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Kexin Guan Date

Associations between short-term exposure to ambient air pollution and emergency department visits for cardiovascular diseases in thirteen U.S. cities

By

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Master of Science in Public Health

Biostatistics and Bioinformatics

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Howard H. Chang, Committee Chair

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By

Kexin Guan

B.S., Emory University, 2021

Thesis Committee Chair: Howard H. Chang, Ph. D

An abstract of
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Abstract

Associations between short-term exposures to ambient air pollution and emergency department visits for cardiovascular diseases in thirteen U.S. cities

By Kexin Guan

Objective

This study aimed to estimate the association between short-term exposures to ambient air pollutants and emergency department (ED) visits for cardiovascular diseases (CVD) in 13 cities in the United States during the period 2005-2014.

Methods

Daily counts of ED visits were obtained from hospital associations or health departments in 9 US states. Daily air pollution and meteorological data were retrieved from data fusion products. Quasi-Poisson log-linear regression models were adopted to analyze the association between same-day exposures to six air pollutants (NO_2, SO_2, O_3, CO, $PM_{2.5}$, PM_{10}) and ED visits for CVD and CVD subgroups, adjusted for temporal trends and meteorology. Co-diagnosis of diabetes was explored as a potential effect modifier.

Results

For all CVD ED visits, we found positive associations for CO (RR = 1.002, 95% CI = [1.001, 1.003]), $PM_{2.5}$ (1.001, [1.000, 1.002]), and SO_2 (1.001, [1.000, 1.002]) per interquartile range (IQR) increase in same-day pollutant concentration. An IQR increase in NO_2 was associated with increased risk in ED visits for ischemic heart disease (1.005, [1.001, 1.008]) and congestive heart failure (1.006, [1.001, 1.010]). Moreover, we found evidence of increased risks among patients with diabetes for several pollutants. For example, among patients with a diabetes co-diagnosis, ED visits for all CVD was associated with PM_{10} (1.004, [1.001, 1.006]), $PM_{2.5}$ (1.004, [1.002, 1.006]), and SO_2 (1.002, [1.000, 1.003]), while associations among patients without a diabetes co-diagnosis were weaker or null. Diabetes co-diagnosis also increased the risk of ischemic heart disease ED visits associated with NO_2 (1.008, [1.003, 1.013]), as well as risk for acute myocardial infarction ED visits with NO_2 (1.020, [1.004, 1.036]) and SO_2 (1.007, [1.001, 1.014]) concentrations. However, diabetes co-diagnosis had a protective effect on associations of O_3 and congestive heart failure ED visits (e.g., for those with a diabetes co-diagnosis, RR = 0.994, [0.988, 0.999]).

Conclusions

We found adverse effects of short-term ambient air pollutants on ED visits for cardiovascular diseases, and that diabetes mellitus may increase patients' vulnerability toward certain air pollutants.

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1 Introduction

Air pollution has become one of the major risks to health for the post-industrialization human society (Manisalidis et al., 2020). In the past decades, the effect of short-term ambient (outdoor) air pollutants on cardiovascular health has been extensively studied in epidemiologic research around the world. Many previous studies have found significant adverse effects of short-term air pollutants on hospital admissions and mortality of cardiovascular and respiratory diseases (de Bont et al., 2022).

Two categories of air pollutants, gaseous and particulate-matter pollutants, have both been found to be associated with increased risk of cardiovascular disease of people who are exposed to them in long-term and short-term (Song et al., 2016). Among particulate-matter pollutants, particles less than 10 μm (PM_{10}) and particles less than 2.5 μm ($PM_{2.5}$) in diameter were frequently investigated and found to have significant positive association with increased risk of hospital admission and death for CVD (Dominski et al., 2021). For gaseous pollutants, carbon dioxide (CO_2), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) were often observed to be associated with increased risk in CVD (Franchini & Mannucci, 2012). Research also suggests NO_2 to be particularly associated with myocardial infarction and ischemic heart disease (Milojevic et al., 2014; Stieb et al., 2020). Some studies found ozone (O_3) to have significant associations with the risk for cardiovascular injury (Srebot et al., 2009), while a systemic review by Song et al. (2016) resulted in opposite findings.

Identification and assessment of associations among vulnerable population sub-groups is also an extensively studied topic in the area. Among factors conferring vulnerability, diabetes mellitus is one of the most explored co-morbidities with cardiovascular disease that may increase vulnerability to air pollution. A systematic review by Tibuakuu et al. (2018) identified that being

a racial minority, female, or diabetic, having prior heart disease, or smoking will lead to higher risk of adverse effect from exposure to air pollution. A study conducted in Tehran, Iran (Akbarzadeh et al., 2018), suggested that certain subgroups, including older, diabetic, and non-hypertensive patients, were more susceptible to the adverse effect of $PM_{2.5}$ and PM_{10}. Their conclusions are consistent with the findings of Chen et al. (2013) and Zhang et al. (2016). Another study carried out in São Paulo, Brazil by Filho et al. (2008) again found that diabetic patients were vulnerable to the adverse effects of air pollutants. However, some research such as the one conducted by Rich et al. (2010) failed to find any significant effect modification by diabetes.

Moreover, research results often vary depending on the location and time period of the study. In the past, a large number of studies have been focused on the metropolitan area in North America and Europe. However, a meta-analysis by Song et al. (2016) pointed out that stronger associations are likely to be found in Asia compared to Europe or North America, which aligns with the findings by Stieb et al. (2020).

Although multiple studies have been conducted on the topic of air pollutants and CVD, many focused on long-term air pollutants instead of short-term, and focused on mortality or hospitalization rate of CVD as the outcome instead of emergency department (ED) visits. Moreover, most studies have limited their geographic representation to the common choice of urban area in single mega city. Hence, in this study, we aimed to investigate the association between same-day air pollutant concentration and ED visits for CVD, as well as the effect modification of diabetes mellitus on such association, leveraging a multi-state study that allows for broader geographic representation. ED visits were chosen as the measure of morbidity instead of mortality or hospital admission to cover a wider range for the severity of illness. A total of six

air pollutants were inspected, including NO_2, SO_2, O_3, CO, $PM_{2.5}$, and PM_{10}. Data was collected from 13 cities defined by core-based statistical areas (CBSAs) among 9 states in the United States over a 10-year period of 2005-2014.

2 Methods

2.1 Study population

ED visit data for this analysis were obtained for 2005-2014 from 9 U.S. states: Arizona (Department of Health Services, 2010-2014), California (Department of Health Care Access and Information, 2005-2014), Georgia (Georgia Hospital Association, 2011-2014), Maryland (Department of Health, 2005-2014), Missouri (Department of Health and Senior Services, 2005-2014), New Jersey (Department of Health, Center for Health Statistics & Informatics, 2005-2014), New York (Department of Health, 2005-2014), North Carolina (North Carolina Hospital Discharge Database, 2007-2014), and Utah (Department of Health, 2005-2014). To avoid low counts of daily ED visits, 13 cities with the largest populations defined by core-based statistical areas (CBSAs) were selected from these 9 states, covering 157 counties in total (Table 1).

