Journal of Thrombosis and Haemostasis, **8**: 669–674 DOI: 10.1111/j.1538-7836.2010.03760.x

IN FOCUS

Air pollution and hospitalization for venous thromboembolic disease in Chile

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To cite this article: Dales RE, Cakmak S, Vidal CB. Air pollution and hospitalization for venous thromboembolic disease in Chile. *J Thromb Haemost* 2010; **8:** 669–74.

See also Mannucci PM. Fine particulate: it matters. This issue, pp 659–61; Bonzini M, Tripodi A, Artoni A, Tarantini L, Marinelli B, Bertazzi PA, Apostoli P, Baccarelli A. Effects of inhalable particulate matter on blood coagulation. This issue, pp 662–8.

Summary. *Background:* Ambient air pollution is a risk factor for stroke and myocardial infarction, possibly because of alterations in coagulation that influence the arterial circulation. Whether air pollution influences diseases associated with peripheral venous thrombogenesis remains largely unknown. *Objectives:* To determine the association between air pollution and venous thromboembolic disease (VTE) in a sample of the general population. *Methods:* A time-series analysis was used to test the association between daily air pollution and VTE hospitalizations in Santiago between 2001 and 2005. Results were adjusted for long-term trends, day of the week and average daily humidex. *Results:* From a population of 5.4 million, there were, on average, 2.3 admissions for VTE per day. Pooled estimates of relative risk (RR) [95% confidence interval (CI)] of hospitalization for venous disease were: 1.07 (1.05, 1.09) for a 58.4 p.p.b. increase in ozone (O_3); 1.06 (1.02, 1.09) for a 5.85 p.p.b. increase in sulphur dioxide (SO_2); 1.08 (1.03, 1.12) for a 29.25 μg/m^3 increase in nitrogen dioxide (NO_2); and 1.05 (1.03, 1.06) for a 20.02 μg/m^3 increase in particulate matter ≤ 2.5 μm in mean aerodynamic diameter ($PM_{2.5}$). For pulmonary embolism (PE) results were: 1.10 (1.07, 1.13) for O_3; 1.05 (1.02, 1.08) for SO_2; 1.07 (1.04, 1.09) for NO_2; and 1.05(1.03, 1.06) for $PM_{2.5}$, respectively. *Conclusion:* Air pollution appears to be a risk factor for venous thrombosis and PE, a disease with a significant fatality rate.

keywords: air pollution, environment, epidemiology, venous thromboembolic disease.

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Received 21 October 2009, accepted 12 January 2010

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Introduction

Each year venous thromboembolism (VTE) occurs in approximately one in every thousand people [1–3]. A study of inhabitants in South West France reported 1.25 cases of deep venous thrombosis (DVT) and 0.60 cases of pulmonary embolism (PE) per thousand [4]. In Malmo, Sweden, the annual incidence of DVT as determined by phlebography was 1.6 per 1000 residents [5]. In central Norway between 1995 and 2001, the incidence rate for VT and PE among adults was 1.43 and 0.93 per thousand person years of observation, respectively [6]. The 1-month case fatality is approximately 5–6% for DVT and 10–12% for PE [6,7]. Risk factors include old age, pregnancy, prolonged immobility, malignancy, major surgery and multiple trauma. Deficiencies in antithrombin, protein C and protein S http://circ.ahajournals.org/cgi/content/full/107/23_suppl_1/I-9 - R79-M03-00006#R79-M03-00006, elevated plasma concentrations of factors (F)VIII, IX and XI; and factor (F)V Leiden and prothrombin G20210A mutations may also confer an increased risk [8].

Although air pollution influences coagulation and increases the risk of stroke and myocardial infarction, [9] disorders of the systemic arterial circulation, there are only two epidemiologic studies of the adverse effect of air pollution on VT. A case–control study in the Lombardy area of Italy found an association between DVT and estimated exposure over the previous year to particulate air pollution < 10 μm in mean aerodynamic diameter (PM_{10}) [10]. Another case–control study in the same geographic area found that the risk of being diagnosed with DVT was higher among those living closer to a major traffic route [11]. The present study supports this association, and contributes new information by looking at the acute effects of air pollution on hospitalization for VT and PE. We used time-series analysis to compare the frequency of VTE on days with higher air pollution to days of lower air pollution in Santiago, Chile. This city has high levels of air pollution by North American and Western European standards [12].

