Short-term ambient air pollution and blood pressure in Croatia: preliminary results from the EH-UH 2 study

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This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 1 March 2026
Accepted: 22 April 2026
Published: 26 June 2026

Citation:
Nikić J, Vukšić A, Jelaković A, Stupin A, Abramović I, Baković D, Marinović Glavić M, Gajski G, Herceg Bulić I, Domislović M, Bilajac L, Belančić A, Josipović J, Reiner Ž, Pećin I, Jelaković B. Short-term ambient air pollution and blood pressure in Croatia: preliminary results from the EH-UH 2 study 573=74-75 (2026): 16-26
DOI: 10.21857/yrvgqtdz39

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Abstract

Introduction: Evidence on short-term ambient air pollution and blood pressure in Croatia is limited, particularly for delayed and non-linear associations. We examined whether short-term ambient air-pollution exposure was associated with office blood pressure (BP) in participants from the Croatian EH-UH 2 study.

Materials and Methods: This cross-sectional environmental epidemiological analysis linked EH-UH 2 blood-pressure and participant-level data with date- and location-specific air-pollution and meteorological data. Daily 24-hour mean concentrations of particulate matter ($PM_{2.5}$ and PM_{10}), sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) were obtained from CAMS European air quality forecasts. Each pollutant was analyzed in a separate distributed lag non-linear model over lag 0-6 days. The main model was adjusted for age, sex, body mass index, smoking, air temperature, and season.

Results: The primary office systolic BP (SBP) analytic sample included 1528 participants. In the primary model, SO_2 was the only pollutant with a positive, statistically significant association with office SBP. The cumulative contrast comparing the 75th with the 25th percentile of SO_2 exposure over lag 0-6 days was associated with an 11.7 mmHg higher office SBP (95% CI 4.6 to 18.8; p = 0.001). $PM_{2.5}$, PM_{10}, and O_3 showed positive but non-significant estimates. NO_2 and NO_x showed inverse associations with office SBP, but these estimates were sensitive to county adjustment. The SO_2 association was retained after alternative temperature adjustment, urban/rural adjustment, clinical adjustment, cluster-robust standard errors and additional pollutant adjustment, but was attenuated after adjustment for county and calendar time. Secondary home and combined analyses showed smaller and non-significant SO_2 estimates.

Conclusions: In this analysis of EH-UH 2 study data, short-term ambient SO_2 exposure was associated with higher office systolic BP, although the finding was sensitive to regional and temporal adjust-

ment. Further studies with improved exposure assessment and careful control of regional differences are needed.

Keywords: air pollution; blood pressure; distributed lag non-linear models; public health

Sažetak

Kratkotrajno onečišćenje zraka iz okoliša i arterijski krvni tlak u Hrvatskoj: preliminarni rezultati istraživanja EH-UH 2

Uvod: Dokazi o kratkotrajnom utjecaju onečišćenja vanjskog zraka na arterijski tlak u Hrvatskoj su ograničeni, osobito u pogledu odgođenih i nelinearnih povezanosti. Ispitali smo je li kratkotrajan utjecaj onečišćenja zraka povezan s ordinacijski izmjerenim arterijskim tlakom u sudionika istraživanja EH-UH 2.

Materijali i metode: U ovoj presječnoj okolišno-epidemiološkoj analizi, podaci o arterijskom tlaku i obilježjima sudionika EH-UH 2 istraživanja povezani su s podacima o onečišćenju zraka i meteorološkim podacima prema datumu i lokaciji. Dnevne 24-satne srednje koncentracije $PM_{2.5}$, PM_{10}, sumporovog dioksida (SO_2), ozona (O_3), dušikovog dioksida (NO_2) i dušikovih oksida (NO_x) dobivene su iz CAMS europskih prognoza kvalitete zraka. Svaki onečišćivač analiziran je u zasebnom distribuiranom nelinearnom modelu s veremenskom odgodom tijekom razdoblja od 0 do 6 dana. Glavni model bio je prilagođen za dob, spol, indeks tjelesne mase, pušenje, temperaturu zraka i godišnje doba.

Rezultati: Primarni analitički uzorak za ordinacijski sistolički arterijski tlak uključivao je 1528 sudionika. U primarnom modelu SO_2 je bio jedini onečišćivač s pozitivnom i statistički značajnom povezanošću s ordinacijskim sistoličkim arterijskim tlakom. Pri usporedbi 75. i 25. percentila izloženosti SO_2 tijekom razdoblja od 0 do 6 dana, procijenjena kumulativna razlika u ordinacijskom sistoličkom arterijskom tlaku iznosila je 11.7 mmHg (95% CI 4.6 do 18.8; p = 0,001). $PM_{2.5}$, PM_{10} i O_3 pokazali su pozitivne, ali statistički neznačajne učinke. NO_2 i NO_x su pokazali inverznu povezanost s ordinacijskim sistoličkim arterijskim tlakom, no rezultati su bili osjetljivi na prilagodbu za županiju. Povezanost SO_2 sa sistoličkim tlakom zadržala se nakon alternativne prilagodbe za temperaturu, urbano/ruralno područje, kliničke prilagodbe, uz primjenu standardnih pogrešaka robusnih na grupiranje i dodatne prilagodbe za druge onečišćivače, ali je oslabjela nakon prilagodbe za županiju i kalendarsko vrijeme. Sekundarne analize kućnih i kombiniranih mjerenja pokazale su manje i statistički neznačajne rezultate za SO_2.