Primary diagnosis codes using the International Classification of Disease (ICD) version 9 and version 10 (World Health Organization, 2019) were used to identify CVD ED visits: all circulatory diseases (ICD-9: 390-459, ICD-10: I00 - I99), ischemic heart disease (ICD-9: 410-414, ICD-10: I20-I25), acute myocardial infarction (ICD-9: 410, ICD-10: I21, I22), and congestive heart failure (ICD-10: 428, ICD-10: I50). We also identified diabetes mellitus as the effect modifier using secondary diagnosis codes (ICD-9: 250, ICD 10: E10-E14). Daily time-series of ED visit counts for each CVD outcome were created by aggregating visits by day within each county.

Table 1. Summary for study period and cities defined by core-based statistical areas

State	Cities	Number of Counties	Time Span
Arizona	Phoenix, Tucson	6, 1	07/01/2010 – 12/31/2014
California	Los Angeles, San Francisco	5, 6	01/01/2005 – 12/31/2014
Georgia	Atlanta	37	01/01/2011 – 12/31/2014
New Jersey	New York City [a]	14	01/01/2005 – 12/31/2014
New York	New York City	9	01/01/2005 – 12/31/2014
North Carolina	Charlotte, Raleigh	11, 12	01/01/2007 – 12/31/2014
Maryland	Baltimore	13	01/01/2005 – 12/31/2014
Missouri	St. Louis, Kansas City	16, 19	01/01/2005 – 12/31/2014
Utah	Salt Lake City, Ogden	6, 2	01/01/2005 – 12/31/2014

[a] Different parts of New York City core-based statistical area were used for New Jersey and New York.

2.2 Air pollutants and meteorological data

Ambient air pollutant concentration data were obtained from a bias-corrected Community Multiscale Air Quality Model (CMAQ) product, which provided daily average concentration from 2005 to 2014 in the United States with a 12 km spatial resolution (Senthilkumar et al., 2022). Six pollutants were selected as exposures of the study, including NO_2, SO_2, O_3, CO, $PM_{2.5}$, and PM_{10}. We first calculated daily ZIP code level concentrations by overlaying the CMAQ data grid on ZIP code polygons, followed by averaging observations for all overlapped CMAQ grid cells. Then, population-weighted county-level pollutant concentrations were calculated, for use as the exposures in epidemiologic analyses, by applying annual ZIP code population numbers.

Daily maximum and minimum air temperature, along with water vapor pressure, were obtained from Daymet, which contains 1 km daily surface weather data (Hufkens et al., 2018). Daily mean air temperature was calculated by taking average of maximum and minimum temperature. Meteorological data were assigned to each ZIP code using ZIP code centroids, and

county-level averages were then calculated by averaging the meteorological data of the included ZIP codes.

2.3 Statistical methods

We utilized Quasi-Poisson log-linear models to estimate the association between concentrations of selected air pollutants and risk of ED visits for cardiovascular diseases. To mitigate possible non-linear effects of time-varying confounds, cubic splines for date, daily mean air temperature, and water vapor pressure as a measure of humidity, were included in the model. Additionally, we adjusted for indicators for weekday (Monday to Sunday) and federal holidays. The model can be expressed as:

$$log(E(Y_t)) = \alpha + cs_1(Tmean_t, df_1) + cs_2(VP_t, df_1) + cs_3(Date, df_2) + \beta_1 Pollutant_t + \beta_2 DOW_t + \beta_3 Holiday_t$$

where for a particular county, $E(Y_t)$ is the expectation of count for CVD ED visits on day t and α is the intercept of the model. The two cubic splines for meteorological covariates, cs_1 for lag 0 average daily air temperature and cs_2 for water vapor pressure, share the same degrees of freedom df_1, which was set to 6 in the primary model. Cubic splines for date are represented by cs_3 with df_2 set to 8 per year. Parameter β_1 represents the log relative risks for the pollutant of interest (lag 0), while β_2, β_3 are additional parameters for confounders.

Implementation of the model was conducted in two stages. In the first stage, we fitted the time-series models within each county, and in the second stage we performed a meta-analysis to obtain pooled estimations for each pollutant-outcome combination. We reported the pooled relative risk per interquartile range increase in the pollutant concentration. In the first stage, we excluded county-outcome combinations that led to non-convergence in regression results due to low daily counts in ED visits, which mainly appeared in MI and CHF outcomes. The second-

stage pooling assumes a random-effect model that accounts for between-county heterogeneity in associations.

Several sensitivity analyses were conducted by adjusting the degrees of freedom for cubic splines to examine the robustness of the model. Two situations were tested separately, one for holding df_1 for meteorological variables as 6 and changing df_2 for date from 6 to 12 per year, and the other for holding df_2 as 8 per year and switching df_1 from 6 to 8. The choice for degrees of freedom for the primary model were based on previous studies of air pollution and CVD hospital admissions (Dominici et al., 2006).

3 Results

Table 2 gives the summary statistics for daily air pollution and meteorology by state. Among all the states, New York has the highest average CO (0.63 ppm), SO_2 (6.86 ppb) and NO_2 (23.53 ppb) levels. Arizona along with Utah have the highest average concentration of O_3 (0.05 ppm). California, including Los Angeles and San Francisco, has the highest number in PM_{10} (22.23 μg/m^3). Meanwhile, Baltimore in Maryland has the highest average level of $PM_{2.5}$ (10.79 μg/m^3). The overall IQR for pollutants presented in Table 2 were later used for scaling the estimated relative risks.

Table 2. Means, minimum, maximum, and interquartile ranges (IQR) for air pollutants and meteorological data in 9 states.