Methods

Air pollution data

Daily air pollution data for Santiago Province between April 1998 and August 2005 were obtained from seven monitoring stations in seven municipalities: Las Condes, Cerillos, El Bosque, La Florida, Independencia, Santiago and Pudahuel. These stations measured the pollutants O_3, NO_2, SO_2, CO, PM_{10} and $PM_{2.5}$. NO_2 is not measured at Independencia, La Florida, or El Bosque. Fine particulate matter is not measured at Independencia. We assigned the air pollution concentrations from each of these seven monitored areas to their adjacent municipalities. For analysis, we used 24 h averaged daily mean air pollution concentrations except for O_3, which is expressed as the average of the maximum 1-h daily means.

Hospitalization data

The daily number of hospitalizations was obtained from the Instituto Nacional de Estadisticas, the official source of statistical data in Chile from April 1998 to August 2005. We defined VT as the disorders coded as discharge diagnosis I80, according to the International Classification of Disease, 10th Revision (ICD-10) (http://www.who.int/classifications/icd/en/). This code includes deep VT, thrombosis of the lower extremity and thrombophlebitis of the femoral vein. 2.5% of the I80 codes in the Chile database corresponded to superficial venous disease. PE was coded as I26.

Statistical methods

We assumed a Poisson distribution, and used time-series analyses. A linear association between ambient air pollution and daily admission to hospital was assumed on a logarithmic scale [13]. We tested natural splines with 1, 2, 3, 4, 6, 12 and 24 degrees of freedom (d.f.) per year to control for secular trends in the data. We then selected a model with 2 d.f. per year based minimizing the Akaike information criterion (AIC), a measure of model prediction and on evidence that the model residuals did not display any type of structure, including serial correlation, using Bartlett's test [14].

We plotted model residuals of admissions against time and found neither a significant pattern nor correlation.

We assessed the 24-h mean humidex (a combination of humidity and temperature) every 0–14 days. With humidex in the model, temperature and barometric pressure were not significant modifiers if taken between 0 and 3 days apart. The final model included humidex readings on the day of VTE admission and the day prior to that. We accounted for potential non-linear associations with VTE using natural spline functions at 3 d.f. for both humidex terms. Indicator functions for the day of the week were also included. We used an unconstrained distributed lag model to estimate the effect size between 0 and 14 days [15] and expressed the results as an increase in relative risk (RR) of VTE for an interquartile increase in each pollutant. Results from each region were pooled using a random effects model.

Results

The seven regions (the municipality where the air pollution was measured and the adjacent municipalities) varied in population from 420 000 in Independencia to 1 335 000 in La Florida (Table 1). The mean number of daily admissions for VT (1.5) was double that for PE (0.75). The 24-h mean air pollutant concentrations varied approximately 2-fold between regions (Table 2). Cerrillos had the greatest concentrations of PM_{10}, SO_2 and NO_2, and the second highest concentration of SO_2. Las Condes had the highest levels of O_3. Concentrations of air pollutants correlated with each other, with the exception of O_3. The greatest and smallest regional correlation coefficients for $PM_{2.5}$ were: 0.85 to 0.92 for PM_{10}, –0.32 to –0.14 for O_3, 0.4 to 0.83 for CO, 0.73 to 0.92 for NO_2 and 0.72 to 0.83 for SO_2. The RR point estimates by region, tended to be higher for associations between pollutant concentration and PE, than for VT (Table 3). Although the incidence of PE was approximately half that of VT, the lower 95% confidence intervals (CI) exceeded one more often for PE. For PE, RR exceeded 1.2 for the associations with CO in Las Condes, and O_3 in El Bosque and La Florida. With regions pooled, the RR in single pollutant models varied from 1.044 between VT and PM_{10} to 1.102 between PE and O_3 (Table 4). Significant effects of air pollutants were also found in multi-pollutant models, with the exception of SO_2 and $PM_{2.5}$ for VT. The greatest RR for both PE and VT in the multi-pollutant models were O_3, 1.044 (95% CI 1.021, 1.068) and 1.059 (95% CI 1.0341, 1.084), respectively. For the associations between air pollutants and VT and PE, there were no statistical differences between 2-, 7- and 14-day unconstrained distributed lags, although the maximum point estimates of effect size for $PM_{2.5}$ were found at 14 days for VT and 7 days for PE. $PM_{2.5}$ effects were 1.017 (95% CI 0.990, 1.044) at 2 days, 1.022 (95% CI 0.996, 1.055) at 7 days and 1.031 (95% CI 0.987, 1.076) at 14 days. For PE respective values were: 1.052 (95% CI 1.028, 1.076) at 2 days, 1.062 (95% CI 1.032, 1.092) at 7 days and 1.048 (95% CI 1.009, 1.089) at