Zaključci: U ovoj analizi podataka EH-UH 2 istraživanja, kratkoročna izloženost ambijentalnom SO_2 bila je povezana s višim ordinacijskim sistoličkim arterijskim tlakom, iako je rezultat bio osjetljiv na regionalnu i vremensku prilagodbu. Potrebna su daljnja istraživanja s preciznijom procjenom izloženosti uz pomno uvažavanje regionalnih razlika.

Ključne riječi: onečišćenje zraka; arterijski tlak; nelinearni modeli s raspodijeljenim vremenskim pomakom; javno zdravstvo

Introduction

Hypertension is one of the most important modifiable contributors to cardiovascular risk worldwide. The World Health Organization (WHO) estimates that approximately 1.4 billion adults aged 30–79 years had hypertension in 2024, with approximately one quarter having their blood pressure controlled (1). In Croatia, hypertension research has also shown a substantial burden of elevated blood pressure and insufficient control. The EH-UH 1 study reported a hypertension prevalence of approximately 37% in Croatia, with control achieved in approximately one fifth of all hypertensive individuals (2). In addition to established individual risk factors such as age, adiposity, smoking, diet, and physical inactivity, environmental exposures are increasingly recognized as relevant contributors to elevated blood pressure and hypertension. Among these, ambient air pollution has attracted particular attention because exposure is common and may affect vascular function and blood pressure regulation. A recent position paper of the European Society of Hypertension emphasized air pollution as one of the environmental exposures consistently linked with hypertension and cardiovascular disease (3). Several biological pathways may help explain these

associations, including oxidative stress, systemic inflammation, endothelial dysfunction, reduced nitric oxide bioavailability, and sympathetic nervous system activation (3). These processes may affect vascular tone and blood pressure regulation even in individuals without overt cardiovascular disease. Previous studies have linked air pollution with blood pressure and hypertension across both long-term and short-term exposure windows. For blood pressure measured on a given day, relevant short-term exposure may include not only same-day pollution levels but also exposure during the preceding days. Use of the lagged exposure windows in blood pressure analyses is supported by the literature. In a study of office workers, higher $PM_{2.5}$ levels were associated with increased blood pressure across several previous daily lags (4). The relationship between pollutant concentration and blood pressure does not necessarily follow a simple linear pattern. In this setting, distributed lag non-linear models are useful because they can examine whether associations vary both by pollutant concentration and across lag days, from same-day exposure to exposure during the days before blood pressure measurement (5). EH-UH 2 provides an opportunity to examine these questions in a Croatian setting. This nationwide survey was designed to assess arterial hypertension, salt intake, and related health characteristics in Croatia, and included standardized home and office blood pressure measurements together with relevant demographic, lifestyle, clinical, and laboratory information (6). For the present analysis, we linked EH-UH 2 measurements with date- and location-specific environmental data, enabling assessment of recent air pollution exposure histories before blood pressure measurement. Evidence on short-term ambient air pollution and office blood pressure in Croatia remains limited, especially when considering delayed and non-linear associations. We hypothesized that higher short-term concentrations of ambient air pollutants would be associated with higher office blood pressure, and that these associations might vary across same-day and preceding-day exposures. The primary aim of this study was to evaluate the association between short-term ambient air pollution and office systolic and diastolic blood pressure in the EH-UH 2 study using distributed lag non-linear models.

Materials and Methods

Study design and population

This was a cross-sectional environmental epidemiological analysis within the EH-UH 2 study, which was conducted between 2018 and 2021 and included home and office assessments. In our analysis, EH-UH 2 blood pressure and participant-level data were linked with date- and location-specific ambient air-pollution and meteorological data. Participants were included in each model if the relevant blood pressure outcome, measurement date, residential location, exposure variables, and model covariates were available.

Blood pressure outcomes

The primary outcome was office SBP. Office diastolic blood pressure (DBP), home SBP, and home DBP were evaluated as secondary outcomes, together with additional combined analyses of home and office blood pressure measurements. During both home and office assessments, blood pressure was measured three times and the mean of the second and third readings was used for analysis. Blood pressure measurements were conducted at multiple locations across Croatia.

Air-pollution and meteorological exposure assessment

Ambient air-pollution data were obtained from the Copernicus Atmosphere Monitoring Service (CAMS) European air quality forecasts (7). We analyzed daily 24-hour mean concentrations of particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), particulate matter with aerodynamic diameter ≤10 μm (PM_{10}), sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x). Meteorological data, including air temperature, were obtained from the Copernicus European Regional ReAnalysis (CERRA) sub-daily regional reanalysis data for Europe (8). Participants were first geocoded according to their residential information. When a full residential address was available, the corresponding residential coordinates were used. For participants without a full address, coordinates of the center of the reported city or place of residence were assigned. Date- and location-specific daily pollutants and meteorological data were then linked to these coordinates for analysis.

