·m ^{−3}	27.0±14.5	23.8	7.5	18.0	32.0	214.0			−0.03
Relative humidity %	75.7±10.4	77.1	43.4	68.6	83.3	96.4			

PM₁₀: particles with a 50% cut-off aerodynamic diameter of 10 µm. [#]: May 2006–September 2008, n=858 days; [¶]: Spearman correlation coefficient (ρ).

TABLE 2 Participant characteristics of the Heinz Nixdorf Recall study at the first follow-up examination[#]

AHI events·h ^{−1}	11.2±11.4, 7 [3–15] [¶]
Age years	63.8±7.5
BMI kg·m ^{−2}	28.1±4.4
Male sex	902 [51]
Education years	
<10	162 [9]
11–13	996 [56]
14–18	417 [24]
>18	198 [11]
Smoking status	
Current smoker	283 [16]
Former smoker	707 [40]
Never-smoker	783 [44]
Alcohol consumption g·week ^{−1}	62.3±97.1
Physical activity >0 times per week	1051 [59]
Systolic BP mmHg	133±19
Diastolic BP mmHg	79±10
Congestive heart failure	63 [4]
Coronary heart disease	136 [8]
Hypertension	1150 [65]
Diabetes	317 [18]
Stroke	57 [3]

Data are presented as mean±SD or n [%], unless otherwise stated. AHI: apnoea-hypopnoea index; BMI: body mass index; BP: blood pressure. [#]: May 2006–September 2008; [¶]: median (interquartile range).

the estimates noticeably. In models including both temperature and ozone, estimates attenuated and associations were not statistically significant.

We observed that associations for temperature were stronger in summer (n=423 subjects), yielding a 32.4% (95% CI 0.0–75.3%) increase in AHI per 8.6°C. The p-value for the interaction term for summer with temperature was 0.08. Due to small sample sizes we did not find any statistically significant associations between temperature and AHI in spring (n=484 subjects, increase in AHI 4.1% (95% CI −10.3–20.8%)), autumn (n=506 subjects, increase in AHI 1.6% (95% CI −13.3–19.2%)) and winter (n=360 subjects, increase in AHI 9.9% (95% CI −15.6–43.0%)). Similarly, estimates for ozone were elevated across all seasons; however, season-specific sample sizes were too small to observe statistically significant associations. In fully adjusted models, an increase in ozone of 39.5 µg·m^{−3} was associated with an increase in AHI of 8.3% (95% CI −7.9–27.3%) in spring, 12.3% (95% CI −4.6–32.2%) in summer, 6.0% (95% CI −10.6–25.5%) in autumn and 12.0% (95% CI −12.8–43.9%) in winter.

Across all seasons, the observed associations corresponded to an increase in AHI of 1.2 events·h^{−1} per IQR increase in temperature and ozone at the population mean, whereas in summer an IQR elevation in daily temperature was associated with an increase in AHI of 3.4 events·h^{−1}.

We did not find a statistically significant association of PM₁₀ with AHI (−0.7% (95% CI −5.1–3.9%)) (figure 2) and observed the same for the specific seasons spring, summer, autumn and winter.