Table 1 City-specific population and mean number of daily hospitalizations in Santiago Province between 2001 and 2005

Region*	Population ($\times 10^5$)	Daily admissions for VT	Daily admissions for PE
Las Condes	5.01	0.170 (0, 1)†	0.080 (0, 1)
Cerrillos	8.92	0.217 (0, 2)	0.120 (0, 1)
El Bosque	9.15	0.236 (0, 2)	0.128 (0, 1)
La Florida	13.35	0.344 (0, 3)	0.141 (0, 2)
Independencia	4.21	0.279 (0, 1)	0.081 (0, 1)
Parque	4.98	0.121 (0, 1)	0.071 (0, 1)
Pudahuel	8.08	0.197 (0, 1)	0.125 (0, 1)
Total	53.7	1.549	0.754

VT, venous thrombosis; PE, pulmonary embolism. *The municipality where the air pollution is monitored and the adjacent municipalities to which the air pollution is assumed to apply. †In parentheses is the minimum and maximum number of daily admissions.

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Table 2 Ambient air pollution concentrations in Santiago Province between 2001 and 2005. Values are 24-h averaged daily means except for O_3 which is expressed as the average of the maximum 1-h daily means

Municipality	CO (p.p.m.)	O_3 (p.p.b.)	NO_2 (p.p.b.)	SO_2 (p.p.b.)	PM_{10} (μg m^{-3})	PM_{25} (μg m^{-3})
Las Condes	0.80	85.49	52.77	5.76	52.46	26.11
	(0.56)*	(89.42)	(30.21)	(3.17)	(22.11)	(12.15)
Cerrillos	0.92	68.70	44.40	10.46	73.30	NA
	(1.13)	(50.47)	(33.02)	(7.64)	(41.81)	
El Bosque	1.23	62.16	NA	11.32	77.87	NA
	(1.24)	(49.98)		(7.20)	(40.12)	
La Florida	1.26	73.00	NA	8.37	76.83	34.25
	(1.23)	(63.21)		(4.91)	(36.78)	(19.09)
Independencia	1.04	58.44	NA	11.11	67.60	NA
	(1.24)	(58.07)		(6.25)	(33.57)	
Parque	1.08	70.80	44.72	9.32	70.25	35.43
	(1.33)	(61.8)	(32.70)	(6.44)	(39.43)	(24.58)
Pudahuel	1.07	64.95	40.10	7.30	73.71	33.67
	(1.04)	(47.77)	(21.78)	(5.02)	(42.25)	(23.61)
Average	1.09	69.05	44.73	9.12	72.34	32.99
	(1.13)†	(58.43)†	(29.25)†	(5.85)†	(37.63)†	(20.02)†

CO, carbon monoxide; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulphur dioxide PM, particulate matter *Values in parentheses are the interquartile range. †Population weighted average pollutant concentration.