Covariates

The main adjusted model included age at measurement, sex, body mass index (BMI), smoking status, air temperature, and season of measurement. Air temperature was included as a meteorological covariate to account for short-term temperature conditions. It was represented by the 24-hour mean temperature averaged over lag days 0–6 and modeled using a natural spline with 3 degrees of freedom. Month of measurement, county, urban/rural residence, calendar time, clinical variables, and additional pollutant adjustment were evaluated in sensitivity analyses.

Statistical analysis

Descriptive statistics were summarized for the primary office SBP analytic sample. Continuous variables were presented as medians with interquartile ranges, and categorical variables as counts and percentages. Differences by sex were assessed using the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. The primary analysis evaluated the association between short-term ambient air pollution and office SBP. Each pollutant was analyzed in a separate distributed lag non-linear model (DLNM). Lag 0 denoted the day of blood pressure measurement, while lags 1–6 denoted the preceding days. The primary lag window

was defined as lag 0–6. Following the distributed lag non-linear modeling framework described by Gasparrini et al., each pollutant was represented in the regression model by a cross-basis (5). This cross-basis was constructed using natural spline basis functions with 3 degrees of freedom for the pollutant-concentration dimension and 3 degrees of freedom for the lag dimension. The primary effect estimate was the cumulative difference in blood pressure compared to the 75th with the 25th percentile of the observed lagged exposure distribution across the lag window. Results were reported as differences in blood pressure in mmHg, with 95% confidence intervals and p-values. A secondary cumulative contrast comparing the 90th with the 50th percentile was also estimated. Office DBP, home SBP, and home DBP were analyzed as secondary outcomes using the same modeling approach. Because the same participant could be measured in both home and office settings, combined home-office models used a mixed-effects model with a participant-level random intercept and included measurement setting as an additional covariate. Nominal p-values were reported, and findings were interpreted according to direction, magnitude and consistency across sensitivity analyses. Two-sided p-values <0.05 were considered statistically significant.

Sensitivity analyses

Several sensitivity analyses were performed to examine the robustness of the primary findings. First, we evaluated alternative lag and model specifications, including an extended pollutant lag window from lag 0 to lag 14, a linear distributed lag model, and alternative spline specifications for the exposure-response and lag-response dimensions. We also evaluated a model using the month of measurement instead of the season. Second, we examined alternative adjustments for short-term temperature conditions. In addition to the main temperature specification based on lag 0–6, sensitivity models included natural splines with 3 degrees of freedom for mean temperature over lag 3–6 and lag 3–11. Third, we assessed whether results were sensitive to additional adjustment for calendar time and regional characteristics. These analyses included adjustment for calendar time using a natural spline with 3 degrees of freedom, county fixed effects, urban/rural residence, and a combined model including both calendar time and county. Fourth, we examined the influence of clustering and influential observations. Cluster-robust standard errors were evaluated using two clustering definitions: residential location, based on latitude and longitude, and date-location, defined as the combination of measurement date and residential location. In linear models, influential observations were assessed using Cook's distance, and models were refitted after the removal of observations with Cook's distance greater than 4/N. Cook's distance diagnostics were not applied to mixed-effects combined models. Fifth, additional clinical model adjustment was explored. These models included antihypertensive medication and diabetes status. An extended clinical model additionally included cholesterol and daily sodium chloride intake, and a further extended clinical model added estimated glomerular filtration rate (eGFR). Finally, additional models were fitted for SO_2. In these analyses, each of the other pollutants was added separately as a linear lag 0–6 covariate to the main SO_2 DLNM model. All analyses were performed in R version 4.5.3.

Ethics

All EH-UH 2 participants were adults aged 18 years or older and provided with written informed consent. During the home-visit component of the study, written consent was obtained before study measurements were performed. The EH-UH 2 study was approved by the Ethics Committee of the University of Zagreb School of Medicine (registration number: 380-59-10106-17-3931; class: 641-01/17-02/01; approval date: 13 July 2017). The study was conducted in accordance with the Declaration of Helsinki. EH-UH 2 was organized and conducted by the Croatian Society of Hypertension and the Croatian Hypertension League and was supported by the Croatian Science Foundation (grant IP-2016-06-9033, PI Bojan Jelaković).

Results

Study sample

The primary office SBP analytic sample included **1528 participants**. Characteristics of this sample are shown in **Table 1**.