State	Variable[a]	Mean	IQR	Min	Max	State	Variable	Mean	IQR	Min	Max
AZ	CO	0.32	0.17	0.09	1.66	NC	CO	0.36	0.20	0.06	4.56
	NO_2	6.03	4.03	0.31	65.52		NO_2	10.73	8.07	0.78	73.65
	O_3	0.05	0.01	0.01	0.12		O_3	0.04	0.02	0.00	0.12
	PM_{10}	20.61	9.85	2.72	212.73		PM_{10}	15.71	6.28	1.53	92.40
	$PM_{2.5}$	5.01	2.09	0.76	68.53		$PM_{2.5}$	9.82	4.91	0.69	42.82
	SO_2	1.35	1.20	0.00	69.93		SO_2	3.54	3.07	0.00	193.85
	VP [b]	880.93	679.79	74.10	3651.48		VP	1351.21	1308.04	147.27	3342.79
	Tmean	18.27	13.35	-16.70	39.33		Tmean	15.74	14.97	-10.35	33.24
CA	CO	0.52	0.38	0.05	7.18	MD	CO	0.44	0.30	0.05	8.25
	NO_2	17.13	17.34	0.50	133.62		NO_2	18.30	15.01	1.11	100.41
	O_3	0.04	0.02	0.00	0.17		O_3	0.04	0.02	0.00	0.12
	PM_{10}	22.23	11.28	1.85	262.72		PM_{10}	17.31	7.06	2.46	60.32
	$PM_{2.5}$	8.81	5.06	0.68	114.69		$PM_{2.5}$	10.79	5.96	0.96	45.52
	SO_2	1.94	1.77	0.00	132.23		SO_2	6.76	6.66	0.01	142.74
	VP	799.08	413.63	84.57	2860.06		VP	1252.00	1209.04	106.94	3728.91
	Tmean	16.39	8.72	-11.95	41.91		Tmean	13.21	16.44	-17.73	33.92
GA	CO	0.37	0.22	0.04	2.30	MO	CO	0.28	0.15	0.04	4.52
	NO_2	11.38	9.19	0.61	66.48		NO_2	11.22	9.47	0.51	143.32
	O_3	0.04	0.02	0.00	0.12		O_3	0.04	0.02	0.00	0.12
	PM_{10}	14.89	5.64	3.33	70.47		PM_{10}	17.40	8.09	2.36	88.07
	$PM_{2.5}$	9.07	4.17	1.27	32.25		$PM_{2.5}$	9.83	4.74	0.74	53.82
	SO_2	2.26	1.77	0.01	70.74		SO_2	4.33	3.50	0.01	154.52
	VP	1408.82	1260.89	139.13	3215.23		VP	1199.90	1269.99	67.24	3607.01
	Tmean	16.48	13.88	-13.11	32.58		Tmean	12.66	17.75	-21.47	34.76
NJ	CO	0.60	0.38	0.03	3.94	UT	CO	0.44	0.30	0.04	10.34
	NO_2	23.26	17.35	0.69	108.99		NO_2	13.43	14.02	0.22	110.20
	O_3	0.04	0.02	0.00	0.12		O_3	0.05	0.02	0.00	0.09
	PM_{10}	18.47	8.10	1.50	135.17		PM_{10}	16.73	9.03	1.80	171.65
	$PM_{2.5}$	10.41	6.00	1.21	51.90		$PM_{2.5}$	6.00	3.50	0.71	68.30
	SO_2	5.76	5.71	0.03	86.55		SO_2	1.57	1.43	0.00	44.86
	VP	1157.11	1106.60	87.00	3776.30		VP	652.72	409.63	25.89	3971.84
	Tmean	12.01	16.53	-16.89	34.14		Tmean	8.86	16.19	-25.33	34.67
NY	CO	0.63	0.40	0.04	4.26	**Overall**	CO	0.44	0.32	0.03	10.34
	NO_2	23.53	19.37	0.61	108.74		NO_2	15.60	15.87	0.22	143.32
	O_3	0.04	0.02	0.00	0.13		O_3	0.04	0.02	0.00	0.17
	PM_{10}	18.20	8.08	2.05	61.17		PM_{10}	17.96	8.26	1.50	262.72
	$PM_{2.5}$	10.32	6.12	1.20	47.97		$PM_{2.5}$	9.45	5.40	0.68	114.69
	SO_2	6.86	6.42	0.04	72.22		SO_2	4.13	3.86	0.00	193.85
	VP	1168.51	1111.38	77.08	3720.05		VP	1125.38	1018.16	25.89	3971.84
	Tmean	11.64	16.28	-18.47	33.49		Tmean	13.65	14.97	-25.33	41.91

[a] The units for variables are CO (ppm), NO_2 (ppb), O_3(ppm), PM_{10} ($\mu g/m^3$), $PM_{2.5}$ ($\mu g/m^3$), SO_2 (ppb), VP (pa), Tmean (degrees C).

[b] VP = water vapor pressure, Tmean = mean air temperature.

Table 3 shows the total counts and average daily ED visits for 4 types of CVD outcomes by states. Amongst all states, New Jersey has the smallest sample size. Acute myocardial infarction (MI) and congestive heart failure (CHF) have relatively lower counts compared to the other two outcomes.

Table 3. Summary statistics for ED visits for four CVD outcomes by states and combined.

State	Outcome [a]	Total Counts	Daily Mean	State	Outcome	Total Counts	Daily Mean
Arizona	CIRC	442542	269.02	North Carolina	CIRC	4360511	1492.3
	IHD	111905	68.03		IHD	1002173	342.98
	MI	11604	7.05		MI	119998	41.07
	CHF	48499	29.48		CHF	643280	220.15
California	CIRC	3495445	957.13	Maryland	CIRC	2458613	673.22
	IHD	781644	214.03		IHD	569513	155.95
	MI	97054	26.58		MI	59600	16.32
	CHF	542049	148.43		CHF	352697	96.58
Georgia	CIRC	2257355	1545.08	Missouri	CIRC	2069622	566.71
	IHD	453155	310.17		IHD	510717	139.85
	MI	44199	30.25		MI	58140	15.92
	CHF	297681	203.75		CHF	317577	86.96
New Jersey	CIRC	52974	14.51	Utah	CIRC	611659	167.49
	IHD	12617	3.45		IHD	102296	28.01
	MI	1522	0.42		MI	14155	3.88
	CHF	5386	1.47		CHF	67098	18.37
New York	CIRC	2328128	637.49	**Overall**	CIRC	18076849	4949.85
	IHD	560282	153.42		IHD	4104302	1123.85
	MI	61538	16.85		MI	467810	128.1
	CHF	351719	96.31		CHF	2625986	719.05

[a] CIRC = all circulatory diseases, IHD = ischemic heart disease, MI = acute myocardial infarction, CHF = congestive heart failure.

Figure 1(a) - 1(d) and Table 4 present the estimated overall relative risks and 95% confidence intervals for CVD ED visits associated with per IQR increase in air pollutant concentration (IQR for CO: 0.32 ppm; NO_2: 15.87 ppb; O_3: 0.02 ppm; PM_{10}: 8.26 μg/m^3; $PM_{2.5}$:

5.40 μg/m^3; SO_2: 3.86 ppb). The results for all circulatory disease indicate significant associations with CO (RR=1.002, 95% CI = [1.001, 1.003]), $PM_{2.5}$ (RR=1.001, 95% CI = [1.000, 1.002]), and SO_2 (RR=1.001, 95% CI = [1.000, 1.002], Figure 1(a)). Among specific CVD outcomes, an IQR increase in NO_2 was also significantly associated with increased risk on ED visits for ischemic heart disease (1.005, 95% CI = [1.001, 1.008], Figure 1(b)) and congestive heart failure (1.006, 95% CI = [1.001, 1.010], Figure 1(d)). No significant overall association was found between O_3 and PM_{10} with ED visits for any CVD outcomes investigated (Table 4). Moreover, our results did not identify pollutants with significant adverse effect on ED visits for acute myocardial infarction (Figure 1(c)), except marginally for SO2.