Table 3 Relative risks (95% CI) for hospitalization associated with changes in pollutant concentrations equivalent to their interquartile ranges by region. Results were adjusted for long-term trends, day of the week and average humidex on the day of hospitalization as well as the preceding day. Data from Santiago Province between 2001 and 2005

Regions	Disease	CO (1.13 p.p.m.)*	O_3 (58.43 p.p.b.)	NO_2 (29.25 μg m^{-3})	SO_2 (5.085 p.p.b.)	PM_{10} (37.63 μg m^{-3})	PM_{25} (20.02 μg m^{-3})
Las Condes	VT	1.122	1.121	1.148	1.132	1.068	1.054
		(1.056, 1.191)†	(0.955, 1.201)	(1.08, 1.219)	(1.056, 1.213)	(1.016, 1.122)	(1.009, 1.100)
	PE	1.048	1.115	1.071	1.059	1.063	1.042
		(1.014, 1.092)	(0.979, 1.217)	(1.014, 1.131)	(1.009, 1.111)	(1.005, 1.125)	(0.997, 1.089)
Cerillos	VT	1.039	1.052	1.040	1.041	1.030	NA
		(1.002, 1.077)	(0.986, 1.091)	(0.989, 1.094)	(0.999, 1.084)	(1.002, 1.058)	
	PE	1.065	1.054	1.036	1.053	1.029	NA
		(1.025, 1.107)	(1.009, 1.120)	(1.004, 1.070)	(1.020, 1.87)	(1.003, 1.056)	
El Bosque	VT	1.055	1.053	NA	1.043	1.049	NA
		(1.011, 1.101)	(1.022, 1.133)		(1.007, 1.081)	(1.018, 1.081)	
	PE	1.059	1.183	NA	1.040	1.053	NA
		(1.023, 1.100)	(1.035, 1.445)		(1.015, 1.067)	(1.028, 1.079)	
Florida	VT	1.029	1.059	1.059	1.095	1.042	1.092
		(0.992, 1.066)	(1.016, 1.138)	(1.018, 1.102)	(1.034, 1.160)	(1.010, 1.074)	(1.002, 1.191)
	PE	1.070	1.175	NA	1.052	1.058	1.062
		(1.027, 1.115)	(1.033, 1.425)		(1.023, 1081)	(1.030, 1.087)	(1.033, 1.093)
Independencia	VT	1.040	1.085	NA	1.075	1.037	NA
		(0.987, 1.097)	(1.005, 1.183)		(1.007, 1.147)	(0.999, 1.077)	
	PE	1.178	1.073	NA	1.072	1.062	NA
		(1.091, 1.273)	(0.969, 1.113)		(1.028, 1.119)	(1.028, 1.097)	
Parque	VT	1.029	1.061	NA	1.032	1.021	1.019
		(0.993, 1.066)	(0.984, 1.108)		(0.999, 1.066)	(0.992, 1.051)	(0.984, 1.057)
	PE	1.049	1.057	NA	1.039	1.031	1.047
		(1.021, 1.078)	(1.007, 1.120)		(1.014, 1.065)	(1.005, 1.058)	(1.017, 1.078)
Pudahuel	VT	1.026	1.058		1.018	1.021	1.020
		(0.997, 1.056)	(0.945, 1.058)		(0.999, 1.038)	(0.995, 1.048)	(0.989, 1.052)
	PE	1.067	1.056		1.028	1.027	1.033
		(1.023, 1.114)	(1.015, 1.132)		(1.002, 1.054)	(1.002, 1.052)	(1.009, 1.058)

VT, venous thrombosis; PE, pulmonary embolism. *Interquartile range †95% CI.

14 days. For all pollutants, those 64 years or older had a greater RR of VTE than those aged less than 64 years (Table 5). There was no consistent evidence for effect modification by gender or season. Consistent with the strong clinical association between VT and PE, the statistical associations between VTE (VT and PE combined) and air pollutants were not significantly different than the associations with VT and PE individually. For VTE the RR were: 1.062 (95% CI 1.028,

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Table 4 Pooled city estimates of relative risk (95% CI) of hospitalization associated with changes in pollutant concentrations equivalent to their interquartile range by model type. Results were adjusted for long-term trends, day of the week and average humidex on the day of hospitalization as well as the preceding day. Data from Santiago Province between 2001 and 2005