Primary DLNM analysis of office systolic blood pressure

In the primary distributed non-linear model for office SBP, associations differed across pollutants (Table 2, Figure 1). SO_2 showed the clearest positive association with office SBP. The cumulative P75 versus P25 contrast was associated with an 11.7 mmHg higher office SBP (95% CI 4.6 to 18.8; p = 0.001). $PM_{2.5}$, PM_{10} and O_3 showed positive estimates, but the associations were not statistically significant: 2.6 mmHg for $PM_{2.5}$ (95% CI -3.8 to 9.0; p = 0.425), 1.7 mmHg for PM_{10} (95% CI -3.1 to 6.6; p = 0.487) and 8.1 mmHg for O_3 (95% CI -4.0 to 20.3, p = 0.191). In contrast, NO_2 and NO_x showed inverse associations with office SBP: -8.1 mmHg for NO_2 (95% CI -12.6 to -3.6; p < 0.001) and -7.4 mmHg for NO_x (95% CI -12.0 to -2.8; p = 0.002). The cumulative exposure-response pattern for SO_2 was non-linear (Figure 2A). Using the 25th percentile as a reference, the estimated cumulative association increased modestly at the median exposure level, was most pronounced around the 75th percentile, and was weaker at the 90th percentile. Specifically, the estimated cumulative difference was 1.1 mmHg at the median SO_2 level (95% CI -2.5 to 4.6), 11.7 mmHg at the 75th percentile (95% CI 4.6 to 18.8), and 1.6 mmHg at the 90th percentile (95% CI -5.3 to 8.5). The SO_2 lag-response pattern suggested that the cumulative association was not confined to the day of blood-pressure measurement (Figure 2B). The lag-specific

estimates for the P75 versus P25 contrast were positive across the lag 0–6 window, with the largest estimates at lag 5 (2.1 mmHg, 95% CI 0.3 to 4.0) and lag 6 (3.3 mmHg, 95% CI -1.7 to 8.3).

Secondary and sensitivity analyses

Secondary outcome analyses are summarized in Table 3. For office DBP, the SO_2 association was positive but not statistically significant (3.8 mmHg, 95% CI -0.4 to 7.9; p = 0.074). NO_2 and NO_x showed inverse associations with office DBP: -5.3 mmHg for NO_2 (95% CI -7.9 to -2.6; p < 0.001) and -4.8 mmHg for NO_x (95% CI -7.5 to -2.1; p < 0.001). In home SBP analyses, the SO_2 estimate was smaller than in the office SBP analysis and was not statistically significant (1.9 mmHg, 95% CI -0.1 to 4.0; p = 0.064). $PM_{2.5}$ and PM_{10} were not associated with home SBP. In home DBP analyses, SO_2 was close to the null (0.7 mmHg, 95% CI -0.6 to 1.9; p = 0.298). In combined home-office mixed-effects models, the SO_2 association with SBP was also smaller and not statistically significant (0.9 mmHg, 95% CI -0.9 to 2.7; p = 0.318), indicating that the strongest SO_2 signal was observed in the primary office SBP analysis.

Sensitivity analyses for SO_2 and office SBP are shown in Table 4. The positive SO_2 association was retained after alternative temperature adjustment, including mean temperature over lag 3–6 (11.9 mmHg, 95% CI 4.9 to 18.8; p < 0.001) and lag 3–11 (12.2 mmHg, 95% CI 5.0 to 19.3; p < 0.001). It was also retained after urban/rural adjustment (12.1 mmHg, 95% CI 5.1 to 19.2; p < 0.001), clinical adjustment, cluster-robust standard errors by residential location and date-location and refitting after removal of high-influence observations. In clinical sensitivity models, the SO_2 estimate remained positive after adjustment for antihypertensive medication and diabetes (11.1 mmHg, 95% CI 3.4 to 18.8; p = 0.004), after extended adjustment including total cholesterol and estimated sodium chloride intake (12.0 mmHg, 95% CI 4.3 to 19.7; p = 0.002), and after additionally adding eGFR (12.3 mmHg, 95% CI 4.6 to 20.0; p = 0.002). SO_2 models additionally adjusted for other pollutants also retained positive, statistically significant estimates, ranging from 10.2 mmHg after additional PM_{10} adjustment to 15.2 mmHg after additional NO_2 or NO_x adjustment. However, the SO_2 estimate was attenuated or became less precise in several model specifications. The extended lag 0–14 model yielded a smaller and non-significant estimate (3.4 mmHg, 95% CI -3.6 to 10.5; p = 0.342). The linear distributed lag model also did not support a positive association (0.2 mmHg, 95% CI -2.3 to 2.8; p = 0.848). Adjustment for calendar time reduced the estimate (7.9 mmHg, 95% CI -0.9 to 16.7; p = 0.079), while county fixed effects further attenuated the association (4.6 mmHg, 95% CI -8.1 to 17.4; p = 0.476). In the model including both calendar time and county, the estimate remained positive but was highly imprecise (8.4 mmHg, 95% CI -13.3 to 30.1; p = 0.447). For NO_2 and NO_x, the inverse associations observed in the primary office SBP model were sensitive to county adjustment. The inverse NO_2 association persisted after calendar-time adjustment (-5.2 mmHg, 95% CI -9.9 to -0.4; p = 0.033) and urban/rural adjustment (-7.5 mmHg, 95% CI -12.2 to -2.8; p = 0.002), but changed direction and became non-significant after county fixed effects (2.4 mmHg, 95% CI -9.5 to 14.3; p = 0.693) and after combined calendar-time and county adjustment (2.2 mmHg, 95% CI -10.4 to 14.7; p = 0.735). A similar pattern was observed for NO_x. Across the remaining pollutants, $PM_{2.5}$ and PM_{10} did not show consistent associations with office SBP across the primary and sensitivity analyses. O_3 showed positive estimates in some specifications, but in general, the direction and precision were less consistent than for SO_2.