Table 4. Relative risk of ED visits for CVD associated with an IQR increase of pollutant concentration and 95% confidence intervals, combined and by diabetic status.

Outcome[a]	Pollutant	Overall RR (95% CI)	RR for Diabetic Patients (95% CI)	RR for Non-diabetic Patients (95% CI)
CIRC	PM_{10}	1.000 (0.999, 1.002)	1.004 (1.001, 1.006) *	0.999 (0.998, 1.001)
	$PM_{2.5}$	1.001 (1.000, 1.002) *	1.004 (1.002, 1.006) *	1.001 (1.000, 1.002)
	O_3	0.999 (0.997, 1.001)	0.998 (0.995, 1.001)	0.999 (0.997, 1.001)
	SO_2	1.001 (1.000, 1.002) *	1.002 (1.000, 1.003) *	1.001 (1.000, 1.002)
	CO	1.002 (1.001, 1.003) *	1.002 (1.000, 1.004) *	1.002 (1.000, 1.003) *
	NO_2	1.003 (0.994, 1.012)	1.007 (1.004, 1.010) *	1.004 (1.002, 1.006) *
IHD	PM_{10}	1.000 (0.998, 1.002)	1.003 (1.000, 1.007)	0.998 (0.996, 1.001)
	$PM_{2.5}$	1.002 (1.000, 1.003)	1.003 (1.000, 1.006)	1.001 (0.999, 1.003)
	O_3	0.999 (0.996, 1.003)	0.997 (0.992, 1.001)	1.001 (0.996, 1.005)
	SO_2	1.000 (0.999, 1.002)	1.000 (0.997, 1.004)	1.000 (0.999, 1.002)
	CO	1.001 (0.999, 1.003)	1.002 (0.999, 1.006)	1.001 (0.998, 1.003)
	NO_2	1.005 (1.001, 1.008) *	1.008 (1.003, 1.013) *	1.001 (0.994, 1.009)
MI	PM_{10}	0.995 (0.988, 1.001)	1.001 (0.990, 1.011)	0.994 (0.986, 1.001)
	$PM_{2.5}$	1.000 (0.994, 1.006)	1.005 (0.996, 1.014)	0.997 (0.990, 1.004)
	O_3	1.001 (0.992, 1.009)	1.002 (0.987, 1.016)	1.000 (0.989, 1.011)
	SO_2	1.004 (1.000, 1.008)	1.007 (1.001, 1.014) *	1.002 (0.997, 1.007)
	CO	1.003 (0.997, 1.008)	1.004 (0.995, 1.014)	1.002 (0.995, 1.009)
	NO_2	1.003 (0.994, 1.013)	1.020 (1.004, 1.036) *	0.995 (0.983, 1.007)

CHF	PM_{10}	1.000 (0.997, 1.003)	1.001 (0.996, 1.005)	1.000 (0.996, 1.003)
	$PM_{2.5}$	1.000 (0.998, 1.003)	1.000 (0.997, 1.003)	1.000 (0.996, 1.004)
	O_3	0.997 (0.993, 1.001)	0.994 (0.988, 0.999) *	0.999 (0.994, 1.004)
	SO_2	1.001 (0.999, 1.002)	1.000 (0.998, 1.002)	1.002 (1.000, 1.004)
	CO	1.002 (0.999, 1.004)	1.000 (0.997, 1.004)	1.003 (1.000, 1.007)
	NO_2	1.006 (1.001, 1.010) *	1.004 (0.992, 1.017)	1.006 (1.001, 1.012) *

[a] CIRC = all circulatory diseases, IHD = ischemic heart disease, MI = acute myocardial infarction, CHF = congestive heart failure.

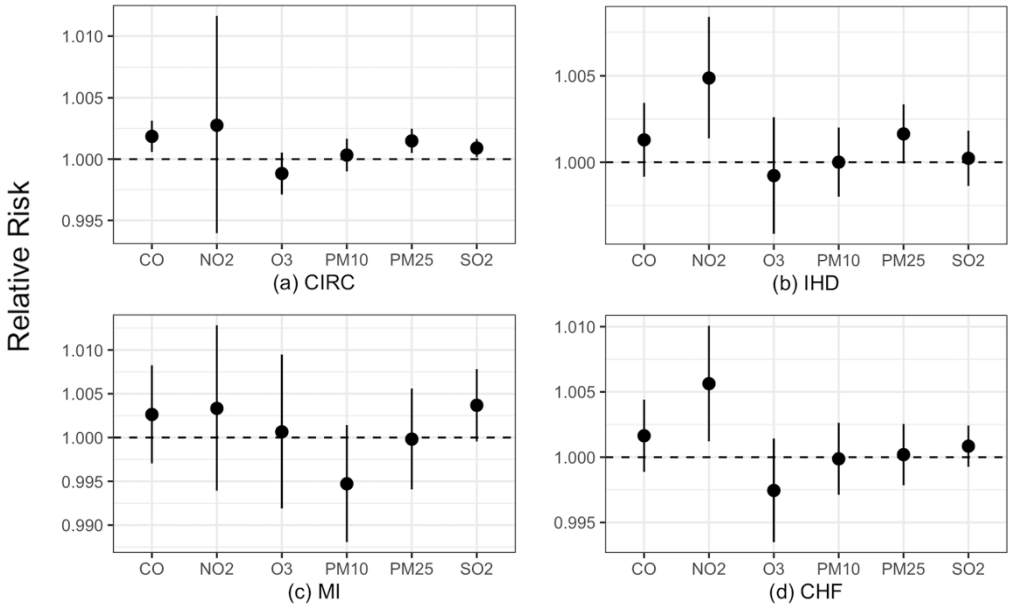

Figure 1. Relative risk and 95% confidence interval estimation of emergency department visits for different cardiovascular diseases with an IQR increase of air pollutant concentrations.

Diabetes mellitus as a potential effect modifier on the association between air pollution and CVD ED visits was inspected by dividing ED visits into two separate time-series. Amongst ED visits for all circulatory diseases, 30.14% had a diabetes co-diagnosis. This number was 39.56% for ischemic heart disease, 34.75% for acute myocardial infarction, and 41.98% for congestive heart failure.