Single pollutant model						
Disease	CO (1.13 p.p.m.)*	O_3 (58.43 p.p.b.)	NO_2 (29.25 μg m^{-3})	SO_2 (5.85 p.p.b.)	PM_{10} (37.63 μg m^{-3})	PM_{25} (20.02 μg m^{-3})
Venous thrombosis	1.049 (1.036, 1.062)	1.070 (1.046, 1.094)	1.075 (1.032, 1.118)	1.062 (1.019, 1.089)	1.044 (1.032, 1.054)	1.046 (1.029, 1.063)
Pulmonary embolism	1.077 (1.064, 1.090)	1.102 (1.074, 1.130)	1.065 (1.039, 1.091)	1.049 (1.023, 1.075)	1.046 (1.033, 1.058)	1.046 (1.033, 1.059)
Multi pollutant model						
Disease	CO (p.p.m.)	O_3 (p.p.b.)	NO_2 (μg/m^3)	SO_2 (p.p.b.)	PM_{10} (μg/m^3)	PM_{25} (μg/m^3)
Venous thrombosis	1.016 (1.004, 1.028)	1.059 (1.034, 1.084)	1.040 (1.002, 1.079)	1.012 (0.997, 1.028)	1.017 (1.004, 1.029)	1.015 (0.971, 1.062)
Pulmonary embolism	1.025 (1.002, 1.049)	1.044 (1.021, 1.068)	1.035 (1.014, 1.058)	1.018 (1.007, 1.029)	1.024 (1.008, 1.041)	1.022 (1.006, 1.039)

*Interquartile range.

Table 5 Pooled city estimates of relative risk (95% CI) of hospitalization associated with changes in pollutant concentrations equivalent to their interquartile range, by age, gender, season and lagging time. Results were adjusted for long-term trends, day of the week and average humidex on the day of hospitalization as well as the preceding day Data from Santiago Province between 2001 and 2005

Disease	Category		CO (1.13 p.p.m.)*	O_3 (58.43 p.p.b.)	NO_2 (29.25 μg m^{-3})	SO_2 (5.85 p.p.b.)	PM_{10} (37.63 μg m^{-3})	PM_{25} (20.02 μg m^{-3})
Venous thrombosis	Age (year)	≤ 64	1.036 (1.015, 1.062)†	1.031 (1.001, 1.067)	1.062 (1.018, 1.109)	1.033 (1.023, 1.043)	1.028 (1.013, 1.047)	1.031 (1.009, 1.058)
		> 64	1.049 (1.019, 1.067)	1.074 (1.049, 1.100)	1.075 (1.033, 1.114)	1.034 (1.008, 1.061)	1.047 (1.020, 1.113)	1.073 (1.008, 1.169)
	Gender	Male	1.056 (1.034, 1.078)	1.048 (1.008, 1.091)	1.078 (1.039, 1.119)	1.044 (1.019, 1.071)	1.037 (1.011, 1.062)	1.042 (1.009, 1.075)
		Female	1.042 (1.012, 1.071)	1.045 (1.002, 1.089)	1.082 (1.025, 1.142)	1.052 (1.026, 1.079)	1.036 (1.006, 1.066)	1.035 (1.003, 1.068)
	Season	Apr–Sep	1.042 (1.012, 1.072)	1.095 (1.025, 1.171)	1.058 (1.021, 1.098)	1.051 (1.018, 1.085)	1.034 (1.003, 1.067)	1.049 (1.018, 1.079)
		Oct–Mar	1.057 (1.036, 1.079)	1.037 (1.001, 1.074)	1.107 (1.084, 1.131)	1.032 (1.015, 1.049)	1.051 (1.033, 1.071)	1.056 (1.023, 1.089)
Pulmonary embolism	Age (year)	≤ 64	1.053 (1.038, 1068)	1.029 (1.003, 1.0599)	1.061 (1.033, 1.087)	1.031 (1.018, 1.045)	1.038 (1.022, 1.056)	1.042 (1.020, 1.070)
		> 64	1.061 (1.017, 1.099)	1.079 (1.049, 1.110)	1.079 (1.041, 1.120)	1.041 (1.028, 1.058)	1.063 (1.013, 1.121)	1.069 (1.017, 1.125)
	Gender	Male	1.089 (1.072, 1.107)	1.092 (1.056, 1.130)	1.071 (1.05, 1.108)	1.052 (1.016, 1.088)	1059 (1.033, 1.086)	1.051 (1.021, 1.081)
		Female	1.084 (1.020, 1.151)	1.041 (1.004, 1.079)	1.084 (1.060, 1.108)	1.062 (1.046, 1.079)	1.077 (1.058, 1.097)	1.046 (1.015, 1.079)
	Season	Apr–Sep	1.038 (1.003, 1.075)	1.062 (1.037, 1.088)	1.077 (1.050, 1.104)	1.040 (1.022, 1.058)	1.066 (1.048, 1.085)	1.083 (1.012, 1.159)
		Oct–Mar	1.064 (1.028, 1.102)	1.101 (1.078, 1.124)	1.119 (1.095, 1.144)	1.063 (1.043, 1.083)	1.049 (1.029, 1.068)	1.063 (1.024, 1.103)