Discussion

In this analysis of the EH-UH 2 study data, the associations between ambient air pollution and office blood pressure varied by pollutant. SO_2 was the only pollutant with a positive, statistically significant association with office SBP in the primary analysis. The SO_2 association was distributed across the 0–6-day lag window, with the largest lag-specific estimate at lag 6 and the clearest positive interval at lag 5. In contrast, NO_2 and NO_x showed inverse associations with office SBP and DBP in the primary models, while $PM_{2.5}$ and PM_{10} were not consistently associated with office blood pressure. O_3 showed some positive estimates, but these were less precise and less consistent across model specifications. Overall, the findings suggest that short-term pollutant–blood pressure associations in this population differed by pollutant, outcome, and model specification. Previous studies evaluating SO_2 in relation to blood pressure and hypertension-related outcomes have reported heterogeneous findings. In a Turkish nested panel study that compared office, home, and 24-hour ambulatory blood-pressure measurements, higher SO_2 concentrations were associated with higher office SBP and DBP, as well as higher 24-hour ambulatory SBP and DBP, whereas no association was observed for home blood-pressure measurements (9). This pattern is relevant to our findings because the statistically significant, positive SO_2 effect in the present analysis was also observed for office SBP, while home and combined home-office estimates were smaller and not statistically significant. In a time-series analysis from Iran, Nouri et al. reported that short-term SO_2 exposure was associated with an increased number of hospital admissions for hypertensive cardiovascular disease, particularly for the 6-day moving average of SO_2 (10). In contrast, a Serbian panel study of healthy women did not find significant associations between short-term SO_2 exposure and SBP, DBP, or heart rate (11). Evidence from long-term exposure studies is also mixed, but partly supportive of a positive SO_2 association. Dong et al. reported that long-term SO_2 exposure was associated with higher SBP, higher DBP, and higher odds of hypertension in China, but only in men (12). Taken together, these studies

suggest that positive SO_2-blood pressure associations have been reported previously, but that results vary by population, group, exposure window, blood-pressure measurement method, and outcome definition.

Our inverse NO_2 and NO_x estimates differ from most previous findings for NO_2. Choi et al. reported that short-term NO_2 exposure was associated with higher SBP and DBP within several hours of exposure, while SO_2 was associated with lower blood pressure (13). In the population-based study in Teheran, Khajavi et al. reported that short-term NO_2 exposure increased SBP with a delayed effect, although long-term NO_2 exposure was associated with a lower risk of incident hypertension in some exposure windows (14). Dong et al. found no clear positive association between long-term NO_2 exposure and SBP, DBP, or hypertension (12). Further analysis are needed to explain difference between our and other findings.

The positive SO_2 association with office SBP is the most notable finding of the present analysis. The SO_2 association was positive and statistically significant in the primary model and remained so after alternative temperature adjustment, urban/rural adjustment, clinical covariate adjustment, cluster-robust standard errors, and removal of high-influence observations. Positive estimates were also retained after separate adjustments for each additional pollutant. Nevertheless, the finding requires cautious interpretation. First, the exposure-response curve did not show a simple steady increase across the SO_2 distribution. Second, the estimate was attenuated and became imprecise after county adjustment and after combined adjustment for calendar time and county. The inverse NO_2 and NOx estimates also deserve attention. These inverse associations were present in the primary office SBP and DBP models, but they were attenuated, became non-significant, or changed direction after adjustment for county. The attenuation of SO_2 estimates and the disappearance of inverse NO_2 and NO_x estimates after county adjustment may partly reflect differences between counties in pollution levels, pollution sources, participant characteristics, or timing of measurements.

This study has several strengths. It used data from a national Croatian study with standardized home and office blood pressure measurements and individual-level demographic, lifestyle, clinical, and laboratory information. Using CAMS and CERRA datasets allowed date- and location-specific exposure assignment across the study area, rather than relying only on a limited number of fixed monitoring stations. The analysis included multiple pollutants, used distributed lag non-linear models to account for both concentration-response and lag-response patterns, and included sensitivity analyses addressing temperature adjustment, seasonality, calendar time, county, urban/rural residence, influential observations, clinical covariates, and adjustment for other pollutants. Importantly, all available pollutants were analyzed and reported using the same primary framework, reducing selective presentation of only the most favorable finding.

