Long-Term Fine Particulate Matter Exposure and Mortality From Diabetes in Canada

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OBJECTIVE—Recent studies suggest that chronic exposure to air pollution can promote the development of diabetes. However, whether this relationship actually translates into an increased risk of mortality attributable to diabetes is uncertain.

RESEARCH DESIGN AND METHODS—We evaluated the association between long-term exposure to ambient fine particulate matter ($PM_{2.5}$) and diabetes-related mortality in a prospective cohort analysis of 2.1 million adults from the 1991 Canadian census mortality follow-up study. Mortality information, including ~5,200 deaths coded as diabetes being the underlying cause, was ascertained by linkage to the Canadian Mortality Database from 1991 to 2001. Subject-level estimates of long-term exposure to $PM_{2.5}$ were derived from satellite observations. The hazard ratios (HRs) for diabetes-related mortality were related to $PM_{2.5}$ and adjusted for individual-level and contextual variables using Cox proportional hazards survival models.

RESULTS—Mean $PM_{2.5}$ exposure levels for the entire population were low (8.7 $\mu g/m^3$; SD, 3.9 $\mu g/m^3$; interquartile range, 6.2 $\mu g/m^3$). In fully adjusted models, a 10-$\mu g/m^3$ elevation in $PM_{2.5}$ exposure was associated with an increase in risk for diabetes-related mortality (HR, 1.49; 95% CI, 1.37–1.62). The monotonic change in risk to the population persisted to $PM_{2.5}$ concentration <5 $\mu g/m^3$.

CONCLUSIONS—Long-term exposure to $PM_{2.5}$, even at low levels, is related to an increased risk of mortality attributable to diabetes. These findings have considerable public health importance given the billions of people exposed to air pollution and the worldwide growing epidemic of diabetes.

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F ine particulate matter (particles measuring <2.5 μm in aerodynamic diameter [$PM_{2.5}$]) in ambient air is among the leading causes of worldwide mortality (1). Elevations in short-term exposures (1 day to several days) are associated with an increased risk of death from all causes and from cardiovascular (CV) diseases by 1–3% per 10-$\mu g/m^3$ increase in $PM_{2.5}$. Longer-term exposures attributable to living in regions for years or decades with higher levels of pollution, however, lead to substantially larger health risks (1,2). We demonstrated recently that among 2.1 million Canadians, a 10 $\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure estimated by satellite observations elevates the risk for nonaccidental and ischemic heart disease deaths by 15 and 31%, respectively (3). One explanation for the ~10-fold greater CV risk posed by long-term relative to short-term exposures may be that continuous or recurrent inhalation of air pollutants over years is capable of promoting chronic disease states, thereby further augmenting future mortality risk (1). In support of this hypothesis, human and animal studies have demonstrated that $PM_{2.5}$ can accelerate the progression of atherosclerosis (4).

Similarly, long-term exposure to ambient air pollution has been associated with an increased risk of developing diabetes (5–8). Experimental studies also have provided a rational underlying mechanistic basis for this observation (9). However, few studies have evaluated if this relationship translates into more individuals actually dying from diabetes-related causes (10–13). It is possible that air pollution could worsen the underlying diabetes disease course by exacerbating insulin resistance or by instigating adverse biological responses (e.g., endothelial dysfunction) that promote future diabetes complications and diabetes-related fatal events (1,9).

Diabetes has reached global epidemic proportions, impacting ~347 million adults (14). Its health consequences are enormous and disproportionately impact developing nations (14,15). Given the vast number of individuals affected by diabetes and exposed to air pollution, contributions of $PM_{2.5}$ to diabetes mortality could be of growing public health importance. As such, we sought to investigate if long-term $PM_{2.5}$ exposure is associated with higher rates of mortality attributable to diabetes.

RESEARCH DESIGN AND METHODS

Study cohort
The study cohort was constructed from the 1991 Canadian census mortality

follow-up (16). All individuals older than age 25 years who completed the 1991 census long form (randomly selected 20% of population) were linked using deterministic and probabilistic methods to the Canadian Mortality Database from 4 June 1991 to 31 December 2001 (16). Individuals born outside of Canada have unknown historical exposures, tend to settle in communities with higher levels of pollution (17), and live longer than native-born Canadians (18,19). Hence, we excluded immigrants (~600,000) from the analytical sample, leaving ~2.1 million subjects.

