

The 2016 global and national burden of diabetes mellitus attributable to PM_{2.5} air pollution

Benjamin Bowe, Yan Xie, Tingting Li, Yan Yan, Hong Xian, Ziyad Al-Aly



Summary

Background PM_{2.5} air pollution is associated with increased risk of diabetes; however, a knowledge gap exists to further define and quantify the burden of diabetes attributable to PM_{2.5} air pollution. Therefore, we aimed to define the relationship between PM_{2.5} and diabetes. We also aimed to characterise an integrated exposure response function and to provide a quantitative estimate of the global and national burden of diabetes attributable to PM_{2.5}.

Methods We did a longitudinal cohort study of the association of PM_{2.5} with diabetes. We built a cohort of US veterans with no previous history of diabetes from various databases. Participants were followed up for a median of 8·5 years, we and used survival models to examine the association between PM_{2.5} and the risk of diabetes. All models were adjusted for sociodemographic and health characteristics. We tested a positive outcome control (ie, risk of all-cause mortality), negative exposure control (ie, ambient air sodium concentrations), and a negative outcome control (ie, risk of lower limb fracture). Data for the models were reported as hazard ratios (HRs) and 95% CIs. Additionally, we reviewed studies of PM_{2.5} and the risk of diabetes, and used the estimates to build a non-linear integrated exposure response function to characterise the relationship across all concentrations of PM_{2.5} exposure. We included studies into the building of the integrated exposure response function if they scored at least a four on the Newcastle-Ottawa Quality Assessment Scale and were only included if the outcome was type 2 diabetes or all types of diabetes. Finally, we used the Global Burden of Disease study data and methodologies to estimate the attributable burden of disease (ABD) and disability-adjusted life-years (DALYs) of diabetes attributable to PM_{2.5} air pollution globally and in 194 countries and territories.

Findings We examined the relationship of PM_{2.5} and the risk of incident diabetes in a longitudinal cohort of 1729 108 participants followed up for a median of 8·5 years (IQR 8·1–8·8). In adjusted models, a 10 µg/m³ increase in PM_{2.5} was associated with increased risk of diabetes (HR 1·15, 95% CI 1·08–1·22). PM_{2.5} was associated with increased risk of death as the positive outcome control (HR 1·08, 95% CI 1·03–1·13), but not with lower limb fracture as the negative outcome control (1·00, 0·91–1·09). An IQR increase (0·045 µg/m³) in ambient air sodium concentration as the negative exposure control exhibited no significant association with the risk of diabetes (HR 1·00, 95% CI 0·99–1·00). An integrated exposure response function showed that the risk of diabetes increased substantially above 2·4 µg/m³, and then exhibited a more moderate increase at concentrations above 10 µg/m³. Globally, ambient PM_{2.5} contributed to about 3·2 million (95% uncertainty interval [UI] 2·2–3·8) incident cases of diabetes, about 8·2 million (95% UI 5·8–11·0) DALYs caused by diabetes, and 206 105 (95% UI 153 408–259 119) deaths from diabetes attributable to PM_{2.5} exposure. The burden varied substantially among geographies and was more heavily skewed towards low-income and lower-to-middle-income countries.

Interpretation The global toll of diabetes attributable to PM_{2.5} air pollution is significant. Reduction in exposure will yield substantial health benefits.

Funding US Department of Veterans Affairs.

Copyright © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Air pollution is an important global health problem.¹ PM_{2.5}—the most widely studied air pollutant—is associated with increased risk of cardiovascular disease, pulmonary disease, kidney disease, and other non-communicable diseases,^{2,3} and contributed to about 4·2 million premature deaths in 2015.⁴ A growing body of evidence strongly suggests an association between PM_{2.5} pollution and the risk of diabetes.^{5–11}

The *Lancet* Commission¹² on pollution and health published its report in October, 2017, and it provided a

comprehensive review of the effect of the so-called pollutome on human health. The Commission outlined a glaring deficiency in evidence and provided a set of recommendations to fill important knowledge gaps. One of the recommendations outlined by the Commission is to “define and quantify the burden of diabetes attributable to PM_{2.5} air pollution”.¹² An assessment of the global and national burden of diabetes attributable to PM_{2.5} would provide a better understanding of the epidemiology of diabetes, identify endemic areas, and further contribute to the global and national discussions

Lancet Planet Health 2018;
2: e301–12

See [Comment](#) page e287

Clinical Epidemiology Center, Research and Education Service (B Bowe MPH, Y Xie MPH, T Li MD, Prof Y Yan MD, Prof H Xian PhD, Z Al-Aly MD), and Nephrology Section, Medicine Service (Z Al-Aly), VA Saint Louis Health Care System, Saint Louis, Missouri, MO, USA; Department of Medicine (T Li, Z Al-Aly), and Division of Public Health Sciences, Department of Surgery (Prof Y Yan), Washington University School of Medicine, Saint Louis, MO, USA; Department of Epidemiology and Biostatistics, Saint Louis University, Saint Louis, MO, USA (B Bowe, Prof H Xian); and Institute for Public Health, Washington University in Saint Louis, Saint Louis, MO, USA (Z Al-Aly)

Correspondence to:
Dr Ziyad Al-Aly, Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, MO 63106, USA
zalaly@gmail.com

Research in context

Evidence before this study

Previous epidemiological evidence suggests that environmental exposure to PM_{2.5} is associated with risk of diabetes. However, the *Lancet* Commission on pollution and health identified knowledge gaps and outlined several research recommendations including the need to further “define and quantify the burden of diabetes attributable to PM_{2.5} air pollution”.

