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Air pollution and hospitalization for acute complications of diabetes in Chile

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ABSTRACT

Exposure to air pollution has been shown to cause insulin resistance in mice. To determine the relevance to humans, we tested the association between daily air pollution concentrations and daily hospitalization for acute serious complications of diabetes, coma and ketoacidosis, in Santiago between 2001 and 2008, using generalized linear models with natural splines to control for long term trends.
For an interquartile range (IQR) increase in air pollutant, the relative risks (95% CI) of hospitalization for diabetes were: 1.15 (1.10, 1.20) for carbon monoxide (IQR = 1.00); 1.07 (0.98, 1.16) for ozone (IQR = 63.50); 1.14 (1.06, 1.22) for sulfur dioxide (IQR = 5.88); 1.12(1.05, 1.20) for nitrogen dioxide (IQR = 27.94); 1.11 (1.07, 1.15) for particulate matter ≤ 10 μm diameter(IQR = 34.00); and 1.11 (1.06, 1.16) for fine particulate matter ≤ 2.5 μm diameter (IQR = 18.50). Results were similar when stratified by age, sex and season. Air pollution appears to increase the risk of acute complications of diabetes requiring hospitalization, suggesting that improvements in air quality may reduce morbidity from diabetes.

1. Introduction

Diabetes is a major public health problem. The U.S. Centers for Disease Control and Prevention estimated that 8% of Americans, and 27% of those over sixty-four years old have diabetes, which is the most common cause of renal impairment, non-accidental lower limb amputation and a common cause of blindness (http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf). A population survey in Chile revealed prevalences of diabetes, defined by blood glucose, of 2% among adults between twenty and forty-four years old, and 11% among those between forty-five and sixty-four years old. (Baechler et al., 2002). A population-based incidence study of Chilean children less than fifteen years old estimated the incidence of type 1, insulin-dependent diabetes to be 4 per hundred thousand. (Carrasco et al., 2006). Several studies have observed that diabetics are more susceptible to the adverse cardiovascular effects of air pollution (Pereira Filho et al., 2008; Zanobetti and Schwartz, 2002; Zeka et al., 2006) but there are only a few reports suggesting that air pollution increases the incidence of, or mortality from diabetes. (Brook et al., 2008; Kah et al., 2004; Pearson et al., 2010). Whether or not short-term changes in air pollution influence acute diabetic control is not known.

There is evidence that air pollution can trigger oxidative stress and inflammation (Gurgueira et al., 2002; Hirano et al., 2003) and this type of inflammation may increase insulin resistance. (Sun et al., 2009). Therefore, it is biologically plausible that hospitalizations for diabetes could be increased on days of higher air pollution. We tested the hypothesis that air pollution increases the risk of hospital admissions for diabetic ketoacidosis and diabetic coma which are the most serious manifestations of acute loss of diabetic control. Of 312 admissions for diabetes with ketoacidosis, a hyperosmolar state or both, mortality was % 4.8 at an Australian tertiary care hospital between 1986 and 1999 (MacIsaac et al., 2002).We chose to study the population of Santiago, Chile because of the availability of high quality administrative databases and relatively high levels of air pollution (Kavouras et al., 2001).

2. Materials and methods

2.1. Air pollution data

In Santiago there are seven ambient air quality monitoring stations, in the communas Las Condes, La Florida, Independencia, El Bosque, Parque O´Higgins, Pudahuel, and Cerrillos. Monitors were not within 15 m of the nearest street or stationary combustion source, or within 50 m of roadways with at least 2500 vehicles passing daily.

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Cluster analysis identified four large sectors each of which have similar air pollution patterns, geography and meteorology (Gramsch et al., 2006) which are: Las Condes, Cerrillos + Pudahuel + Parque O´Higgins, Independencia, El Bosque + La Florida. Geographic areas (km^2) were: 11,748, 615, 139, 243 and 87. In sectors with more than one monitoring station, air pollution measurements were averaged and air pollution data from these monitors was assigned to all people within that sector. We used twenty-four hour means of air pollution data collected between January 2001 and December 2008. Ozone was measured by chemiluminescence with xylene, NO_2 by chemiluminescence with ozone, SO_2 by ultraviolet fluorescence, CO by infrared absorption, and PM_{10} and $PM_{2.5}$ were measured by low volume dichotomous samplers. La Florida, and El Bosque stations did not measure NO_2, and Independencia did not have measures of NO_2 or $PM_{2.5}$. Daily calibration was performed using reference gases and a calibrated ozone generator.