We included individual-level risk factors for mortality available from the census long-form (Table 1). The underlying cause of death and date of death were ascertained from the Canadian Mortality Database (coded by ICD-9 for those deaths before 2000 and by ICD-10 for those deaths registered from 2000 onwards). The ICD-9 code 250 and the ICD-10 codes E10–E14 were used to identify underlying diabetes-related causes.

The 1991 Canadian census mortality follow-up study received approval by the Statistics Canada Policy Committee (reference number 012-2001) after consultation with the Statistics Canada Confidentiality and Legislation Committee, the Data Access and Control Services Division, and the Federal Privacy Commissioner. This approval is equivalent to that of standard research ethics boards. All sample sizes presented have been rounded to the nearest hundred for confidentiality reasons.

Contextual variables
Census data from 1991 characterizing the demographic and socioeconomic environment of each subject's home neighborhood (census tracts [CTs]) and community (census divisions [CDs]) were compiled. We subtracted the CD mean from the CT values to make comparisons between CTs within each CD. The proportion of unemployed adults (15 years of age and older), the proportion of adults who had not completed high school, and the proportion of individuals in the lowest income quintile were compiled for both scales for each cohort member. A five-level categorical variable representing the population size of the subject's home community was created as an additional mortality risk factor (Table 1).

Exposure assignment
Subject-level $PM_{2.5}$ exposures were created by averaging concentrations for the period 2001–2006 using estimates of $PM_{2.5}$ derived from satellite remote sensing observations of aerosol optical depth with a spatial resolution of ~10×10 km (3,20) and assigning these values to each subject by their place of residence in 1991. The population-weighted average number of days in which satellite observations were available over the 10 Canadian provinces for the 6-year period of 2001–2006 was 355 days. Satellite retrievals were not available because of a number of factors, including cloud and snow cover. An atmospheric model was used to compensate for the impact of this sampling frequency. Historical (1987–2001) average $PM_{2.5}$ concentrations in 11 of Canada's largest cities were highly correlated ($r = 0.89$) with corresponding $PM_{2.5}$ estimates based on remote sensing over the 2001–2006 time period. This method of exposure assessment provided a strategy to assign exposure to all members of the cohort because only 43% of subjects lived in a CD with historical $PM_{2.5}$ monitoring information (20).

Statistical methods
The follow-up time in the Cox proportional hazards model was defined by calendar time in days from 4 June 1991 to 31 December 2001. Subjects dying from causes other than diabetes were censored at the date of death, as were subjects alive at the end of follow-up. The baseline hazard function was stratified by single-year age-groups and sex. We examined the sensitivity of the $PM_{2.5}$ association with mortality from diabetes to the stochastic structure of the Cox survival model by extending the standard Cox model to include random effects (REs) defined by CD. The REs account for spatial variation in diabetes mortality not explained by the predictor variables (3,21). We further extended the RE model to include correlation in the REs between adjacent CDs. Hazard ratios (HRs) and 95% CIs were calculated for an increment of 10 $\mu g/m^3$ in $PM_{2.5}$ based on both the standard Cox and spatial RE models.

We also explored the sensitivity of the estimated HRs and uncertainty to inclusion of different sets of predictor variables: none, all individual-based variables, urban size, and selected contextual variables. We tested the HR for variation among the categories of selected diabetes-related mortality risk factors (sex, education, income, and community size) using the Cochran Q test.

RESULTS—The analytical cohort consisted of 2,145,400 subjects, with 5,200 subjects dying of an underlying cause coded as diabetes over the nearly 10 years of follow-up. This accounted for 2.7% of all nonaccidental deaths ($n = 192,300$). $PM_{2.5}$ exposures were similar for both sexes and all age-groups, averaging 8.7 $\mu g/m^3$ (SD, 3.9 $\mu g/m^3$; interquartile range, 6.2 $\mu g/m^3$), but increased with higher measures of socioeconomic position (SEP) such as education, occupation, and income (Table 1). Canadians with higher SEP tend to live in areas of higher pollution (i.e., southern Ontario and Quebec). The risk of dying from diabetes was higher for subjects with lower SEP (Table 1). People of aboriginal ancestry also had a higher risk of dying from diabetes, whereas married individuals experienced lower risks. Individuals living in smaller communities had higher diabetes mortality rates compared with those in larger cities.

