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Interplay between climate, pollution and COVID-19 on ST-elevation myocardial infarction in a large metropolitan region

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ABSTRACT

Background: Collective risk factors such as climate and pollution impact on the risk of acute cardiovascular events, including ST-elevation myocardial infarction (STEMI). There is limited data however on the precise temporal and independent association between these factors and STEMI, and the potentially interacting role of government policies against Coronavrus Disease 2019 (COVID-19), especially for Latin America.

Methods: We retrospectively collected aggregate data on daily STEMI admissions at 10 tertiary care centers in the Buenos Aires metropolitan area, Argentina, from January 1, 2017 to November 30, 2020. Daily measurements for temperature, humidity, atmospheric pressure, wind direction, wind speed, and rainfall, as well as carbon monoxide (CO), nitrogen dioxide, and particulate matter <10 µm (PM10), were retrieved. Exploratory analyses focused on key COVID-19-related periods (eg first case, first lockdown), and stringency index quantifying the intensity of government policy response against COVID-19.

Results: A total of 1498 STEMI occurred over 1430 days, for an average of 0.12 STEMI per center (decreasing from 0.130 in 2018 to 0.102 in 2020, p=0.016). Time series analysis showed that lower temperature and higher concentration of CO and PM10 were all significantly associated with an increased rate of STEMI (all p<0.05), whereas COVID-19 outbreak, lockdown, and stringency of government policies were all inversely associated with STEMI (all p<0.05). Notably, environmental features impacted as early as 28 days before the event (all p<0.05), even if same or prior day associations proved stronger (all p<0.05). Multivariable analysis suggested that maximum temperature (p=0.001) and PM10 (p=0.033) were the strongest predictor of STEMI, even after accounting for COVID-19-related countermeasures (p=0.043).

Conclusions: Lower temperature and higher concentrations of CO and PM10 are associated with significant increases in the rate of STEMI in a large Latin American metropolitan area. The

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reduction in STEMI cases seen during the COVID-19 pandemic is at least in part mediated by improvements in pollution, especially reductions in PM10.

KEY-WORDS

Acute coronary syndrome; Climate; COVID-19; Environment; Pollution; ST-elevation myocardial infarction; Weather

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INTRODUCTION

Morbidity and mortality tolls of cardiovascular disease remain substantial worldwide, with acute myocardial infarction and ST-elevation myocardial infarction (STEMI) having particularly adverse short- and long-term impact of patient survival and quality of life.(1-3) Whereas several individual risk factors have been identified which exert a key prognostic role, in primary as well as secondary prevention (eg smoking, hypertension, dyslipidemia, diet and physical exercise), recently several collective (ie population-level) risk factors for cardiovascular disease have been proposed, ranging from noise to weather and pollution.(4-9) Indeed, it is clear that temperature, on one hand, and carbon monoxide, nitrogen dioxide, and particular matter, on the other hand, are significantly associated with STEMI and other acute cardiovascular events, albeit with substantial between-region and between-season variability.(10-13)

The recent Coronavirus Disease 2019 (COVID-19) has further complicated the epidemiologic assessment of the interplay between environmental features and risk of STEMI, as improvements in pollution have been possibly counterbalanced with a lower likelihood to activate in a timely fashion emergency medical services.(14-15) This holds even truer for Latin America, where few if any analyses on these topics were conducted, and none also considering the additional role of COVID-19.(16-18)

We aimed at appraising the interplay between climate, pollution, and COVID-19-related government policies on daily rates of STEMI in a large Latin American metropolitan region.

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METHODS

We retrospectively collected anonimized aggregate data on aggregate daily STEMI cases from 10 tertiary care centers with primary percutaneous coronary intervention (PCI) capacity in the Buenos Aires metropolitan area, Argentina. The area is large 3,830 km2 and includes almost 13 million inhabitants (ie 28% of all Argentina). The period of interest spanned from January 1, 2017 to November 30, 2020. Definition of STEMI was based on established international guidelines, and typically included clinical history, ECG, laboratory tests, and invasive coronary angiography.(19) No adjunct consent form on top of the routine one used for data privacy and no institutional review board was sought given the reliance on aggregate data without individual features (eg age, gender, or clinical history).