Several limitations should also be considered. First, although distributed lag non-linear models were used to evaluate exposure histories before blood pressure measurement, the observational cross-sectional design cannot establish a causal effect of short-term air-pollution exposure on blood pressure. Second, exposure misclassification is possible because CAMS modeled air-pollution data and CERRA meteorological data are not direct measures of personal exposure. Individual exposure may differ according to time-activity patterns, indoor exposures, occupational or commuting behavior, housing characteristics, ventilation, and recent mobility. Residential geocoding may also have introduced errors, particularly for participants without a full address, for whom coordinates of the center of the reported city or place of residence were assigned. Third, blood pressure was assessed during a single study visit. Although standardized protocols and repeated readings were used, office blood pressure is inherently variable and may be influenced by short-term factors such as recent caffeine or alcohol intake, physical activity, acute stress, sleep, smoking shortly before measurement, acute illness, hydration status, and timing or adherence to antihypertensive medication. The absence of 24-hour ambulatory blood pressure monitoring further limited assessment of short-term blood pressure dynamics. Fourth, even with model adjustments, other hidden factors might still have influenced the results. This is particularly relevant when accounting for location and changes over time, because the SO_2 estimate was attenuated after adjustment for county and calendar time, while the inverse NO_2 and NO_x estimates became non-significant or changed direction after county adjustment. While air temperature was modeled in the primary and sensitivity analyses, other meteorological conditions were not included and may have influenced blood pressure or modified pollutant-related associations. Fifth, multiple pollutants, outcomes, lag windows, exposure contrasts, and model specifications were evaluated, and nominal p-values should therefore be interpreted cautiously. Finally, although additional pollutant adjustment was performed, real-world air pollution represents a complex mixture of correlated pollutants and shared emission sources. The observed SO_2 association may therefore also reflect broader environmental conditions rather than the effect of sulfur dioxide alone. Further studies are needed to determine whether the SO_2 pattern observed here is reproducible in other population-based datasets. Repeated measurements could help determine whether these associations persist across multiple measurements or reflect the variability of single blood pressure readings. Although CAMS and CERRA enabled national date- and location-specific assignment, future work could use more precise residential locations, preferably full addresses rather than city or place centers, and exposure models that capture differences in pollution within the same city, such as proximity to major roads or industrial sources. Land-use regression or hybrid exposure models that combine monitoring data with traffic, land-use, industrial-

source, satellite, and chemical-transport information may be particularly valuable (15).
Overall, this analysis of EH-UH 2 study data suggests that short-term ambient air pollution may be associated with office blood pressure in Croatia, although the magnitude and direction of associations differed across pollutants. SO_2 was the only pollutant showing a positive, statistically significant association with office SBP in the primary analysis, but this finding was attenuated after adjustment for county and calendar time. These results support further investigation of short-term air-pollution exposure and blood pressure using improved exposure assessment and careful control for regional differences.

Tables and Figures

Table 1. Clinical and demographic characteristics of the primary office SBP analytic sample.

Characteristic	Overall	Men	Women	P value
Participants, n	1528	559	969	
Age, years	59.0 [48.0, 67.0]	60.0 [49.0, 68.0]	59.0 [47.0, 67.0]	0.074
BMI, kg/m²	28.3 [25.0, 31.8]	28.8 [26.1, 31.9]	27.9 [24.3, 31.6]	<0.001
Office SBP, mmHg	130.5 [120.0, 143.4]	134.3 [124.0, 147.0]	129.0 [117.3, 140.5]	<0.001
Office DBP, mmHg	81.3 [75.5, 88.0]	83.5 [76.7, 90.0]	80.7 [74.7, 86.5]	<0.001
Home SBP, mmHg	130.0 [119.0, 143.0]	136.0 [124.6, 148.0]	126.5 [116.0, 139.0]	<0.001
Home DBP, mmHg	81.0 [73.5, 88.0]	82.5 [76.1, 91.5]	80.0 [72.5, 86.5]	<0.001
Estimated sodium chloride intake	8.3 [5.6, 11.5]	10.3 [6.6, 13.8]	7.6 [5.3, 10.4]	<0.001
Smoking status: Current	376 (24.6%)	135 (24.2%)	241 (24.9%)	<0.001
Smoking status: Former	326 (21.3%)	172 (30.8%)	154 (15.9%)	
Smoking status: No	826 (54.1%)	252 (45.1%)	574 (59.2%)	
Urban/rural residence: Rural	701 (45.9%)	257 (46.0%)	444 (45.8%)	0.996
Urban/rural residence: Urban	827 (54.1%)	302 (54.0%)	525 (54.2%)	
Antihypertensive medication: No	930 (60.9%)	314 (56.2%)	616 (63.6%)	0.005
Antihypertensive medication: Yes	598 (39.1%)	245 (43.8%)	353 (36.4%)	
Diabetes: No	1094 (83.3%)	359 (77.0%)	735 (86.8%)	<0.001
Diabetes: Yes	219 (16.7%)	107 (23.0%)	112 (13.2%)	
Office hypertension: No	599 (39.2%)	174 (31.1%)	425 (43.9%)	<0.001
Office hypertension: Yes	929 (60.8%)	385 (68.9%)	544 (56.1%)	
Home hypertension: No	403 (39.8%)	115 (30.4%)	288 (45.4%)	<0.001
Home hypertension: Yes	609 (60.2%)	263 (69.6%)	346 (54.6%)	

BMI = body mass index; SBP= systolic blood pressure; DBP = diastolic blood pressure

Table 2. Primary distributed lag non-linear model results for office systolic blood pressure.