Association between $PM_{2.5}$ exposure and diabetes mortality
$PM_{2.5}$ was positively associated with diabetes mortality in the Cox survival model with the baseline hazard function stratified by age and sex (Table 2; model 1: HR, 1.10; 95% CI, 1.03–1.18). Including diabetes mortality risk factors measured at the subject level increased the association (model 2: HR, 1.30; 95% CI, 1.21–1.39). Inclusion of the size of the community (model 3: HR, 1.51; 95% CI, 1.39–1.64) further increased the HR compared with model 2. The HR was insensitive to further inclusion of other contextual variables (model 4: HR, 1.49; 95% CI, 1.37–1.62).

Including REs in the statistical model marginally increased the HR from the standard Cox model (model 4) to 1.53 (95% CI, 1.31–1.78; Table 2; model 5), with a wider CI compared with the Cox model. This suggests that the mortality predictor variables included in the survival model could not explain all the variation in diabetes mortality across the country. The HR was reduced to 1.47 (95% CI, 1.16–1.72; Table 2; model 6) when the RE of adjacent CDs was assumed to be correlated. This suggests a spatial clustering of diabetes mortality not entirely accounted for by the covariates in the model.

The positive association between $PM_{2.5}$ and diabetes mortality was observed to be monotonic across the range of $PM_{2.5}$ in Canada, extending to relatively

Table 1—*Descriptive statistics for the study cohort*

Variable	Subjects, n (%)†		PM$_{2.5}$ mean	PM$_{2.5}$ SD	HR for diabetes mortality	95% CI
Full cohort	2,145,400	(100)	8.7	3.9	NA	NA
Sex						
Male	1,059,400	(49)	8.6	3.9	NA	NA
Female	1,086,000	(51)	8.7	3.9	NA	NA
Age at entry, years						
25–34	6,552,200	(30)	8.7	4.0	NA	NA
35–44	566,900	(26)	8.5	3.8	NA	NA
45–54	349,800	(16)	8.5	3.8	NA	NA
55–69	374,100	(17)	8.8	4.0	NA	NA
70 and older	202,400	(9)	8.8	4.0	NA	NA
Any aboriginal ancestry‡						
No*	2,047,500	(95)	8.8	3.9	1	NA
Yes	97,900	(5)	6.3	3.3	2.29	2.03–2.58
Visible minority§						
No*	2,124,600	(99)	8.6	3.9	1	NA
Yes	20,800	(1)	10.0	4.7	1.22	0.91–1.65
Marital status						
Married/common law*	1,572,900	(73)	8.5	3.8	1	NA
Divorced/separated/widowed	285,700	(13)	8.9	4.0	1.38	1.28–1.48
Single	286,800	(13)	9.4	4.2	1.45	1.32–1.60
Highest level of education						
Less than high school graduation	747,700	(35)	8.2	3.8	1.59	1.31–1.86
High school graduation with or without trade certificate	793,500	(37)	8.6	3.9	1.27	1.09–1.50
Some postsecondary or college diploma	334,000	(16)	8.9	3.9	1.05	0.88–1.27
University degree or higher*	270,200	(13)	9.7	4.2	1	NA
Employment status						
Employed*	1,412,500	(66)	8.8	3.9	1	NA
Unemployed	130,800	(6)	8.0	3.9	1.10	0.90–1.35
Not in the labor force	602,100	(28)	8.5	3.9	1.78	1.54–2.05
Occupation classification						
Management	174,600	(8)	9.1	4.0	1.17	0.89–1.54
Professional*	240,000	(11)	9.2	4.1	1	NA
Technical	521,600	(24)	8.4	3.8	1.12	0.88–1.42
Semiskilled	528,700	(25)	8.7	3.9	1.20	0.95–1.52
Unskilled	161,500	(8)	8.2	3.8	1.58	1.23–2.03
Not applicable	519,000	(24)	8.6	3.9	1.67	1.30–2.13
Low-income cutoff quintile¶						
Lowest*	470,700	(22)	8.4	3.8	1	NA
Lower-middle	450,300	(21)	8.5	3.8	0.86	0.80–0.92
Middle	377,500	(18)	8.7	3.9	0.79	0.72–0.87
Upper-middle	437,900	(20)	8.8	3.9	0.72	0.65–0.79
Upper	409,100	(19)	9.0	4.1	0.57	0.51–0.64
Size of home community (population)						
Rural/farm	585,900	(27)	6.5	2.6	1.17	1.05–1.31
Small town (<30,000)	326,400	(15)	6.6	2.8	1.21	1.08–1.35
Urban 3 (30,000–99,999)	216,200	(10)	7.6	2.7	1.22	1.10–1.36
Urban 2 (100,000–499,999)	233,600	(11)	9.4	4.1	1.06	0.96–1.17
Urban 1 (>500,000)*	783,400	(37)	11.1	3.8	1	NA
Contextual covariates‖						
% of adults with less than high school diploma						
CD level	NA	NA	NA	NA	1.08	1.03–1.14
CT level	NA	NA	NA	NA	1.11	1.06–1.16