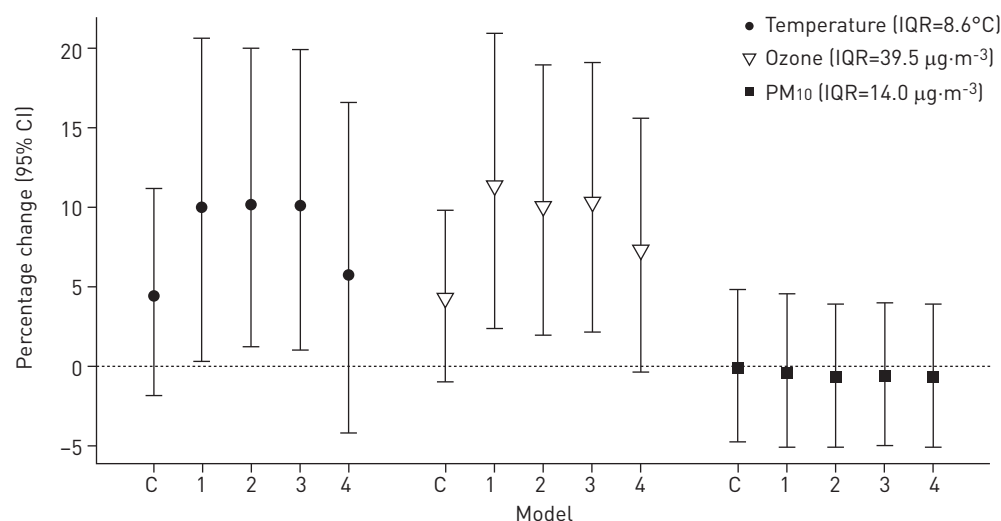


FIGURE 2 Estimated percentage change (95% CI) in apnoea-hypopnoea index per interquartile range (IQR) in daily temperature, daily ozone level and daily PM₁₀ (particles with a 50% cut-off aerodynamic diameter of 10 µm) level for all seasons (n=1773). The crude (C) model and four adjusted models are shown, as follows. Model 1: relative humidity, season, PM₁₀ (for models related to temperature and ozone) or temperature (for model related to PM₁₀). Model 2: model 1 plus age, sex, body mass index, alcohol consumption, smoking habits, physical activity and education. Model 3: model 2 plus hypertension, coronary heart disease, congestive heart failure, stroke and diabetes. Model 4: model 3 plus temperature (for models related to ozone and PM₁₀) or ozone (for model related to temperature).

Using longer averaging times such as the moving averages for lag 0–1 day and lag 0–2 days attenuated the associations for temperature and ozone but did not change the results for PM₁₀ (results not shown). We found no indication for a departure from linearity in any of the investigated exposures.

Discussion

The present study shows that short-term increases in temperature and ozone are associated with an increase in AHI in the general population, independent of well-known risk factors for SDB. Thus, our findings extend scarce evidence that environmental exposures such as air pollution and ambient temperature might have an impact on the severity of SDB.

This is the first study investigating the relationship between short-term levels of ozone and SDB in the general population. Across all seasons, elevations in ozone concentration were associated with an increase in AHI. This observation is in accordance with findings suggesting that increases in short-term ozone induce diminished vital capacity and elevated airway resistance [22, 23], both of which are related to obstruction of upper airways [24, 25]. However, our findings are not in line with a recent Brazilian retrospective study that consisted of a highly selected study population of patients admitted to a sleep laboratory due to suspected sleep disorders. The authors did not find any association between ozone concentration and AHI [17].

The observed association between short-term temperature and AHI qualitatively and quantitatively agrees with results from the SHHS, which reported an increase in AHI of 11.5% per increase in temperature by 14.2°C on the day of sleep examination [16]. However, as opposed to the SHHS, we found stronger associations during summer compared with other seasons. As air conditioning is uncommon in German households and windows are often kept open during the night in summer, ambient temperature reflects indoor temperature well in summer, but not necessarily in winter. This may explain the closer association of exposures with AHI in the warm season.

A mechanistic study in healthy adults analysing the impact of inspired air temperature on upper airway dilator muscle activity may provide a biological explanation for our findings of an association of temperature with the degree of SDB [26]. The authors found that upper airway dilator muscle activity, measured by genioglossus electromyograms, was greater during cold air breathing than during baseline or warm air breathing. As reduced upper airway muscle activity leads to greater pharyngeal collapsibility, frequency of apnoeas and hypopnoeas may increase in a warmer environment [27].