As shown in Figure 2(a) and Table 4, diabetic patients are more vulnerable to the risk of all circulatory ED visits due to increased concentration of PM_{10} (RR = 1.004, 95% CI = [1.001, 1.006]), $PM_{2.5}$ (RR = 1.004, 95% CI = [1.002, 1.006]) and SO_2 (RR = 1.002, 95% CI = [1.000, 1.003]) compared to non-diabetic patients. Being diabetic also increases the risk of IHD ED visits (RR=1.008, 95% CI = [1.003, 1.013]) with increase in NO_2 concentration (Figure 2(b)). Figure 2(c) suggests that diabetic patients are more susceptible to the effect of NO_2 (RR = 1.020, 95% CI = [1.004, 1.036]) and SO_2 (RR = 1.007, 95% CI = [1.001, 1.014]) on the ED visits for MI. However, result for CHF (Figure 2(d)) shows a protective effect of diabetes on O_3 and CHF (RR=0.994, 95% CI = [0.988, 0.999]), indicating a decreased risk of CHF ED visits when O_3 concentration increases.

Furthermore, we observed in Table 4 that NO_2 has significant adverse effect on CIRC ED visits for both diabetic (RR = 1.007, 95% CI = [1.004, 1.010]) and non-diabetic (RR = 1.004, 95% CI = [1.002, 1.006]) groups separately, but becomes insignificant for the combined group (RR = 1.003, 95% CI = [0.994, 1.012]). Such situation could be caused by overdispersion in the model, or possibility of large underlying differences in baseline risks between diabetic and non-diabetic groups.

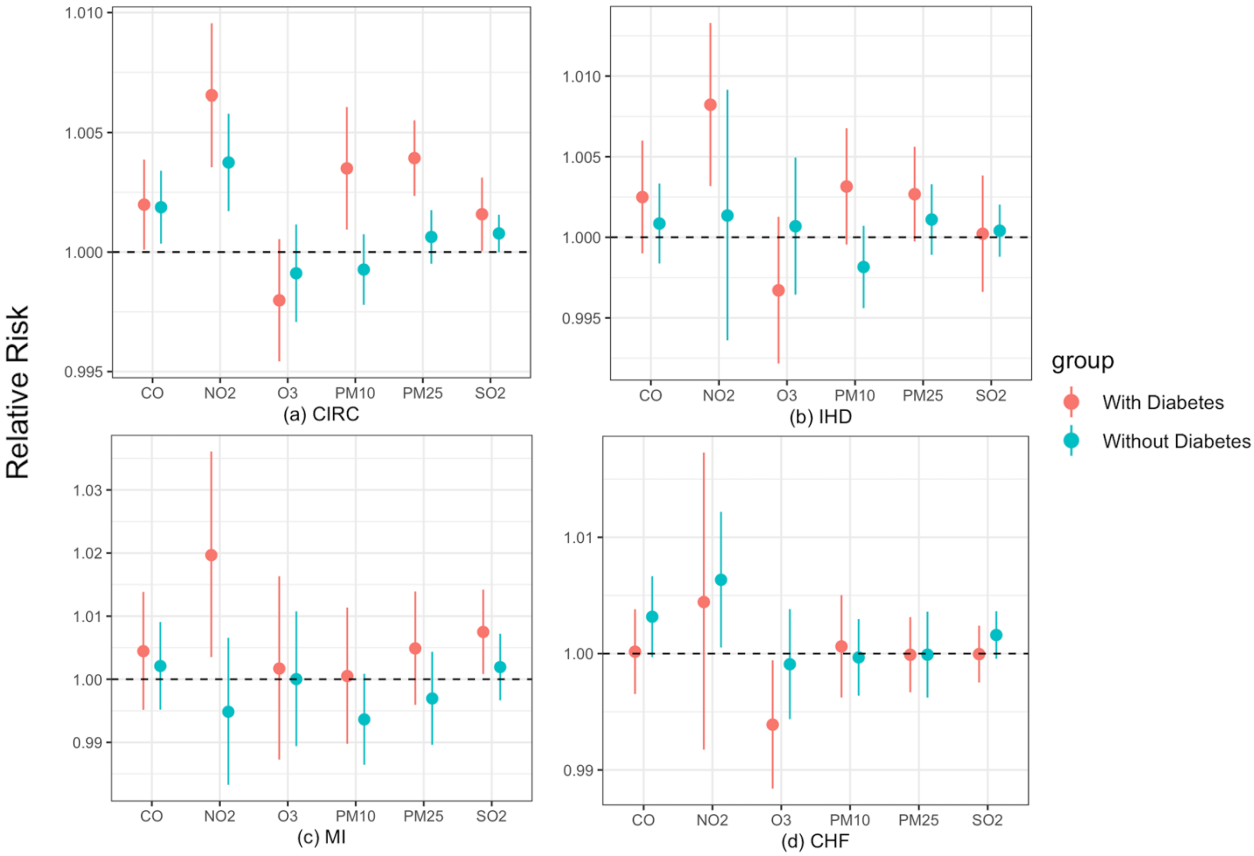

Figure 2. Relative risk and 95% confidence interval estimates of CVD ED visits associated with an IQR increase of pollutant concentration, stratified by diabetic and non-diabetic patients.

Sensitivity analysis was conducted by adjusting the degrees of freedom for cubic splines to test the robustness of the model. In Figure 3(a) - 3(d), the degrees of freedom for mean air temperature and water vapor pressure were held at 6, while the degrees of freedom for date was adjusted from 6 to 12 per year. The relative risk and 95% confidence intervals show possible residual confounding by time trend for several combinations of pollutants and health outcomes when degrees of freedom for date was set to 6, including O_3 on CIRC, NO_2 and O_3 on IHD, and O_3 on CHF. Another abnormality observed is that the confidence intervals are noticeably wider for PM_{10} when df = 12 in Figure 3(a), df = 7 in Figure 3(b), and df = 7 and 10 in Figure 3(c) compared to other df specifications. These abnormalities are partly due to non-divergence of the

quasi-passion log-linear regressions. Larger degrees of freedom per year resulted in more frequent non-convergence models and hence a larger confidence interval. In general, estimated pooled relative risks show good robustness with higher degrees of freedom for date beyond that used by the primary model (df = 8 per year).