Table 1—*Continued*

Variable	Subjects, n (%)†	PM$_{2.5}$ mean	PM$_{2.5}$ SD	HR for diabetes mortality	95% CI
% of adults in the lowest low-income cutoff quintile					
CD level	NA	NA	NA	NA	1.05	1.02–1.07
CT level	NA	NA	NA	NA	0.99	0.95–1.03
% of adults unemployed					
CD level	NA	NA	NA	NA	0.99	0.97–1.02
CT level	NA	NA	NA	NA	1.02	0.98–1.05

Descriptive statistics for the study cohort and HR estimates for predictor variables for diabetes-related mortality based on standard Cox model with baseline hazard stratified by single-year age-groups and sex and adjusted for all variables listed and PM$_{2.5}$. NA, not applicable. *Reference category. †Rounded to nearest hundred. ‡Aboriginal status refers to those persons who reported at least one aboriginal ethnic origin, i.e., North American Indian, Métis, or Inuit, and/or reported being registered under the Indian Act of Canada. §Visible minorities are persons (other than aboriginal persons) who are non-Caucasian in race or nonwhite in color. ¶Adjusted for family and community size. ‖HR evaluated at interquartile range: 2 and 3% for the % unemployed; 10 and 12% for % without a high school diploma; and 4 and 10% for % in the lowest income quintile for CD and CT, respectively.

low levels (Fig. 1). Natural splines with two, three, and four degrees of freedom also were examined but did not improve the fit according to the value of the Bayesian Information Criteria that was compared with that of the linear model.

We performed analyses excluding subjects younger than 45 years of age (<300 deaths) at the start of the study to reduce the possibility of capturing deaths more likely attributable to type 1 diabetes among young patients. This had minimal effect on the findings, with model 4 results staying basically the same (HR, 1.49; 95% CI, 1.37–1.63). Excluding subjects younger than 55 years old (<700 deaths) produced similar results (HR, 1.55; 95% CI, 1.38–1.65). Finally, the association between PM$_{2.5}$ and diabetes-related mortality was found to be positive in all subgroups analyzed (sex, education status, income level, and

community size) (Table 3). No significant effect modification was observed for these factors ($P > 0.13$ for all interaction terms using Cochran Q test).

We also accessed information of all mentions on the death certificate for the entire country in a subset of the data available (from 2004 to 2008 inclusive), the only available time period for this information. During this 5-year period, 1,158,622 Canadians died, 3.3% with diabetes as the underlying cause and 7.3% with diabetes as the contributing cause. We then assigned our estimate of PM$_{2.5}$ exposure to the home address postal code centroid for each death and compared the exposure distributions of those who died with diabetes as the underlying cause versus the contributing cause. These two distributions were nearly identical (data not shown), suggesting that there was no coding bias in the position of diabetes on the death certificate.

CONCLUSIONS—Long-term exposure to PM$_{2.5}$ was associated with a significant increase in diabetes-related mortality. This relationship was observed among all subgroups despite the relatively low concentrations of air pollution throughout Canada (1). Our findings suggest that air pollution may be an important modifiable environmental factor contributing to the mortality of diabetic individuals.