Meteorological data were provided by the National Meteorological Service, after collection at the Buenos Aires Observatory station, located in the center of the city (34 ° 35’S 58 ° 30’W) (Figure 1S). Specifically, the following weather features were measured on a daily basis hourly: temperature (measured in ° Celsius), distinguishing daily minimum, maximum, mean and absolute within-day maximum difference (from hourly data); humidity (%); atmospheric pressure (measured in hPa); wind direction (measured in °); wind speed (measured in km/h); rainfall (measured in mm). All weather measurements were provided as a single-item per the whole metropolitan area.

Pollutant data were provided by the Buenos Aires Environmental Protection Agency, as measured Buenos Aires City Air Quality Monitoring Network Equipment (as detailed in Table 1S).(20-21) Specifically, 3 separate measuring stations were used. The Centenario (urban background) station is located in the geographical centre of Buenos Aires City (34°36'20.8"S 58°25'57.4"W), and station monitors a characteristic commercial/residential area with mild traffic and low contribution of stationary sources. The Córdoba (traffic) station is located beside one of Buenos Aires main artery (34°35'59.0"S 58°23'28.8"W), close to City downtown. With a high contribution of air pollution

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from mobile sources, this monitoring station acquires air quality data that is representative of the neighbouring areas of Buenos Aires City main avenues. Finally, the La Boca (industrial) station is located in the southern east corner of Buenos Aires City (34°37'31.1"S 58°21'56.0"W). This is a characteristic residential/industrial area, with a low contribution of mobile sources and significant emissions from stationary sources. Pollution measurements included, on a daily basis: carbon monoxide (CO, measured in ppm); nitrogen dioxide (NO2, measured in ppb), and particulate matter <10 µm (PM10, measured in $\mu g/m^3$). Average daily values for each of the three stations were abstracted, and then daily minimum, maximum, mean and absolute difference values were computed. Furthermore, a distance metric was computed, for each participating center, from each measurement station, and also computing minimum, maximum, and mean distance.

As key indicators of COVID-19, we relied on the date of the first reported case in Argentina (March 1, 2020), on the date of lockdown enforcement, and on daily changes in the Oxford stringency index, a quantitative index summarizing responses of national governemetnts to COVID-19 developed and maintained by the University of Oxford (with ranging from 0, representing minimal stringency, to 100, representing maximal stringency).(22-23)

Variables were described as mean, minimum, 1st quartile, median, 3rd quartile, maximum, and displayed with histograms. Furthermore, 95% confidence intervals of mean values were generated with percentile bootstrap (1000 samples). Inferential analysis was based on time series models, and in particular an autoregressive conditional heteroskedasticity family of estimator (ARCH) model to account for center-clustering, and vector autoregression (VAR) to obtain lag-order selection statistics, relying on Hannan and Quinn information criterion (HQIC) for optimal lag selection, with maximum lag of 30 days. Notably, primary analyses were based on non-transformed variables, and sensistivity analyses based on, when appropriate according to histogram inspection, natural logarithm transformation of variables. Statistical significance was set

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at the two-tailed 0.05 level, without multiplicity adjustment nor multiple imputation.

Computations were performed with R 3.6 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 13 (StataCorp, College Station, TX, USA).

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RESULTS

A total of 1498 STEMI occurred over 1430 days, for an average of 0.12 STEMI/day per center (decreasing from 0.130 in 2018 to 0.102 in 2020, p=0.016). These and additional univariate statistics are provided in Table 1, with histograms diplayed in Figures 2S, 3S, 4S, 5S, and 6S. Notably, univariate time series analysis confirmed significant changes over time in STEMI rates, as well as in environmental features (Figure 1; Figure 7S).

Bivariate time series analysis showed that maximum, mean and absolute change in temperature were significantly and inversely associated with STEMI rates (respectively p=0.015, p=0.034, and p=0.044), whereas all other weather features were not significantly associated with STEMI rates (Table 2)(Figures 8S, 9S, 10S, 11S, 12S, and 13S). Among pollutants, minimum, maximum and mean concentrations of CO were significantly and positively associated with STEMI rates (respectively p=0.020, p=0.015, and p=0.005), and the same applied to maximum and mean concentrations of PM10 (respectively p=0.016 and p=0.030).

Lag analysis highlighted that, while the most impactful lag between STEMI and temperature, CO and PM10 ranged between 1 and 4 days, these environmental features were significantly associated with STEMI even as early as 28 days before the actual events (eg 28 days, p=0.020 for maximum CO concentration, and 28 days, p=0.033 for mean PM10 concentration)(Table 3).