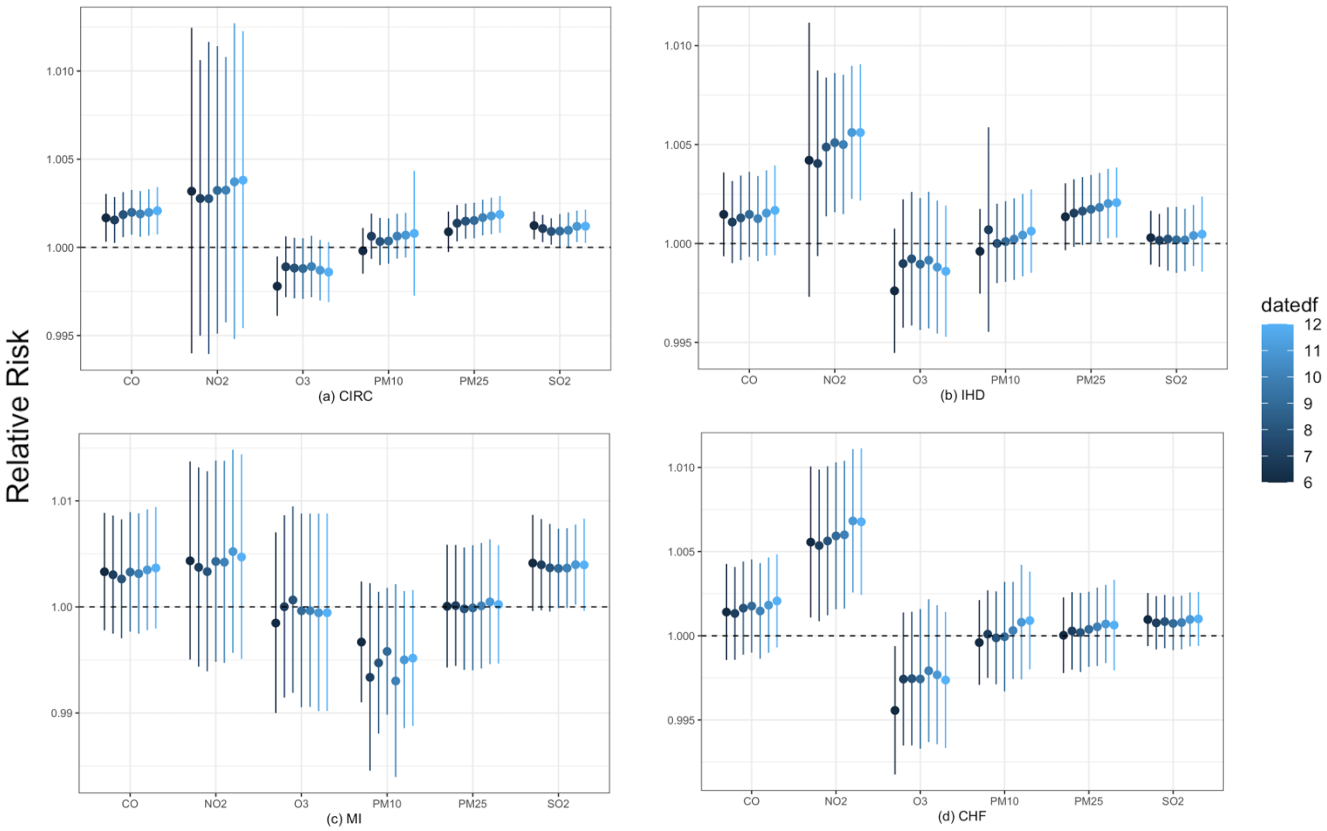

Figure 3. Relative risk and 95% confidence intervals of CVD ED visits associated with an IQR increase of air pollutant concentration, controlling degrees of freedom for mean air temperature and water vapor pressure (df = 6) while testing different degrees of freedom for date (df = 6-12).

Further sensitivity analysis was conducted by changing the degrees of freedom for daily mean air temperature and vapor pressure from 6 to 8 and holding the degrees of freedom for date at 8 per year. The relative risks and 95% CI estimates are consistent as shown in Figure 4. In contrast to adjustment by temporal trend, the change in meteorological df generated a much more stable result, indicating the robustness of the model under different adjustment of meteorology.

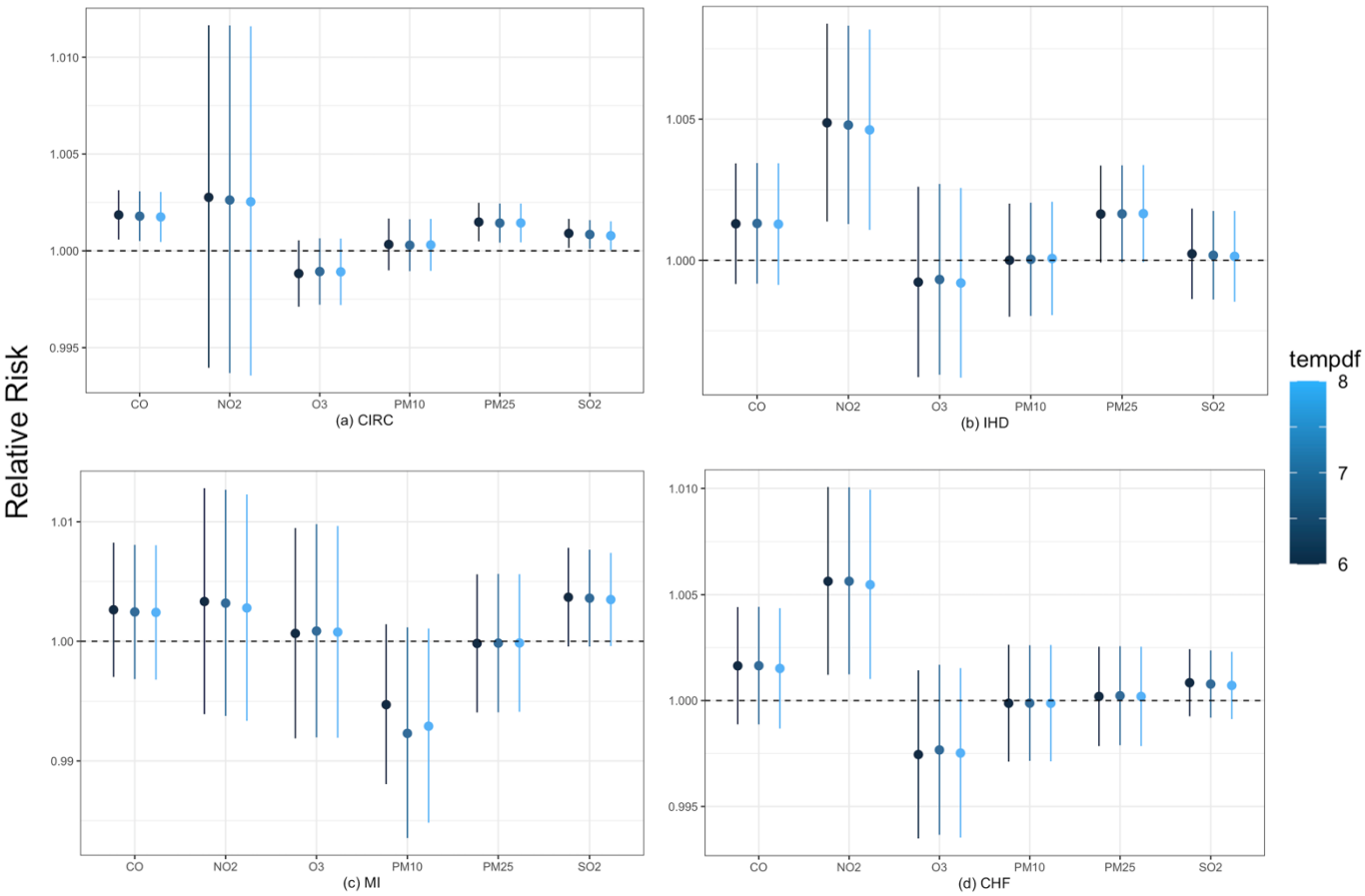

Figure 4. Relative risk and 95% confidence interval estimates of CVD ED visits associated with an IQR increase of air pollutant concentration, controlling for degrees of freedom for date (df = 8) while testing different degrees of freedom for mean air temperature and water vapor pressure (df = 6-8).