We observed lower HRs for subjects living in communities with <100,000 people compared with those subjects living in communities with >100,000 people. There is evidence of much lower utilization of endocrinologists in the smaller towns and in the areas only weakly or not influenced by a metropolitan zone and where access to care is more limited. We also observed lower levels of education, higher rates of unemployment, and lower incomes in the smaller towns and areas not influenced much by metropolitan zones. Thus, it is not surprising that mortality rates from diabetes would be higher in these smaller communities, as we observed in this study. Furthermore, fine particulate matter concentrations are generally lower in these smaller communities, and thus it is appropriate to adjust the PM$_{2.5}$ diabetes mortality association for community size (22).

Previous studies
Higher concentrations of PM$_{2.5}$ during the previous day have been shown in Montreal to be related to an increase in daily counts of mortality among diabetic individuals, particularly those with CV disease (11). Positive associations also were reported with short-term exposures

Table 2—*Diabetes mortality HRs for a 10 μg/m³ change in PM$_{2.5}$ by survival model specification*

Model	HR per 10 μg/m³ PM$_{2.5}$	95% CI
1: Cox model stratified by age and sex with no additional covariates	1.10	1.03–1.18
2: Model 1 including covariates measured at the individual level*	1.30	1.21–1.39
3: Model 2 including community size	1.51	1.39–1.64
4: Model 3 including contextual covariates†	1.49	1.37–1.62
5: Model 4 including REs at CD with no spatial autocorrelation	1.53	1.31–1.78
6: Model 5 including REs in which adjacent CDs were assumed to be correlated	1.47	1.16–1.72

*Individual covariates listed in Table 1 include the following: aboriginal ancestry, visible minority, marital status, education, employment status, occupation, and low income cutoff. †Contextual covariates: % of adults with less than high school diploma, % of adults in the lowest low-income cutoff quintile, and % of adults unemployed determined at both the CD and CT levels.
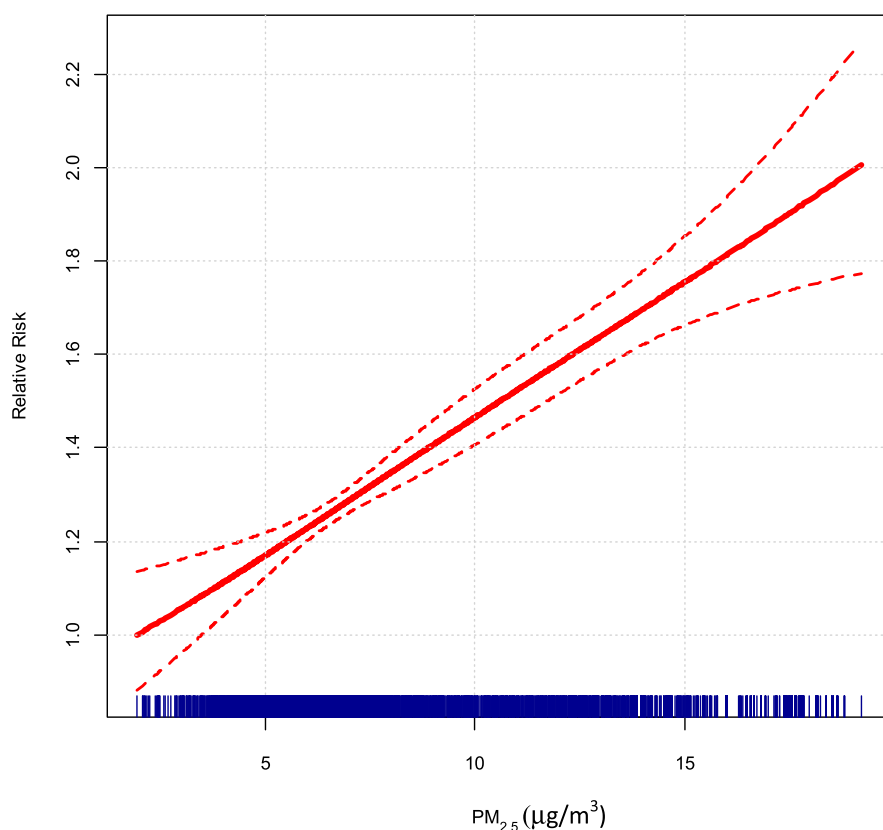
Figure 1—*The association between PM$_{2.5}$ exposure and diabetes-related mortality. The figure demonstrates the relative risk of diabetes-related mortality in relation to long-term PM$_{2.5}$ exposure. The association shown represents the results from the standard Cox survival model (model 3) with a natural spline of PM$_{2.5}$ with two degrees of freedom. Tick marks on the x-axis represent the position of PM$_{2.5}$ concentrations measured in $\mu g/m^3$. Dashed lines represent 95% CIs.*