Multivariable analysis exploring the independent association between such environmental features showed that temperature and PM10 were both significantly and independently associated with STEMI rates (respectively p=0.006 and p=0.017), whereas CO was not significantly associated with STEMI when considering them as well.

Focusing on the current pandemic and its impact on environment and coronary syndromes, STEMI rates were lower after the first COVID-19 case (p=0.017), and after enforcing the first lockdown (p=0.017), even if no evident date threshold was evident (Figure 14S). Similarly, the higher the

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stringency index, the lower were STEMI rates (p=0.010). Even when considering stringency index as additional covariate, temperature and PM10 remained significantly associated with STEMI rates (p=0.001 for temperature, p=0.033 for PM10, and p=0.043 for stringency index).

Sensitivity analyses including distance metrics (minimum, maximum and mean distance from hospital center and measurement station) provided similar results in terms of direction and magnitude of effect, as well as p values.

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DISCUSSION

The impact of climate and pollution on cardiovascular risk in now well established.(5) Their interplaying impact on acute coronary syndromes in general and STEMI in particular represents an intense focus of current research and management efforts.(24) Most recently, COVID-19 has broken havoc globally, impacting dramatically on patients, healthcare systems, and societies at large.(25) Specifically, all cause mortality rates have risen sharply due to COVID-19-related deaths, while several researchers have reported reductions in hospital admissions for STEMI.(14,26) This is clearly partly due to limitations in access to healthcare facilities and avoidance of services or institutions considered at risk for COVID-19 contagion.(27) However, it is clear that COVID-19 countermeasures, such as lockdowns and distance working, have improved pollution features, for instance by decreasing traffic-related pollution.(28)

These concepts have already been the focus of several research efforts, but most were strictly focused on few dimensions of this conundrum.(26,29-32) Most pertinently for this work, none ever focused on the interplay between environment, COVID-19 and STEMI in Latin America.

Our work indeed originally leveraged an extensive dataset from a large Argentinian metropolitan area, including data on daily STEMI from several institutions, accurate measurements on weather and pollution features, and also detailed data on COVID-19, as well as COVID-19 countermeasures (recapitulated with the dedicated stringency index). We found that STEMI rates were lower with raising temperatures in this temperate zone, as well as with decreasing levels of CO and PM10. Lag analysis showed that most of the effect on STEMI rates occurred within 4 days of weather changes, but some measurable and significant effect was still evident almost 1 month afterwards, reinforcing the crucial impact of environmental risk factors on cardiovascular morbidity and mortality. While temperature and PM10 maintained a significant association with STEMI rates at multivariable analysis, CO was no longer significant. This does not invalid the clear impact of

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pollution of STEMI risk, but rather clarifies the multidimensional effects on environment safety of human activities (eg traffic).(28,33)

In accordance with our results, an inverse association with STEMI and temperature has been previous shown in other climate areas.(32,34-36) Detrimental effects of pollutants similar to the one hereby described have been reported also by other research groups.(37-39)

As shown also elsewhere, STEMI rates were lower in the COVID-19 era, irrespective of its definition based on the first reported case or the implementation of lockdown with raising stringency index. Yet, the fact that the association betweeen environmental features and STEMI rates held true even after adjustment for stringency index highlights how pollution still takes its deadly toll even in the pandemic scenario. Most interestingly, the reduction in STEMI cases, while partly due to limitations in access to healthcare facilities, may also be due to improvements in pollutants.

Indeed, this work calls for clear and vigorous actions to improve society at a global and regional as well as local level to reduce pollution, especially in terms of levels of CO and PM10, while increasing protection of individuals at risk from lower ambient temperatures. Furthermore, additional translational, epidemiologic and pragmatic studies are warranted to further elucidate the mechanisms underlying the interplay between environment and STEMI, to better characterize the cardiovascular burden of unfavorable climate and pollution settings, and to propose and test effective means to reduce such burden. For instance, it is clear that pollutants, stress, and COVID-19 may all lead to endothelial dysfunction, prothrombosis, and vascular resistance, among many other adverse effects.(40-41)

Limitations of this work are several, ranging from the epidemiologic and retrospective design to the lack of individual patient data. Most importantly, evidence of statistically significant association is by no means proof of causation, and several epidemiologic fallacy caveats apply to

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this work as well similar ones. Furthermore, we did not collect data on other cardiovascular conditions requiring admission (eg non-ST-elevation acute coronary syndromes). Levels of particulate matter <2.5 µm is not routinely collected by Buenos Aires Environmental Protection Agency, and thus they were not appraised in the present work. Finally, STEMI events not leading to admission remain elusive to capture, especically in the COVID-19 era, and trends in all cause mortality are probably the only means to comprehensively appraise the impact of this deadly infectious disease on patients and society, with the least inaccuracy.