4 Discussion

In this study, we investigated the association between short-term (same-day) ambient air pollutant concentration and the risk of ED visits for CVD, and assessed effect modification by diabetes mellitus. The study included 13 cities in the United States with data collected over 2005-2014.

Our results suggest that short-term exposure to CO, $PM_{2.5}$, and SO_2 was associated with increased risk of ED visits for all circulatory diseases. For more specified CVD outcomes, NO_2

was associated with increased risk for ischemic heart disease and congestive heart failure ED visits. Moreover, significant positive associations between NO_2 and all circulatory disease was found in both diabetic and non-diabetic groups, but not in overall group. As for effect modification by diabetes mellitus co-diagnosis, our results in general indicate that being diabetic is associated with increased vulnerability towards short-term air pollutants. To be specific, we found that diabetes comorbidity increased the risk of $PM_{10,}$ $PM_{2.5}$ and SO_2 on ED visits for all circulatory diseases. It also modifies the effect of NO2 on ischemic heart disease, along with NO2 and SO2 on acute myocardial infarction.

Such findings are consistent with existing studies: a review study by Meo et al. (2015) found strong evidence for the association between PM_{10} and $PM_{2.5}$ and risk for CVD among existing literatures. The association between NO_2 and ED visits for ischemic heart disease aligns with the result of a study in Montreal, Canada (Szyszkowicz, 2007), while a study conducted in South Korean cities also indicated significant association between NO_2 and heart failure (Lee et al., 2021). The effect modification of diabetes also appears to be consistent with findings by previous studies (Tibuakuu et al., 2018; Akbarzadeh et al., 2018).

Despite the null effects of O_3 on CVD ED visits observed in overall group, a protective effect of O_3 on congestive heart failure was found in diabetic patients only. The overall null effect is supported by research of Frampton et al. (2015) who found no consistent effect by ozone on CVD in young healthy adults, but conflicts with previous findings by Pothirat et al. (2019) which suggested a positive association between ozone level and ED visits for heart failure. As for the protective effect of O_3 on congestive heart failure in diabetic patients, further research should be conducted in the future to examine the causation of such findings.

While the clinical mechanisms behind air pollutant and CVD are still under investigation, latest studies suggest particulate matters are likely to influence human health by inducing oxidative stress, inflammation, metabolic dysfunction and dyslipidemia, which leads to vascular dysfunction and atherosclerosis, as well as autonomic dysfunction and hypertension (Aryal et al., 2021). Meanwhile, clinical mechanisms behind the influence of gaseous pollutants on cardiovascular disease are still under-addressed in existing literatures.

Several strengths of this study were identified, with the most prominent one being the scale of the study, which covered all ED visits for CVD in 13 major cities in the time span of a decade, leading to high statistical power. Moreover, our research filled in the gap by adopting ED visits for CVD as the outcome of interest, whereas previous studies largely focused on hospital admissions and mortality. Another strength was that the study population covered all age groups instead of the commonly inspected one single age group of 65+ year-olds so that a more inclusive assessment of the risk was made. At last, effect modification by diabetes was explored in the study to provide a deeper understanding of potential high-risk subgroups within the population.

Besides the strengths, we also recognized some limitations of the study. First, population exposure to air pollutant was assessed by biased-corrected simulations from a numerical model. While this approach provides complete spatial and temporal coverage, it may not represent personal exposures. Second, the locations were mainly chosen to set in the urban areas where air pollution levels are disproportionately high compared to rural areas; while a focus on urban areas can capture a large percentage of the population, it is important to recognize that such a decision may lead to our results not being representative for the overall population (Tibuakuu et al., 2018). Furthermore, we examined each pollutant separately. Future research in the synergy effect

between gaseous pollutants should also be considered as pointed out by a study of Liu et al. (2022) in Liuzhou, China.

In conclusion, we found adverse effect of short-term ambient air pollutant on CVD ED visits, and that diabetes mellitus serves as a modifier to such effect by increasing patients' vulnerability toward certain air pollutants.

5 References

Akbarzadeh, M. A., Khaheshi, I., Sharifi, A., Yousefi, N., Naderian, M., Namazi, M. H., Safi, M., Vakili, H., Saadat, H., Alipour Parsa, S., & Nickdoost, N. (2018). The association between exposure to air pollutants including PM10, PM2.5, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide concentration and the relative risk of developing STEMI: A case-crossover design. *Environmental Research*, *161*, 299–303. https://doi.org/10.1016/j.envres.2017.11.020

Aryal, A., Harmon, A. C., & Dugas, T. R. (2021). Particulate matter air pollutants and cardiovascular disease: Strategies for intervention. *Pharmacology &Amp; Therapeutics*, *223*, 107890. https://doi.org/10.1016/j.pharmthera.2021.107890

Chen, H., Burnett, R. T., Kwong, J. C., Villeneuve, P. J., Goldberg, M. S., Brook, R. D., van Donkelaar, A., Jerrett, M., Martin, R. V., Brook, J. R., & Copes, R. (2013). Risk of Incident Diabetes in Relation to Long-term Exposure to Fine Particulate Matter in Ontario, Canada. *Environmental Health Perspectives*, *121*(7), 804–810. https://doi.org/10.1289/ehp.1205958

de Bont, J., Jaganathan, S., Dahlquist, M., Persson, Å., Stafoggia, M., & Ljungman, P. (2022). Ambient air pollution and cardiovascular diseases: An umbrella review of systematic

reviews and meta-analyses. *Journal of internal medicine*, *291*(6), 779–800. https://doi.org/10.1111/joim.13467

Dominici, F., Peng, R. D., Bell, M. L., Pham, L., McDermott, A., Zeger, S. L., & Samet, J. M. (2006). Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA*, *295*(10), 1127. https://doi.org/10.1001/jama.295.10.1127