residence was significantly related to deaths from diabetes, with the adjusted mortality rate ratio being 2.15 (95% CI, 1.21–3.83) in the upper versus lower quartile of exposures. Overall, these findings support the plausibility of our current results related to long-term PM$_{2.5}$ exposure by showing that a proxy for traffic-related air pollution is similarly associated with diabetes-related mortality over a long-term follow-up. Whether there are differences in the magnitude of health effects between PM$_{2.5}$ and traffic air pollution exposures and the underlying pollutant constituents principally responsible for promoting diabetes mortality requires further study.

Potential mechanisms
Beyond contributing to the acute triggering of diabetes-related mortality, there are two main pathways whereby long-term exposure could, in theory, increase the risk for deaths attributable to diabetes. PM$_{2.5}$ is capable of exacerbating insulin resistance (9,25). This has been experimentally demonstrated to occur by pollution-induced systemic and adipocyte-based inflammatory responses (1,9). The chronic worsening of the underlying diabetic state and inflammatory milieu could increase the risk of mortality attributable to poorly controlled diabetes.

Furthermore, the host of chronically occurring adverse systemic responses (e.g., endothelial dysfunction, enhanced thrombosis) induced by PM$_{2.5}$ could promote fatal events among patients with diabetes (1). A portion of this mortality may be attributed to diabetes as the "underlying cause of death" if the final event was strongly related to or thought to have only occurred because of the presence of diabetes. For example, PM$_{2.5}$ could insidiously contribute to worse glycemic control over years. Individuals with chronic hyperglycemia are rendered more susceptible to the adverse health effects of air pollution (1). As such, future exposures could trigger fatal events that are chiefly attributed to the underlying diabetic state (e.g., acute limb ischemia, CV-related deaths).

It might be possible to provide more insight into the most relevant mechanism underlying our findings if we could assess whether the immediate cause of death was largely because of ischemic heart disease or whether the diabetes-related mortality associated with PM$_{2.5}$ occurred mostly (or only) among patients with preexisting CV diseases. In such cases, PM$_{2.5}$ most likely

to PM$_{10}$ in Shanghai and to black carbon in Boston (12,13). However, these studies were only capable of demonstrating an acute triggering of diabetes-related mortality attributable to air pollutants and could not capture potential cumulative health effects caused by years of exposure.

As far as we are aware, only one previous cohort study, the American Cancer Society Cancer Prevention II study (ACS), reported the effects of long-term exposure specifically regarding PM$_{2.5}$ on diabetes-related mortality (10). PM$_{2.5}$ was not associated with this outcome during 16 years of follow-up (HR, 0.99; 95% CI, 0.86–1.14). It is possible that variations in pollution characteristics or unmeasured co-pollutants (e.g., nitrogen oxides) may have contributed to this null finding. Susceptibility differences compared with the population evaluated in the current Canadian study cannot be excluded. Variations in the tendencies of health care providers between nations to code the underlying cause of death specifically as diabetes related also could be involved. However, this seems unlikely

given that the percentages of diabetes deaths were similar in the ACS cohort (1.9%). Finally, in a Los Angeles–based subsample of the ACS cohort using more refined estimates of PM$_{2.5}$ exposure, the risk for diabetes-related deaths was similarly elevated (relative risk, 1.82; 95% CI, 0.55–6.02 for a 10-$\mu g/m^3$ exposure contrast) (23). This suggests that using more sophisticated estimates of chronic PM exposure may lead to more accurate data that are responsible for producing the positive associations. The risk was not statistically significant in the Los Angeles cohort of the ACS, likely attributable to low statistical power (only 55 deaths). Additional studies investigating the long-term effects of PM$_{2.5}$ on diabetes-related mortality are warranted.