In conclusion, lower temperature and higher concentrations of CO and PM10 are associated with significant increases in the rate of STEMI in a large Latin American metropolitan area. The reduction in STEMI cases seen during the COVID-19 pandemic is at least in part mediated by improvements in pollution, especially reductions in PM10.

AUTHORS' CONTRIBUTIONS

This work was conceived by Drs. Biondi-Zoccai and G. Rodriguez-Granillo, who also performed the analysis and drafted the manuscript. Drs. G. Rodriguez-Granillo, Mercade, Dawidowski, Seropian, Cohen, Sturmer-Ramos, Descalzo, Rubilar, Sztejfman, Zaidel, Pazos, Leguizamon, Cafaro, Visconti, Baglioni, Noya, Fontana, M. Rodriguez-Granillo, Pavlovsky, Alvarez, Lylyk, Versaci, and Abrutzky participated in data collection, provided support in analysis interpretation and offered critical insight for manuscript revision. All authors read and approved the final version of the manuscript.

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Table 1. Descriptive analysis.

Feature	**Mean**	**Median**	**Minimum; maximum**	**1st, 3rd quartile**	**Standard deviation; coefficient of variation**	**Skewness; kurtosis**	**Bootstrapped 95% confidence interval**
STEMI per center	0.120	0.100	0; 0.714	0; 0.200	0.128; 1.1	1.2; 4.7	0.113; 0.127
Temperature (°C)							
Minimum	14.4	14.3	0.6; 27	10.5; 18.6	5.4; 0.4	-0.1; 2.3	18.2; 18.8
Maximum	22.9	22.9	8.8; 37.8	18.1; 27.2	6.1; 0.3	0.1; 2.2	22.6; 23.2
Mean	18.5	18.6	5.3; 31.3	14.2; 22.7	5.6; 0.3	0.1; 2.2	18.2; 18.8
Absolute change	8.4	8.6	1.0; 16.9	6.4; 10.5	3.0; 0.4	-0.1; 2.7	8.3; 8.6
Humidity (%)	69.6	69.8	32.7; 99.5	60.7; 78.6	12.8; 0.2	-0.1; 2.6	68.9; 70.2
Atmospheric pressure (hPa)	1013	1013	998; 1032	1009; 1017	6.0; 0.01	0.3; 2.8	1012.6; 1013.3
Wind direction (°)	19.5	19.3	5.7; 36	13.5; 25.3	7.3; 0.4	0.1; 2.0	19.2; 19.9
Wind speed (km/h)	8.4	8.2	2.1; 18.6	6.4; 10.2	2.9; 0.4	0.5; 3.2	8.3; 8.6
Rainfall (mm)	3.3	0	0; 118	0; 0.2	10.5; 3.2	5.1; 36.5	2.7; 3.8
Carbon monoxide (ppm)							
Minimum	0.44	0.42	0.07; 1.33	0.33; 0.53	0.16; 0.4	1.1; 5.6	0.56; 0.58
Maximum	0.71	0.67	0.21; 2.59	0.55; 0.82	0.24; 0.3	1.3; 6.9	0.69; 0.72
Mean	0.57	0.54	0.17; 1.50	0.45; 0.65	0.17; 0.3	1.0; 5.1	0.55; 0.58
Absolute change	0.26	0.23	0; 2.18	0.12; 0.37	0.21; 0.8	1.6; 9.8	0.25; 0.28
Nitrogen dioxide (ppb)							
Minimum	15.8	15.5	2.0; 35.4	12.1; 29.9	5.5; 0.4	0.3; 3.1	19.2; 19.9
Maximum	23.5	22.6	6.0; 62.7	18.0; 27.9	7.9; 0.3	0.9; 4.7	23.0; 23.9
Mean	19.5	19.1	4.9; 47.1	15.1; 23.1	6.1; 0.3	0.6; 3.7	19.2; 19.9
Absolute change	7.7	6.6	0; 37.3	3.7; 10.1	5.9; 0.8	1.5; 6.4	7.4; 8.0
Particulate matter <10 µm (µg/m^3)							
Minimum	20.9	19.7	0; 66.4	15.2; 25.5	8.1; 0.4	1.2; 5.8	24.3; 25.3
Maximum	29.4	27.4	0; 98.0	20.8; 35.5	12.6; 0.4	1.3; 6.0	28.7; 30.1
Mean	24.8	23.5	6.9; 74.0	18.4; 29.9	9.4; 0.4	1.1; 5.5	24.3; 25.3
Absolute change	8.5	6.5	0; 73.8	3.1; 11.6	8.1; 1.0	2.3; 11.6	8.1; 8.9