*Interquartile range. †95% CI.

1.096) for CO, 1.056 (95% CI 1.026, 1.086) for NO_2 and 1.044 (95% CI 1.014, 1.074) for $PM_{2.5}$.

Discussion

In the present study, VTE was increased on days of greater air pollution. The association was demonstrated for both gases and particles. The high correlations between pollutants, a result of their common source, fossil fuel burning, makes it difficult to isolate the effects of a single pollutant. The findings were both robust and significant for each marker of air pollution, for males and females, and for warmer and colder seasons. Significant effects were more likely to be seen in those over 65 years of age compared with younger people.

The relatively high air pollution in Chile increased our power to detect effects, and reduced the probability of false-negative results. Although there are only a few hospital admissions daily, findings are based on several thousand days of observations and admissions for VTE. This large sample size also contributes to the power to detect small changes. The error in

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estimating personal exposure from fixed site monitors would tend to reduce the probability of detecting an effect and bias air pollution VTE associations towards the null [16]. This suggests that the magnitude of the true effect may be larger than what was observed. Although we used fixed-site monitoring, it has been shown to correlate with both indoor and personal exposure [17]. The present daily time series analysis examined the effects of day-to-day differences in air pollution, not absolute values. Therefore, even if the correlations between indoor and outdoor concentrations were lower, as long as indoor concentrations were on average higher on days of higher outdoor pollution, and indoor concentrations were lower on days of lower outdoor pollution, the positive associations found should reflect changes in personal exposure.

The use of hospitalization data has several advantages. Such data provide a large number of observations, a population-based sample, and allow us to study a disease that is important enough to necessitate hospitalization, an indicator of significant morbidity and financial cost. We lack personal information that may influence VTE, but we do not believe this would confound the observed relation. To be a potential confounder, a factor would have to be a risk factor for the disease, and be associated with day-to-day changes in the concentration of air pollutants. The analysis compares temporal changes in VTE with temporal changes in air pollution. The population and the distribution of risk factors should generally be the same from day to day and, therefore, should not confound our study.

If the air pollution VTE were causal, one explanation would be that air pollution increases coagulability in the venous circulation. A second pathway could involve an intermediary step. Air pollution may aggravate lung function or increase coagulability in the arterial circulation leading to hospitalization for respiratory or cardiac disease. In turn, the relative immobility associated with illness and hospitalization may increase the risk of VTE. Perhaps an intermediary illness could also explain the results of the case–control studies published. However, the evidence that air pollution affects coagulation profiles and VT in laboratory animals suggests that an intermediary step may not be necessary. We looked for an association between VTE and cardiac and respiratory diseases. Only 10% of discharge diagnoses had a secondary diagnosis listed and none of the primary discharge diagnoses for VTE had an accompanying secondary diagnosis of asthma, chronic obstructive pulmonary disease, pneumonia, myocardial infarction or heart failure, diseases that have been linked to air pollution. Another explanation for the association is that air pollution may precipitate hospital admission for diseases related to high levels of air pollution. Hospital admission increases medical surveillance, which in turn increases the chance of detecting an existing thrombosis or embolism. However, VTE in this study was considered the diagnosis responsible for admission by the physician, and the probability of a pre-existing acute PE presenting as an incidental finding during an admission for another disease is unlikely.