Recently, diabetes mortality from a population of >52,000 participants in the Danish Diet, Cancer, and Health cohort was evaluated for its association with estimated long-term exposure to traffic-related pollution using dispersion-modeled NO$_2$ levels (24). Over a 13-year follow-up, the NO$_2$ level at each subject's

Table 3—*Diabetes mortality HR for a 10 $\mu g/m^3$ change in $PM_{2.5}$ by category of selected mortality risk factors for standard Cox survival model*

Effect modifier	Category (%)	HR Cox (95% CI)
Sex	Males (49)	1.50 (1.34–1.67)
	Females (51)	1.48 (1.30–1.69)
	P	0.91*
Education	Less than high school (35)	1.39 (1.25–1.54)
	High school (37)	1.66 (1.41–1.97)
	Postsecondary (29)	1.66 (1.29–2.14)
	P	0.13*
Income quintile	First (22)	1.41 (1.23–1.61)
	Second (21)	1.58 (1.33–1.88)
	Third (18)	1.58 (1.27–1.99)
	Fourth (20)	1.43 (1.13–1.81)
	Fifth (19)	1.47 (1.12–1.93)
	P	0.83*
Community size†	Farm/rural (27)	1.73 (1.38–2.16)
	30,000–500,000 (36)	1.38 (1.21–1.57)
	>500,000 (37)	1.58 (1.37–1.83)
	P	0.16*

Model 4 results presented. *P value for test of difference in HR among categories. †Five community size categories were collapsed into three categories of more equal sample sizes to provide for enhanced statistical stability of the HR estimates within each category.

would be serving to increase the susceptibility among patients with diabetes for a host of fatal CV disease–related events. Unfortunately, we do not have data regarding the immediate or contributing cause of death or individual-level data regarding the presence of CV disease co-morbidities. Hence, we are only able to speculate that some combination of the possible pathways described is responsible for the observed associations.

Global health importance
Although the World Health Organization recognizes $PM_{2.5}$ as a leading risk factor for mortality (26), this is principally driven by estimated effects of $PM_{2.5}$ on CV and pulmonary mortality. Our findings demonstrate that $PM_{2.5}$ also may contribute to diabetes-related mortality. Although diabetes accounts for a relatively small portion of deaths in our cohort (2.7%), the impact of diabetes on deaths is likely underestimated because we have not captured all deaths for which diabetes is a contributing cause (not available in our dataset) and because of substantive cross-coding and potential misclassification of the underlying cause of death. Diabetes is already a burgeoning global epidemic, impacting ~347 million adults (14). By 2030, the prevalence is expected to reach almost half a billion people (27). Given the omnipresent nature of air pollution (1,20),

the population-attributable risk may be quite large.

$PM_{2.5}$ exposure was associated with diabetes-related mortality despite the relatively low concentrations across Canada. These results provide evidence that there is a continuous association without a discernible lower "safe" threshold between $PM_{2.5}$ and health risks to the population (1). Furthermore, billions of people among highly polluted regions (e.g., Middle East and Asia) routinely are exposed to concentrations 5- to 10-fold higher than in Canada (20,28). The developing world, disproportionately impacted by diabetes (14,15), faces the highest $PM_{2.5}$ concentrations (20,28). The full extent of the dose–response relationship could not be elucidated in this study because concentrations were <20 $\mu g/m^3$. Should the monotonic relationship persist, or even if the degree of risk elevation is blunted at extreme values as suggested by previous studies related to CV events (29), millions of patients with diabetes encountering high $PM_{2.5}$ concentrations (often exceeding 50 $\mu g/m^3$ in the developing world) would encounter even more marked health risks.

Strengths and limitations
This is the first cohort study to show a strong positive and statistically significant association between $PM_{2.5}$ and diabetes mortality. The large sample size, breadth

of regions evaluated (every province and major city in Canada), and health outcomes using national-level databases are notable strengths. The large number of individuals reliably included despite residing remotely from ground-based monitors (e.g., rural locations) by using the satellite-based exposure methodology is a particular strength. Finally, we adjusted for numerous individual and contextual covariates, as well as for the effects of the spatial stochastic structure of mortality patterns.