STEMI=ST-elevation myocardial infarction

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Table 2. Time series analysis appraising the association between daily ST-elevation myocardial and environmental features.

Feature	Point estimate of effect	95% confidence interval	P value
Temperature (°C)			
Minimum*	-0.001	-0.002; 0.000	0.089
Maximum*	-0.002	-0.003; -0.001	0.015
Mean*	-0.002	-0.003; -0.001	0.034
Absolute change†	-0.014	-0.028; -0.001	0.044
Humidity (%)*	0.001	0.000; 0.002	0.090
Atmospheric pressure (hPa) *	0.001	-0.001; 0.003	0.339
Wind direction (°)*	0.000	-0.001; 0.001	0.615
Wind speed (km/h) *	0.002	-0.001; 0.004	0.151
Rainfall (mm)*	0.000	-0.001; 0.001	0.499
Carbon monoxide (ppm)			
Minimum†	0.020	0.003; 0.037	0.020
Maximum†	0.023	0.004; 0.042	0.015
Mean†	0.030	0.009; 0.051	0.005
Absolute change*	0.011	-0.019; 0.042	0.468
Nitrogen dioxide (ppb)			
Minimum*	0.000	-0.001; 0.001	0.598
Maximum*	0.000	-0.001; 0.001	0.977
Mean*	0.000	-0.001; 0.001	0.842
Absolute change*	0.000	-0.001; 0.001	0.594
Particulate matter <10 µm (µg/m^3)			
Minimum*	0.001	0.000; 0.002	0.064
Maximum†	0.019	0.003; 0.036	0.016
Mean†	0.018	0.002; 0.034	0.030
Absolute change*	0.001	-0.001; 0.003	0.157

*results without trasformation reported, as similar results for magnitude and direction of effect were obtained after natural logarithm transformation; †results after natural logarithm transformation reported

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Table 3. Time series lag analysis for daily ST-elevation myocardial and preceding daily measurements of temperature, carbon monoxide, and particulate matter <10 µm.

Feature	Longest significant lag			Optimal lag		
	Lag (days)	**P value**	**HQIC**	**Lag (days)**	**P value**	**HQIC**
Temperature (°C)						
Maximum	14	0.021	4.06	1	<0.001	3.95
Mean	9	0.003	3.40	4	<0.001	3.36
Absolute change*	10	0.050	-0.14	1	<0.001	-0.30
Carbon monoxide (ppm)						
Minimum*	13	0.024	-0.63	1	<0.001	-0.78
Maximum*	28	0.020	-0.69	3	<0.001	-1.07
Mean*	28	0.050	-0.93	4	<0.001	-1.29
Particulate matter <10 µm (µg/m^3)						
Maximum*	14	0.034	-0.38	1	<0.001	-0.54
Mean*	28	0.033	-0.23	1	<0.001	-0.68

*after natural logarithm transformation; HQIC=Hannan and Quinn information criterion

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Table 4. Multivariable time series analysis appraising the independent association between temperature, carbon monoxide, particulate matter <10 µm, and stringency index with ST-elevation myocardial infarction.

Feature	**Point estimate of effect (95% confidence interval), p value**	
	Model 1*	**Model 2**
Temperature (maximum, °C)	-0.002 (-0.003; 0.001), p=0.006	-0.002 (-0.003; 0.001), p=0.001
Carbon monoxide (mean, ppm)	0.020 (-0.019; 0.059), p=0.311	-
Particulate matter <10 µm (mean, µg/m^3)	0.021 (0.004; 0.039), p=0.017	0.019 (0.002; 0.037), p=0.033
Stringency index	-	-0.018 (-0.035; -0.001), p=0.043

*excluding stringency index, and after natural logarithm transformation of carbon monoxide and particulate matter; †including stringency index and after natural logarithm transformation of particulate matter, but excluding carbon monoxide

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Figure 1. Exploring changes in ST-elevation myocardial infarction (STEMI) rates over time (A), and their association with daily measurements maximum temperature (B), mean carbon monoxide (CO)(C), and particulate matter <10 μm (PM10)(D).