Pollutant	P25 (μg/m³)	P75 (μg/m³)	Difference in office SBP (95% CI), mmHg	P value
$P_{M2.}5$	7.3	13.6	2.6 (-3.8 to 9.0)	0.425
$P_{M1}0$	10.3	19.0	1.7 (-3.1 to 6.6)	0.487
S_O2	1.3	4.2	11.7 (4.6 to 18.8)	0.001
$_O3$	45.7	76.8	8.1 (-4.0 to 20.3)	0.191
NO_2	4.2	8.2	-8.1 (-12.6 to -3.6)	<0.001
NO_x	4.4	8.8	-7.4 (-12.0 to -2.8)	0.002

Results are reported as cumulative differences in office systolic blood pressure (SBP) comparing the 75th with the 25th percentile of the observed lagged exposure distribution over lag 0-6 days. Daily pollutant concentrations are expressed as 24-hour means in μg/m³.

Table 3. Secondary distributed lag non-linear model results for blood pressure outcomes.

Analysis	Pollutant	Difference in blood pressure (95% CI), mmHg	P value
Office DBP	$PM_{2.5}$	0.2 (-3.5 to 3.9)	0.922
Office DBP	$_{PM}10$	1.2 (-1.7 to 4.0)	0.424
Office DBP	SO_2	3.8 (-0.4 to 7.9)	0.074
Office DBP	O_3	1.4 (-5.7 to 8.6)	0.700
Office DBP	N_O2	-5.3 (-7.9 to -2.6)	<0.001
Office DBP	N_Ox	-4.8 (-7.5 to -2.1)	<0.001
Home SBP	$PM_{2.5}$	-0.7 (-4.3 to 3.0)	0.721
Home SBP	PM_{10}	0.0 (-3.6 to 3.7)	0.988
Home SBP	SO_2	1.9 (-0.1 to 4.0)	0.064
Home SBP	$_O3$	2.7 (-2.8 to 8.3)	0.334
Home SBP	NO_2	-3.1 (-5.8 to -0.5)	0.019
Home SBP	NO_x	-3.0 (-5.6 to -0.5)	0.019
Home DBP	$P_{M2.}5$	0.0 (-2.2 to 2.3)	0.982
Home DBP	PM_{10}	0.5 (-1.7 to 2.8)	0.658
Home DBP	SO_2	0.7 (-0.6 to 1.9)	0.298
Home DBP	O_3	2.3 (-1.1 to 5.7)	0.191
Home DBP	NO_2	-0.7 (-2.3 to 0.9)	0.405
Home DBP	NO_x	-0.6 (-2.2 to 1.0)	0.449
Combined home-office SBP	$PM_{2.5}$	-0.4 (-2.6 to 1.7)	0.696
Combined home-office SBP	PM_{10}	0.0 (-2.2 to 2.2)	0.995
Combined home-office SBP	SO_2	0.9 (-0.9 to 2.7)	0.318
Combined home-office SBP	O_3	2.7 (-1.6 to 7.0)	0.223
Combined home-office SBP	NO_2	-2.7 (-4.3 to -1.0)	0.001
Combined home-office SBP	NO_x	-2.7 (-4.3 to -1.1)	0.001
Combined home-office DBP	$PM_{2.5}$	-0.1 (-1.4 to 1.2)	0.904
Combined home-office DBP	PM_{10}	0.5 (-0.8 to 1.8)	0.461
Combined home-office DBP	SO_2	0.8 (-0.3 to 1.9)	0.138
Combined home-office DBP	O_3	1.7 (-0.9 to 4.3)	0.192
Combined home-office DBP	NO_2	-0.6 (-1.6 to 0.4)	0.212
Combined home-office DBP	NO_x	-0.6 (-1.6 to 0.4)	0.230

Results are reported as cumulative differences in blood pressure comparing the 75th with the 25th percentile of the observed lagged exposure distribution over lag 0-6 days. Combined analyses used mixed-effects models with a participant-level random intercept. SBP= systolic blood pressure; DBP = diastolic blood pressure

Table 4. Sensitivity analyses for SO_2 and office systolic blood pressure.

Sensitivity analysis	N	Difference in office SBP (95% CI), mmHg	P value
Alternative temperature adjustment: mean temperature lag 3–6	1528	11.9 (4.9 to 18.8)	<0.001
Alternative temperature adjustment: mean temperature lag 3–11	1528	12.2 (5.0 to 19.3)	<0.001
Additional adjustment for urban/rural residence	1528	12.1 (5.1 to 19.2)	<0.001
Refit after removal of high-influence observations	1451	12.0 (6.0 to 18.1)	<0.001
Clinical adjustment: antihypertensive medication and diabetes	1313	11.1 (3.4 to 18.8)	0.004
Extended clinical adjustment: medication, diabetes, cholesterol, and sodium chloride intake	1226	12.0 (4.3 to 19.7)	0.002
Extended clinical adjustment plus eGFR	1226	12.3 (4.6 to 20.0)	0.002
Additional adjustment for $PM_{2.5}$	1528	10.6 (3.4 to 17.9)	0.004
Additional adjustment for $P_{M1}0$	1528	10.2 (3.0 to 17.5)	0.006
Additional adjustment for O_3	1528	12.4 (5.3 to 19.5)	<0.001
Additional adjustment for NO_2	1528	15.2 (8.0 to 22.4)	<0.001
Additional adjustment for NO_x	1528	15.2 (8.0 to 22.4)	<0.001
Extended lag window: lag 0–14	1528	3.4 (-3.6 to 10.5)	0.342
Linear distributed lag model	1528	0.2 (-2.3 to 2.8)	0.848
Additional adjustment for calendar time	1528	7.9 (-0.9 to 16.7)	0.079
Additional adjustment for county	1528	4.6 (-8.1 to 17.4)	0.476
Additional adjustment for calendar time and county	1528	8.4 (-13.3 to 30.1)	0.447