2.2. Diabetes hospitalization data

Data on daily hospitalizations were provided by the Departmento Estadísticas e Información de Salud, Ministerio de Salud, the official source of the health statistics data in Chile from January 2001 through to December 2008. Diabetes was coded using the International Classification of Disease, 10th Revision (ICD-10) (http://www.who.int/classifications/icd/en/). Analysis was restricted to diabetes as the principal diagnosis. The codes were E10 (insulin-dependent diabetes) and E11 (non-insulin-dependent diabetes). We further restricted admissions to those with acute deterioration of diabetic control by using only E10 and E11 code modifiers of .0 (with coma) and .1 (with ketoacidosis). This was done to minimize the probability of including cases where diabetes was present but not the reason for admission.

2.3. Statistical methods

We tested the log-linear association between air pollution and acute diabetic complications using generalized linear models (S-PLUS: Copyright (c) 1988, 2003 Insightful Corp. Professional Edition Version 6.2.1 for Microsoft Windows: 2003. Seattle, USA) assuming a Poisson distribution for the hospitalization data (Hastie and Tibshirani, 1990). To model seasonal and other long term trends in the data, we used natural cubic splines. For each sector we tested many equally spaced intervals for knots; every 15, 30, 60, 90, 120, 180, and 365 days of observation. The number of knots selected was determined by optimizing the Akaike Information Criteria (AIC) goodness of fit test and Bartlett's test for autocorrelation (Priestly, 1981), and visually examining plots of residuals versus time to ensure that no pattern existed. Using stepwise backwards and forwards regression we then tested the climate variables for inclusion using four degrees of freedom, one for each season while holding the variable for time in the model. From twenty-four hour means of temperature, humidity, barometric pressure, and humidex, the latter was selected both the value on the day of the admission and the day before. Humidex is a product of temperature and humidity which reflects discomfort (http://www.weatheroffice.gc.ca/mainmenu/faq_e.html#weather4b). Interactions between 24-hour means of air pollutants and twenty-four hour means of temperature, humidity and humidex were not included in the final model because the interaction terms were not significant at ($p > 0.05$) in models containing the main effects.

We also included an indicator variable for day-of-the-week. The effect of air pollution during the five days prior to admission and the day of admission was estimated using an unconstrained distributed lag model (Zanobetti et al., 2000). Relative risks of hospitalization were presented for an interquartile (twenty fifth to seventy fifth centile) increase in air pollution averaged over 24 h. We did not assume homogeneity of effect between sectors. Rather we used a random effects model with a random slope to pool the results (Lindstrom and Bates, 1990).

The final model was:

$$\mathrm{LogYt} = \mathrm{f}(\mathrm{Xt}, \mathrm{Xt}-1, \mathrm{Xt}-2, \ldots, \mathrm{Xt}-5) + \mathrm{ns}(\mathrm{time},\ \text{one knot/60 days}) + \mathrm{ns}(\mathrm{humidex}_t, 4\mathrm{df}) + \mathrm{ns}(\mathrm{humidext}_{t-1}, 4\mathrm{df}) + \mathrm{e}_t$$

where

Yt	is the response on day t,
x	is pollution variable;
f(•)	is a function of X on the current and previous days up to 5 days into the past; ns is natural splines;
ns	(time, 1 knot/60 days) is natural splines of time to control secular trends;
ns	($\mathrm{humidex}_t$, 4df) + ns($\mathrm{humidext}_{t-1}$, 4df) is natural splines to control for weather variables;
et	is the residual (error term).

3. Results

The general population of the sectors was approximately five million, and there were approximately 1.4 admissions daily for diabetic ketoacidosis or diabetic coma. Pollutant concentrations were lowest in Las Condes for all pollutants except for ozone and NO_2 where the greatest concentrations were observed (Table 1). Concentrations of CO, PM_{10} and $PM_{2.5}$ were greatest in La Florida and El Bosque.