To examine whether our statistical analyses may have provided false-positive results, we also analyzed two acute and two chronic conditions that are not known to be associated with air pollution. The RR and 95% CI were 1.025 (95% CI 0.987, 1.064) for acute prostatitis; 1.058(95% CI 0.997, 1.122) for chronic prostatitis; 1.009 (95% CI 0.998, 1.021) for acute pancreatitis; and 0.962 (95% CI 0.886, 1.044) for chronic pancreatitis. None of these negative controls were significantly associated with air pollution.

There remains the question of whether the identified individual pollutants account for the majority of the observed effect or whether they are a proxy for other pollutants coming from the same source or accompanying pathogens. For example, diesel particles may carry aeroallergens, which may enhance their effect [18].

Intratracheal instillation of ambient PM_{10} from a German city decreased bleeding time and prothrombin and partial thromboplastin times, and increased fibrinogen concentrations and FII, VIII, and X function in mice [19]. This effect was not seen if mice were deficient in interleukin-6 (IL-6) or depleted of alveolar macrophages, suggesting that particulate air pollution stimulates macrophages to produce IL-6 which promotes a thrombogenic state in these mice.

Within 1 h of instilling diesel exhaust particles into the trachea, hamster blood exhibited enhanced platelet aggregation. Adding diesel particles directly to blood had a similar effect [20]. In a hamster model, femoral vein thrombosis was reported to be increased within 24 h of intratracheal instillation of diesel exhaust particles [21]. A review concluded that these experimental studies provided a biologically plausible explanation for the association between air pollution and cardiovascular disease [22]. In a randomized cross-over design study of 20 healthy human subjects, diesel exhaust was found to be thrombogenic. Compared with filtered air, inhaling diesel exhaust at 350 ug/m^3 increased *ex vivo* thrombus formation by 24% ($P = 0.0002$) and platelet-neutrophil and platelet-monocyte aggregation by 52% and 30%, respectively ($P = 0.05$) [23]. In a study of Indian women, the 165 who used biomass as cooking fuel demonstrated greater *ex vivo* leukocyte-platelet aggregation than did 155 Indian women who cooked with gas [24]. Together, these data provide evidence that air pollution affects diseases associated with the circulation.

There are many excellent reviews summarizing the large number of studies supporting an adverse effect of traffic-related air pollution on hospitalization and death from stroke and heart attack, suggesting that air pollution influences hemostasis. The interaction of pollutants with lung tissue may lead to oxidative stress and systemic release of inflammatory mediators. Alternatively, pollutants may cross the alveolar–capillary barrier of the lung and have direct systemic effects on vessels and organs. Fine particulates appear to be the most important pollutant, but it is often difficult to separate the effects of other accompanying pollutants that come from the same source, fossil-fuel combustion. There is ongoing research attempting to determine which size fractions (e.g. fine, ultrafine) and which components of fine particles (e.g. metals, organic compounds) are most toxic. [25–29].

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In comparison to the large volume of studies that focus on the effects of air pollution on disorders associated with the arterial circulation, little is known about effects on the systemic venous side. Baccarelli *et al*. [10] published the first study associating VT with air pollution. Compared with controls, patients with DVT had a higher estimated exposure to PM_{10} in the previous year. The odds ratio was 1.70 (95% CI 1.30, 2.23) for a 10 $\mu g/m^3$ increase in PM_{10}. A second case–control study by Baccarelli *et al*. [11] in the same geographic area found an association between living near major traffic and DVT. Our study differs from, and yet compliments this previous study in several ways. We examined acute effects of short-term changes in air pollution in a population-based study, addressed PE, which is a potentially lethal complication of VT, and measured several different pollutants.

An acute increase in ambient air pollution is associated with an increase in hospital admissions for VTE. If causal, estimates of the burden of illness from air pollution may be currently underestimated, and should be taken into consideration.

Acknowledgements

The authors would like to thank Dra. Danuta Rajs Grzebien of Informacion de Salud, Ministerio de Salud for providing mortality data and JoyceVera Bascour from Comision Nacional Del Medio Ambiente Region Metropolitana. The authors would also like to thank Vladislav Brion of Health Canada for helping with data and analysis. Please note there are no competing financial interests for any authors.

Discloures of Conflict of Interests

The authors state that they have no conflict of interest.

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