Dominski, F. H., Lorenzetti Branco, J. H., Buonanno, G., Stabile, L., Gameiro da Silva, M., & Andrade, A. (2021). Effects of air pollution on health: A mapping review of systematic reviews and meta-analyses. *Environmental Research*, *201*, 111487. https://doi.org/10.1016/j.envres.2021.111487

Frampton, M. W., Pietropaoli, A., Dentler, M., Chalupa, D., Little, E. L., Stewart, J., Frasier, L., Oakes, D., Wiltshire, J., Vora, R., & Utell, M. J. (2015). Cardiovascular effects of ozone in healthy subjects with and without deletion of glutathione-*S*-transferase M1. *Inhalation Toxicology*, *27*(2), 113–119. https://doi.org/10.3109/08958378.2014.996272

Franchini, M., & Mannucci, P. M. (2012). Air pollution and cardiovascular disease. *Thrombosis Research*, *129*(3), 230–234. https://doi.org/10.1016/j.thromres.2011.10.030

Hufkens K, Basler D, Milliman T, Melaas EK, Richardson AD (2018). "An integrated phenology modelling framework in R: modelling vegetation phenology with phenor." *Methods in Ecology & Evolution*, **9**, 1-10. doi:10.1111/2041-210X.12970.

Lee, D. W., Han, C. W., Hong, Y. C., Oh, J. M., Bae, H. J., Kim, S., & Lim, Y. H. (2021). Short-term exposure to air pollution and hospital admission for heart failure among older adults in metropolitan cities: a time-series study. *International Archives of Occupational and Environmental Health*, *94*(7), 1605–1615. https://doi.org/10.1007/s00420-021-01724-9

Liu, H., Zhai, S., Kong, Y. *et al.* Synergistic effects of gaseous pollutants on hospital admissions for cardiovascular disease in Liuzhou, China. *Environ Sci Pollut Res* **29**, 9841–9851 (2022). https://doi.org/10.1007/s11356-021-16334-8

Manisalidis, I., Stavropoulou, E., Stavropoulos, A., & Bezirtzoglou, E. (2020). Environmental and Health Impacts of Air Pollution: A Review. *Frontiers in Public Health*, *8*. https://doi.org/10.3389/fpubh.2020.00014

Meo, S. A., & Suraya, F. (2015). Effect of environmental air pollution on cardiovascular diseases. *European review for medical and pharmacological sciences*, *19*(24), 4890–4897.

Milojevic, A., Wilkinson, P., Armstrong, B., Bhaskaran, K., Smeeth, L., & Hajat, S. (2014). Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. *Heart*, *100*(14), 1093–1098. https://doi.org/10.1136/heartjnl-2013-304963

Pennington, A. F., Strickland, M. J., Gass, K., Klein, M., Sarnat, S. E., Tolbert, P. E., Balachandran, S., Chang, H. H., Russell, A. G., Mulholland, J. A., & Darrow, L. A. (2019). Source-Apportioned PM2.5 and Cardiorespiratory Emergency Department Visits. *Epidemiology*, *30*(6), 789–798. https://doi.org/10.1097/ede.0000000000001089

Pereira Filho, M., Pereira, L., Arbex, F., Arbex, M., Conceição, G., Santos, U., Lopes, A., Saldiva, P., Braga, A., & Cendon, S. (2008). Effect of air pollution on diabetes and cardiovascular diseases in São Paulo, Brazil. *Brazilian Journal of Medical and Biological Research*, *41*(6), 526–532. https://doi.org/10.1590/s0100-879x2008005000020

Pothirat, C., Chaiwong, W., Liwsrisakun, C., Bumroongkit, C., Deesomchok, A., Theerakittikul, T., Limsukon, A., Tajarernmuang, P., & Phetsuk, N. (2019). Acute effects of air

pollutants on daily mortality and hospitalizations due to cardiovascular and respiratory diseases. *Journal of Thoracic Disease*, *11*(7), 3070–3083. https://doi.org/10.21037/jtd.2019.07.37

Rich, D. Q., Kipen, H. M., Zhang, J., Kamat, L., Wilson, A. C., & Kostis, J. B. (2010). Triggering of Transmural Infarctions, but Not Nontransmural Infarctions, by Ambient Fine Particles. *Environmental Health Perspectives*, *118*(9), 1229–1234. https://doi.org/10.1289/ehp.0901624

Senthilkumar, N., Gilfether, M., Chang, H. H., Russell, A. G., & Mulholland, J. (2022). Using land use variable information and a random forest approach to correct spatial mean bias in fused CMAQ fields for particulate and gas species. *Atmospheric Environment*, *274*, 118982. https://doi.org/10.1016/j.atmosenv.2022.118982

Song, X., Liu, Y., Hu, Y., Zhao, X., Tian, J., Ding, G., & Wang, S. (2016). Short-Term Exposure to Air Pollution and Cardiac Arrhythmia: A Meta-Analysis and Systematic Review. *International journal of environmental research and public health*, *13*(7), 642. https://doi.org/10.3390/ijerph13070642

Srebot, V., Gianicolo, E. A., Rainaldi, G., Trivella, M. G., & Sicari, R. (2009). Ozone and cardiovascular injury. *Cardiovascular Ultrasound*, *7*(1). https://doi.org/10.1186/1476-7120-7-30

Stieb, D. M., Zheng, C., Salama, D., Berjawi, R., Emode, M., Hocking, R., Lyrette, N., Matz, C., Lavigne, E., & Shin, H. H. (2020). Systematic review and meta-analysis of case-crossover and time-series studies of short term outdoor nitrogen dioxide exposure and ischemic heart disease morbidity. *Environmental Health*, *19*(1). https://doi.org/10.1186/s12940-020-00601-1

Szyszkowicz, M. (2007). Air Pollution and Emergency Department Visits for Ischemic Heart Disease in Montreal, Canada. *International Journal of Occupational Medicine and Environmental Health*, *20*(2). https://doi.org/10.2478/v10001-007-0015-3

Tibuakuu, M., Michos, E. D., Navas-Acien, A., & Jones, M. R. (2018). Air Pollution and Cardiovascular Disease: A Focus on Vulnerable Populations Worldwide. *Current epidemiology reports*, *5*(4), 370–378. https://doi.org/10.1007/s40471-018-0166-8

World Health Organization. (2019). *International statistical classification of diseases and related health problems* (10th ed.). https://icd.who.int/browse10/2019/en

Zhang, Q., Qi, W., Yao, W., Wang, M., Chen, Y., & Zhou, Y. (2016). Ambient Particulate Matter $PM_{2.5}$/PM_{10}) Exposure and Emergency Department Visits for Acute Myocardial Infarction in Chaoyang District, Beijing, China During 2014: A Case-Crossover Study. *Journal of Epidemiology*, *26*(10), 538–545. https://doi.org/10.2188/jea.je20150209