The range of correlations between air pollutants within each sector are presented in Table 2. Carbon monoxide, particulate matter and nitrogen dioxide were moderately correlated, consistent with being from a common combustion source. Ozone had the lowest correlation coefficients with the other pollutants. In each of the four sectors, at least one air pollutant appeared to increase the risk of an acute diabetic complication (Table 3). Of all the pollutants measured, ozone was the only one that did not have a significant independent effect in any of the four sectors. For CO, PM_{10}, $PM_{2.5}$, the largest relative risks were seen in Florida and El Bosque. For NO_2 and SO_2 the largest relative risks were in Las Condes (Table 3). The observed effects for each pollutant in all 4 sectors were homogenous. For all pollutants combined the 95% confidence intervals overlapped but the largest relative risk was for an interquartile increase in CO which was associated with a 14.6% increase in complications of diabetes requiring hospitalization (Table 4). Ozone did not have a significant independent effect. In an exploratory subgroup analyses, relative risks were stable across sex, age, and season (Table 5). Effect sizes were non-significantly greater in those over eighty-five years old, and in the October to March period.

Two-pollutant models were created. The effect of SO_2 remained significant, defined by the 95% CI excluding zero, when any one of the other pollutant was entered into the model. The effect of NO_2 remained significant when any one of the other single pollutants was entered into the model except for SO_2. Fine particulate matter, PM_{10} and CO remained significant when any one of the other single pollutants was entered into the model except for NO_2. Ozone was not significant when it was accompanied by any other pollutant in the model.

4. Discussion

4.1. Summary of findings

Acute complications of diabetes occurred more frequently on days of greater concentrations of air pollutants, whether gases or particles. The use of distributed lags tends to provide higher relative risks than using a single lag (Zanobetti et al., 2000). Findings were consistent across age and sex and season. The observed effects were relatively consistent across geographic sectors. The relative risks by sector and by pollutant ranged from 1.06 to 1.25. When sectors were combined relative risks by pollutant had a slightly smaller range from 1.07 to 1.15. .Individual effects of air pollutants cannot be easily separated out. They have a common

Table 1
Sector-specific populations, number of daily hospitalizations for diabetic ketoacidosis and coma, and twenty four hour daily mean (interquartile range) [standard deviation] ambient air pollution concentrations. Santiago Province, 2001 through 2008.

Sector	Population [a]10^5	Daily hospitalizations	CO (ppm)	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)	PM_{10} (μg/m^3)	$PM_{2.5}$ (μg/m^3)
Independencia	4.21	0.19	0.95	54.46	NA	10.96	69.75	NA
		[0.44]	(1.14)	(57.82)		(6.33)	(34.17)	
			[0.83]	[33.53]		[5.44]	[30.41]	
Cerillos	21.08	0.57	0.96	62.51	39.23	9.34	72.13	34.22
Pudahuel Parque		[0.8]	(1.16)	(54.84)	(27.32)	(6.08)	(40.37)	(23.78)
			[1.06]	[33.26]	[23.91]	[5.03]	[35.63]	[21.04]
Florida	22.5	0.57	1.18	62.36	NA	9.91	77.43	34.27
El Bosque		[0.8]	(1.15)	(56.59)		(5.95)	(38.85)	(19.09)
			[0.92]	[34.39]		[5.04]	[33.66]	[16.42]
Las Condes	5.01	0.10	0.75	78.3	47.89	5.8	51.25	25.87
		[0.33]	(0.55)	(85.38)	(28.68)	(3.27)	(22.65)	(12.21)
			[0.45]	[49.03]	[26.11]	[2.57]	[18.60]	[11.07]
All sectors	52.8[a]	1.79[a]	0.96	64.41	43.56	9.00	67.64	31.45
			(1.00)	(63.50)	(27.94)	(5.88)	(34.00)	(18.50)
			[0.85]	[38.13]	[25.03]	[4.66]	[27.66]	[16.68]

[a] Total of column.

Table 2
Minimum and maximum Spearman correlation coefficients between air pollutants are for each of seven sectors in Chile.

	O_3	NO_2	SO_2	PM_{10}	$PM_{2.5}$
CO	−0.43, −0.28	0.78, 0.83	0.35, 0.75	0.63, 0.83	0.75, 0.91
O_3		−0.31, −0.17	−0.08, 0.08	−0.18, 0.14	−0.31, −0.15
NO_2			0.36, 0.63	0.63, 0.76	0.67, 0.79
SO_2				0.44, 0.75	0.43, 0.74
PM_{10}					0.82, 0.92

source, combustion of fossil fuels (Bascom, 1996), and therefore are correlated in time and space.