Although two population-based studies now report that an increase of temperature is associated with an increase of AHI, a causal relationship has not yet been shown in healthy controls. However, two mechanistic studies provide some biological evidence supporting the assumption that an association between increased temperature and increased AHI may exist. In contrast to our findings, the Brazilian retrospective analysis showed an inverse relationship between ambient temperature and AHI [17]. As several clinical outcomes exhibit nonlinear relationships with temperature, it can be assumed that this applies for the AHI as well. The Brazilian study was conducted in a subtropical climate (temperature range 8–31°C) and our study in a moderate climate (temperature range –3–28°C). Therefore, it cannot be excluded that the different associations are related to different temperature ranges. Anyway, the observation of the Brazilian study is supported by a previous study investigating the effect of indoor temperature on 52 patients with obstructive sleep apnoea (OSA) during three different nights. Temperatures were set at predefined levels of 16°C, 20°C and 24°C [28]. The authors observed that OSA severity was highest at 16°C. Additionally, a recent study reported that sensitivity to cold in the soft palate was reduced in OSA patients compared with healthy control subjects, possibly explaining different findings in population-based and clinical cohorts [29]. A reduced sensitivity to cold in OSA patients may be explained by snoring-induced upper airway sensory neuropathy occurring in patients with long-standing OSA [30, 31]. Further work is required to establish how these neurogenic changes affect subjects with and without OSA. In general, it must be noted that more studies are needed to gain improved understanding of the exposure–response mechanisms underlying sensitivity of the upper airways and the central respiratory drive to air pollution and temperature.

We also examined the association between short-term PM₁₀ and SDB. We hypothesised that airborne pollutants directly contribute to nasal or pharyngeal inflammatory swelling of local mucous membranes, leading to reduced airway patency and thus increases in upper airway resistance. In addition, we assumed that, due to inflammatory changes in the lower respiratory tract, airborne pollutants may have an impact on the ventilation/perfusion ratio, worsening the hypoxia of SDB [32]. However, our study does not support such mechanistic considerations, as associations of PM₁₀ with AHI were both negligible and not statistically significant. Similar to our study, the Brazilian retrospective analysis reported nonsignificant correlations between AHI and PM₁₀ levels [17].

Our study has several strengths. First, the geographically small and coherent study region is well suited to examining daily changes of environmental conditions and air pollutants with a comparatively homogenous spatial distribution. Secondly, our large, population-based sample of well-examined participants allowed extensive control of possible confounding covariates. We conducted multi-exposure models, adjusting temperature for air pollution and *vice versa*, to allow quantification of the effect of one factor while disregarding the other, maintaining the other constant *via* adjustment. Since meteorology is an unmeasured cause of both air pollution and temperature, and since temperature might have an effect on the air pollution concentration, the resulting associations reflect the direct association of temperature with AHI (the association that is not mediated through air pollution) and the association of air pollution with AHI, independent of temperature [33].

Despite these strengths, we acknowledge some limitations. First, AHI was measured using the single-channel screening device ApneaLink instead of the gold standard PSG. However, compared with PSG, several studies have reported that ApneaLink is an appropriate method for determining SDB with high diagnostic accuracy, possibly slightly overestimating the true AHI [19, 20]. Secondly, due to our sample size calculation, it can be concluded that, relying on the determined assumptions, we were able to find statistically significant associations only over all seasons because, in general, season-specific sample sizes were too small to detect statistically significant associations. Thus, it cannot be excluded that a type II error may have occurred. Thirdly, the use of clinical categories of severity of SDB revealed null results, probably due to the information loss of categorising the outcome data, which leads to a lower power to detect associations. Fourthly, although the findings of mechanistic studies suggest that both temperature and ozone levels have independent effects on SDB, we could not separate associations, due to their moderate to high correlation. Fifthly, we were not able to differentiate between indoor and ambient exposure, as no information on room temperature, indoor sources of air pollution and ventilation habits was available for this analysis. Finally, we could not measure all possible confounders. For instance, nasal congestion leads to breathing with increased resistance, which in turn may cause a tendency for airway collapse [34]. As subjects with nasal congestion due to allergy are 1.8 times more likely to have moderate to severe SDB than those without nasal congestion due to allergy [35], it can be hypothesised that an increase of AHI is associated with the occurrence of airborne allergens (such as grass, rye and ribwort) during warmer seasons. Furthermore, it can also be considered that the AHI could increase in colder seasons because nasal congestion is associated with cold and flu [36]. Since we have no information on the extent of allergy and winter-related colds in our cohort, we are not able to provide a reliable estimate of the effect of nasal congestion on the AHI.

In conclusion, our results show that short-term increases in temperature and ozone levels are associated with the AHI, a measure of severity of SDB, in the general population, independently of risk factors for SDB.

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