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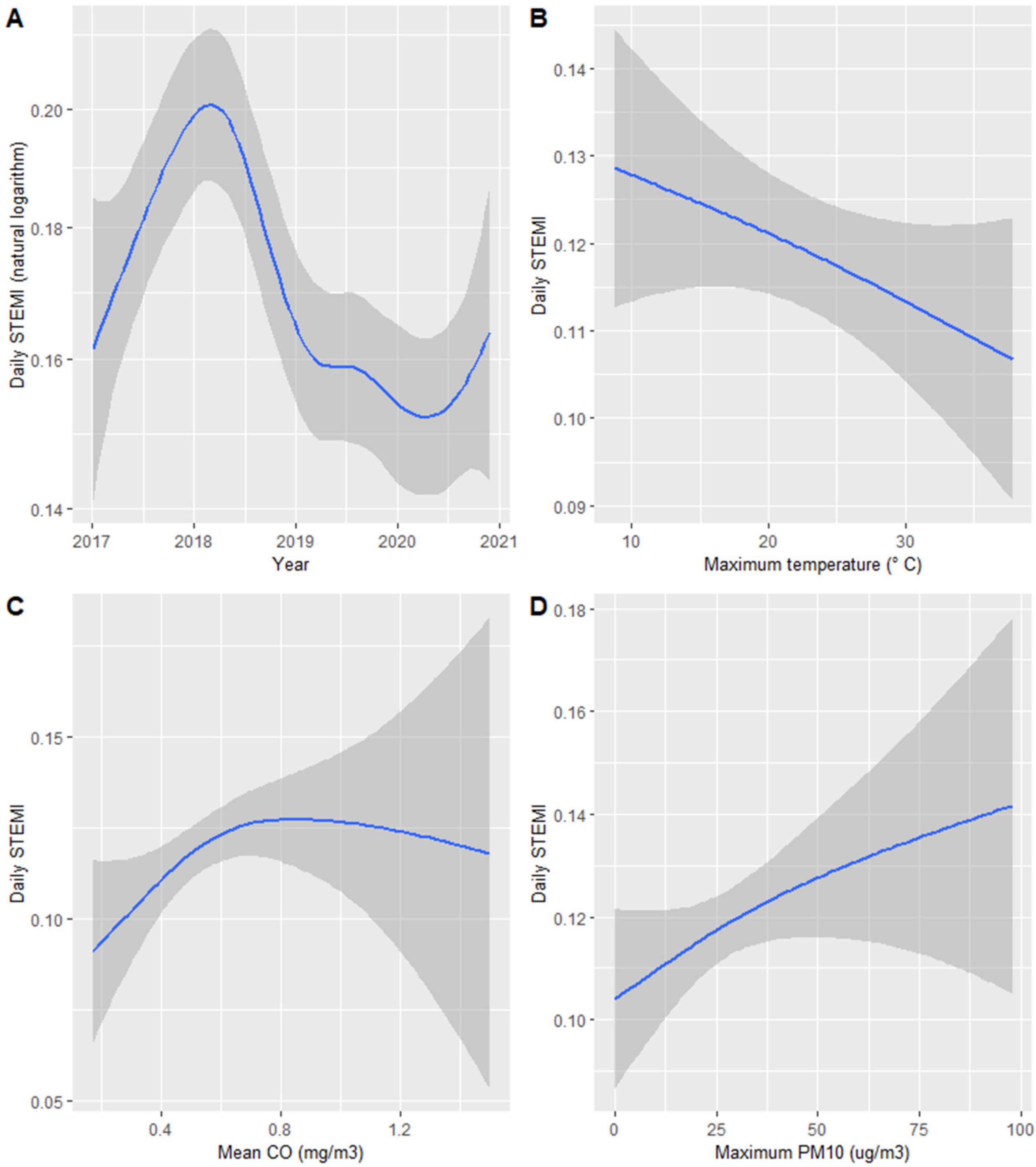

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