4.2. Selected review of relevant literature

There have been several epidemiologic studies of the relation between diabetes and air quality but none have addressed the question of acute diabetic complications. Previous studies suggest that air pollution increases the incidence of diabetes (Brook et al., 2008; Pearson et al., 2010), and that diabetes confers increased susceptibility to the adverse cardiovascular effects of air pollution. (O'Neill et al., 2005; Pereira Filho et al., 2008; Zanobetti and Schwartz, 2002; Zeka et al., 2006). More relevant to the present findings are two studies which addressed the effects of air pollution on mortality among those with diabetes. A daily time-series analysis in Montreal Quebec found that deaths from diabetes were more frequent on days of higher air pollution if there were co-morbidities such as cancer or cardiopulmonary disease. For an interquartile range increase in the mean of $PM_{2.5}$over the previous three days, the percentage increase in daily mortality was 8.37 (95%CI 1.80,15.37) (Goldberg et al., 2006). A second time-series analysis, done in Shanghai, China estimated that a 10 μg/m^3 increase in PM_{10} was associated with a 1.006 (95%CI, 1.000,1.012) relative risk increase in mortality from diabetes after adjusting for weather, and day-of-the-week effect (Kah et al., 2004). It was not clear however if the mortality was due to an acute loss of blood sugar control or due to acute worsening of pre-existing cardiovascular disease.

Animal toxicology supports a causal association between air pollution and acute diabetic complications. Air pollution causes oxidative stress and inflammation (Gurgueira et al., 2002) (Hirano et al., 2003). Exposure to fine particulate air pollution increased adipose tissue inflammation and insulin resistance in mice. Compared to 14 mice exposed to filtered air, 14 mice exposed to $PM_{2.5}$ for 24 weeks had higher blood glucose levels during a glucose tolerance test at 60,90, and 120 min. Stimulated

Table 3
Relative risk (95% CI) of hospitalization for diabetics ketoacidosis and coma associated with changes in pollutant concentrations equivalent to their interquartile ranges by region. A six-day distributed lag was used. Results were adjusted for long term trends, day-of-the week, and average humidex on the day of hospitalization and the day before. Santiago Province 2001 through 2008.

Sector	CO (1.00 ppm)	O_3 (63.50 ppb)	NO_2 (27.94 ppb)	SO_2 (5.88 ppb)	PM_{10} (34.00 μg/m^3)	$PM_{2.5}$ (18.50 μg/m^3)
Independencia	1.24	1.24	NA	1.17	1.14	NA
	(1.09,1.41)	(0.93,1.63)		(1.04,1.31)	(1.04, 1.26)	
Cerillos	1.06	1.08	1.11	1.06	1.06	1.07
Pudahuel Parque	(1.00,1.12)	(0.96,1.21)	(1.03,1.19)	(0.99,1.14)	(0.99, 1.12)	(1.01, 1.15)
Florida	1.25	1.02	NA	1.18	1.17	1.17
El Bosque	(1.17,1.35)	(0.88,1.17)		(1.11,1.27)	(1.10, 1.25)	(1.10, 1.25)
Las Condes	1.14	1.06	1.19	1.24	1.10	1.07
	(0.93,1.41)	(0.77,1.46)	(1.02,1.38)	(1.04,1.47)	(0.92, 1.31)	(0.93, 1.23)

Table 4
Pooled sector estimates of relative risk (95% CI) of hospitalization for diabetic ketoacidosis and coma associated with changes in single pollutant concentrations equivalent to their interquartile range. A six-day distributed lag was used. Results were adjusted for long term trends, day-of-the-week, and average humidex on the day of hospitalization and the day before. Santiago Province, 2001 through 2008.

CO (1.00 ppm)[a]	O_3 (63.50 ppb)	NO_2 (27.94 ppb)	SO_2 (5.88 ppb)	PM_{10} (34.00 μg/m^3)	$PM_{2.5}$ (18.50 μg/m^3)
1.146 (1.098, 1.197)	1.069 (0.982, 1.163)	1.121 (1.05, 1.197)	1.139 (1.064, 1.22)	1.110 (1.069, 1.152)	1.108 (1.063, 1.155)

[a] Interquartile range.