All rows report results for SO_2 and office SBP. Results are reported as cumulative differences in office SBP comparing the 75th with the 25th percentile of the observed lagged exposure distribution. Daily pollutant concentrations are expressed as 24-hour means in μg/m³. SBP= systolic blood pressure; DBP = diastolic blood pressure

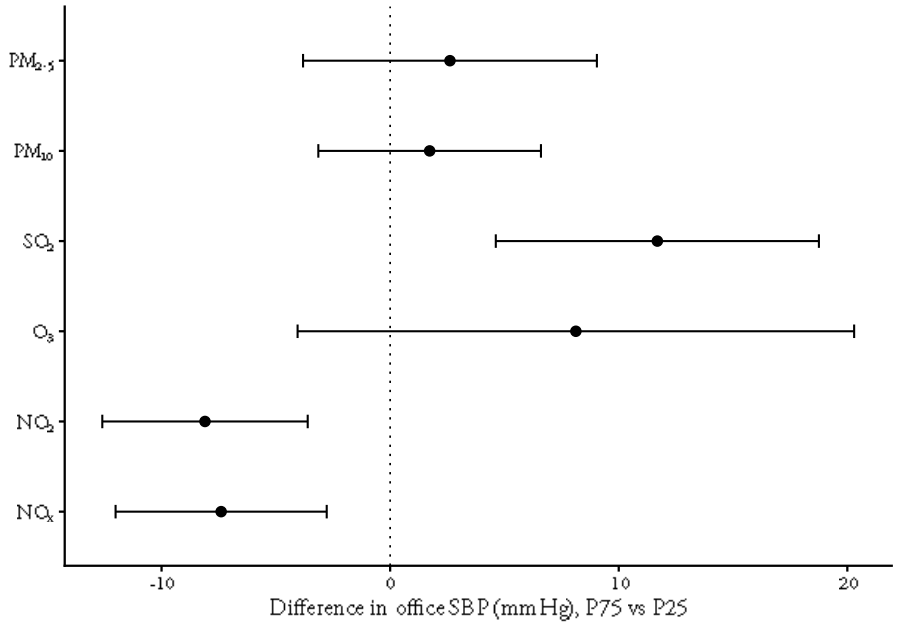

Figure 1. Primary distributed lag non-linear model estimates for office systolic blood pressure by pollutant.

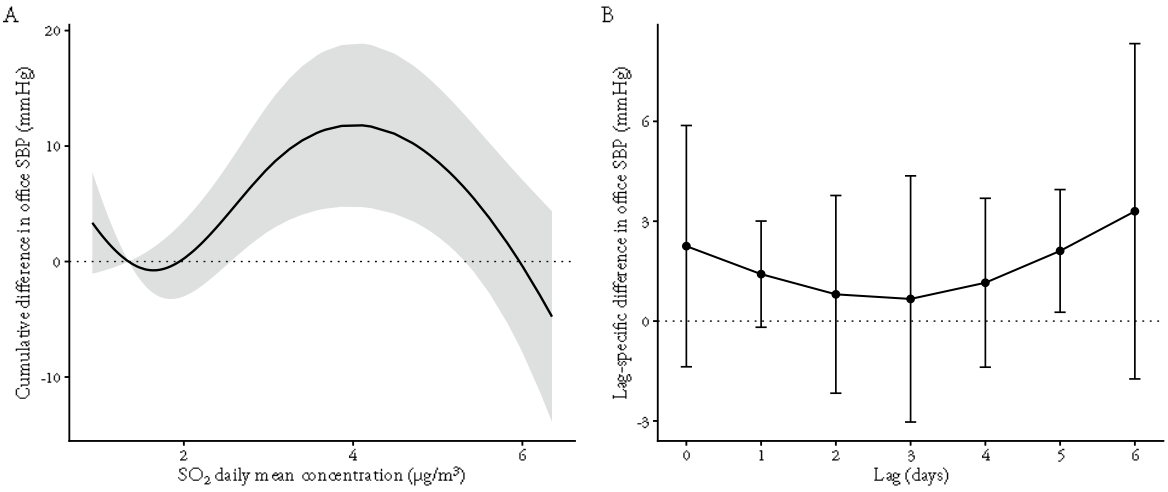

Figure 2. Cumulative exposure-response and lag-response patterns for SO2 and office systolic blood pressure.

Acknowledgements

We are grateful to all participants of EH-UH 2 research study and to all respondents who responded to the measurements. The study was supported by the grant from the Croatian Science Foundation "Epidemiology of arterial hypertension and salt intake in Croatia (EH-UH 2)" (IP-06-2016).

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