Compared with the immediate cause, the underlying cause of death may be difficult to establish, leading to some degree of cross-coding and misclassification of underlying/contributing causes of death (i.e., deaths not attributed to diabetes even when biologically relevant). It is uncertain if this would bias the magnitude of the PM–diabetes association we observed; however, it has been estimated that up to 60% of subjects with diabetes are not captured by using data from death certificates (30). We acknowledge that previous studies suggest that using death certificate data for capturing diabetes as the underlying cause of death likely underestimates the true prevalence of diabetes (31). However, this error (if homogenous throughout the population) itself should not directly alter its associations with $PM_{2.5}$.

Although we have missed some deaths for which diabetes was a contributing cause, those identified in our study are likely not misclassified. In this regard, the authors of the recent Danish cohort study also recognized that using the underlying cause of death from death certificates likely underestimates mortality rates (24). When mortality was defined more broadly in their study as either the underlying or the contributing cause (or the combination thereof) attributable to diabetes, the associations with NO_2 were similar. We do not have similar data for the entire time period of our study and therefore are unable to perform similar sensitivity analyses. However, in our subset analysis of data available for a 5-year period, we did not find any evidence of coding bias in the position of diabetes on the death certificate in relation to $PM_{2.5}$ exposure. We recognize the limitations of relying on death certificate data for drawing conclusions regarding the underlying (or even immediate) cause of death. Even so, in addition to the recent Danish study (24), several previous epidemiological studies regarding the health effects of

environmental factors also have successfully used this approach even in North American locations (32).

The possibility of some confounding by regional differences in coding also cannot be excluded. For example, locations with higher PM$_{2.5}$ levels were in larger cities with higher SEP. It is possible that health care providers in these locations were more prone to code the underlying cause of death as diabetes related. For example, primary care physicians are more likely to record diabetes as the underlying cause of death than other subspecialists (33). This could be an unaccounted-for confounder in our analyses if the underlying primary care physician frequency in the population is collinear with higher air pollution exposures. We do not have data regarding specialist prevalence in relation to PM$_{2.5}$ levels or information regarding the physicians who were responsible for coding diabetes as the underlying cause of death. However, it is unlikely that this is a major limitation given that PM$_{2.5}$ levels were actually higher among urban and more populated locales, where subspecialist care is generally more prevalent. Moreover, significant associations also were found separately within rural and less populated locations (Table 3). If the likelihood of accurately attributing diabetes as the underlying cause of death (i.e., when the chain of events that led to a death was truly initiated by diabetes) is not affected in some manner by the levels of air pollution, then the estimates provided by our analyses should be unbiased. Nevertheless, it remains a possibility that PM$_{2.5}$ levels could be associated with other aspects that predict a higher rate of coding diabetes as the underlying mortality cause (e.g., regional practice style, provincial reimbursement by diagnosis, density of specialist type, training in death certificate completion) that were not apparent in our main or subgroup analyses. Similar studies using the data from large prospective cohort studies or clinical trials that have better adjudication of the causes for mortality and person-level information of the subjects might yield more precise estimates of the risks.

It is also probable that a sizeable portion of diabetes-related deaths were not captured in our study (30,34). Diabetes, CV, and pulmonary diseases have substantial common comorbidities. For example, adults with diabetes are two to four times more likely to have CV disease, and the majority of adults with diabetes die of heart disease or stroke (31). In addition, some degree of exposure misclassification is possible, and unaccounted-for mobility of subjects also could have affected the results. However, these errors are known to typically produce an underestimation of the true association between PM$_{2.5}$ and health risks (3). Finally, we did not control for smoking and obesity, two of the most important risk factors for diabetes mortality. However, we have shown that our PM$_{2.5}$ exposure estimates are inversely related to both smoking habits and BMI in the Canadian population (17). This inverse association is consistent with similar inverse associations between SEP and PM$_{2.5}$ in this cohort. We therefore hypothesize that including smoking and obesity information, if available, would actually serve to further increase the HR for diabetes-related mortality associated with PM$_{2.5}$ (similar to SEP).

Long-term exposure to relatively low levels of PM$_{2.5}$ was associated with an increased risk for mortality attributable to underlying diabetes. In light of the growing epidemics of both diabetes and air pollution, this finding is of global public health importance. Future studies are warranted to corroborate this association, especially among nations with higher rates of diabetes and levels of air pollutants, and to further elucidate the biological pathways involved.

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