Table 5
Pooled sector estimates of relative risk (95% CI) of hospitalization for diabetic ketoacidosis and coma associated with changes in pollutant concentrations equivalent to their interquartile range, by age, gender, and season. Santiago Province, 2001 through 2008.

Category		CO (1.00 ppm)[a]	O_3 (63.50 ppb)	NO_2 (27.94 ppb)	SO_2 (5.88 ppb)	PM_{10} (34.00 μg/m^3)	$PM_{2.5}$ (18.50 μg/m^3)
Gender	M	1.147	0.991	1.132	1.171	1.132	1.142
		(1.073, 1.227)	(0.883, 1.111)	(1.028,1.247)	(1.092, 1.256)	(1.071,1.196)	(1.072, 1.216)
	F	1.137	1.17	1.115	1.134	1.108	1.102
		(1.013, 1.277)	(1.042, 1.313)	(1.017,1.222)	(1.066, 1.207)	(1.052,1.168)	(1.041, 1.166)
Age (yr)	≤64	1.196	1.08	1.180	1.138	1.146	1.157
		(1.137, 1.257)	(0.982, 1.187)	(1.088,1.279)	(1.079, 1.190)	(1.096,1.199)	(1.101, 1.215)
	65–64	1.128	1.043	1.026	1.151	1.109	1.062
		(0.948, 1.342)	(0.77, 1.413)	(0.87, 1.209)	(1.009, 1.313)	(0.985,1.248)	(0.951, 1.188)
	75–84	1.18	1.388	1.133	1.302	1.197	1.196
		(1.015, 1.373)	(1.057, 1.822)	(0.926,1.387)	(1.157, 1.464)	(1.054,1.359)	(0.977, 1.466)
	>85	1.384	1.401	1.346	1.235	1.265	1.333
		(1.023, 1.871)	(1.057, 1.745)	(1.013,1.788)	(1.01, 1.511)	(1.073,1.492)	(1.106, 1.605)
Season	Apr–Sep	1.140	1.23	1.114	1.149	1.110	1.106
		(1.039, 1.251)	(1.057, 1.433)	(1.016, 1.221)	(1.084, 1.219)	(1.029, 1.190)	(1.041, 1.175)
	Oct–Mar	1.209	1.243	1.349	1.115	1.179	1.202
		(1.080, 1.353)	(1.049, 1.474)	(1.051, 1.73)	(1.008, 1.234)	(1.005, 1.384)	(0.994, 1.455)

[a] Interquartile ranges.

vasoconstriction and relaxation of aortic rings was reduced. Adipose tissue macrophages increased and expressed inflammatory mediators such tumor necrosis factors and interleukin-6. The authors suggested that particulate air pollution increases cellular adhesion molecules which increase the migration of macrophages into adipose tissue. This promotes adipose tissue inflammation which inhibits insulin responsiveness (Sun et al., 2009).

4.3. Strengths and limitations of the present study

Analyzing several thousand days of data permitted enough power to detect the effect of air pollution on a relatively uncommon event. It is unlikely that cases of diabetic ketoacidosis or coma recognized in the emergency department or an ambulatory clinic would not be admitted to hospital. Therefore it is likely that hospital admission data captured nearly all diagnosed cases. Evidence that data from fixed site monitors in Santiago are reflective of indoor and personal exposure monitors comes from a study by Rojas-Bracho et al. that found all three monitoring scenarios reported values for $PM_{2.5}$ which were within 5% (Rojas-Bracho et al., 2002). In the present study, we need only assume that changes in outdoor air pollution correlate with changes in personal exposure. The absolute levels are less important than day-to-day changes. If personal exposure to air pollution is aggravating diabetes, then random measurement error resulting from using fixed site monitors would tend to provide an minimize the observed effect leading to an underestimation of the true effect (Zeger et al., 2009). In this time-series analysis confounding by personal factors such as age, sex, smoking, comorbidities, and medications would be unlikely since we compare the hospital experience on high to low air pollution days in the same population. To ensure the methods of analysis do not create artifactual associations we previously tested associations between air pollution and hospitalization for disorders that were not plausibly related to air pollution (acute and chronic prostatitis and pancreatitis) and found no significant effects (Dales et al., 2010).

4.4. Conclusion

Acute increases in ambient air pollution appear to increase the risk of acute serious diabetic complications requiring hospitalization. Air quality can be modified through legislation. This observation should be considered when calculating the health burden and costs to society of air pollution.

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