Added value of this study

This study addresses the research recommendation and provides evidence that ambient PM_{2.5} pollution is associated with increased risk of diabetes. We examined the association in a longitudinal cohort of about 1·7 million US veterans, in which we control for relevant individual-level variables and ecological characteristics. We tested a positive control, as well as negative outcome and exposure controls to address concern about spurious causal inference. The study synthesised previous evidence to build an integrated exposure response function to characterise the risk of diabetes across all PM_{2.5} concentrations experienced by humans. The integrated exposure response function was non-linear in that risk increased substantially above PM_{2.5} concentrations of 2·4 µg/m³, and then exhibited a more moderate increase in risk at concentrations above 10 µg/m³. Additionally, the study suggests that in 2016, there were about 3·2 million cases of incident diabetes, and about 8·2 million

healthy life years lost due to diabetes attributable to air pollution. The burden varied substantially by geography and was most pronounced in less developed countries.

Implications of all the available evidence

Taken together, the findings address the knowledge gap outlined in the *Lancet* Commission on pollution and health to “define and quantify the burden of diabetes attributable to PM_{2.5} air pollution”. Most importantly, the study shows that substantial risk exists at concentrations well below those outlined in the air quality standards of WHO and national and international regulatory agencies. Although the non-linearity of the integrated exposure response function suggests modest reduction in risk unless PM_{2.5} is decreased substantially in high-pollution areas, given the considerable number of people living in heavily polluted geographies, even incremental reductions in PM_{2.5} will ameliorate the burden of diabetes. Finally, we observed that the burden of diabetes attributable to PM_{2.5} exhibited substantial geographical variability, and was more skewed towards regions that are least prepared to cope with the consequences of this excess burden. The results will possibly be helpful to promote the public’s awareness about the effect of PM_{2.5} pollution on the risk of diabetes, and serve to inform and guide policy making aimed at addressing health consequences of environmental air pollution.

on the hazardous effect of air pollution on diabetes. Therefore in this study, we aimed to further define the relationship of PM_{2.5} and diabetes, using a longitudinal cohort study design. We also aimed to characterise an integrated exposure response function, using the body of evidence on the relationship of PM_{2.5} pollution and diabetes; and to provide a quantitative estimate of the global and national burden of diabetes attributable to PM_{2.5} in 194 countries and territories, using the Global Burden of Disease (GBD) methodologies.

Methods

Longitudinal cohort study design

We did a longitudinal cohort study of the association of PM_{2.5} with diabetes. A cohort of US veterans with no previous history of diabetes was built by linking the US Department of Veterans Affairs’ databases^{13–23} with the US Environmental Protection Agency’s (EPA) Community Multiscale Air Quality Modeling System of PM_{2.5},^{24,25} where time of cohort entry was set as date of last outpatient blood panel between Oct 1, 2003, and Sept 30, 2004. Further details on these datasets and cohort construction are provided in the appendix (pp 2–3). Participants were followed up for a median duration of 8·5 years. The outcome of incident diabetes was defined by International Classification of Diseases-9 code, diabetes medication prescription, or an HbA_{1c} measurement more than 6·4% (>46·4 mmol/mol); and

participants were censored at death or end of follow-up (Sept 30, 2012). PM_{2.5} exposure value was assigned on the basis of county of residence at time of cohort entry.

Cox proportional hazard models were used to examine the relationship between PM_{2.5} and the risk of diabetes, with censoring at death or end of follow-up. Selection of covariates was informed by previous studies.^{15,16–18,26} All models were adjusted for age, race, sex, estimated glomerular filtration rate, systolic blood pressure, hyperlipidaemia, chronic lung disease, cardiovascular disease, cancer, body-mass index, smoking status, use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, percentage of people in poverty in each county of residence, population density of county of residence, number of admissions to hospital before beginning of follow-up, and how many times serum creatinine was measured before beginning of follow-up. Further details on data sources, variable definitions, and statistical analyses are included in the appendix (pp 2–11). Missing data were not imputed. In analyses, a 95% CI of a hazard ratio (HR) that does not include unity was considered significant. In all analyses, p<0·05 was considered significant.

We additionally curated data from the US County Health Rankings datasets and controlled for US county level characteristics in the following six domains: health outcomes, health behaviours, clinical care, social and economic factors, physical environment, and demographics.^{27,28} We

See Online for appendix

also did a restricted cubic spline analysis to characterise the morphology of a non-linear association between $PM_{2.5}$ and the risk of diabetes;²⁹ assessed exposure in quartiles; assessed exposure in time-varying models, where geographical location was updated as participants moved and average annual exposure was matched to geographical location at any specific time; used the National Aeronautics and Space Administration's (NASA) Socioeconomic Data and Applications Center's Global Annual $PM_{2.5}$ Grids from Moderate Resolution Imaging Spectroradiometer, Multi-angle Imaging Spectroradiometer, and Sea-Viewing Wide Field-of View Sensor's aerosol optical depth remote spaceborne satellite sensing data^{30,31} as an alternative data source for exposure; varied the spatial resolution of exposure definition where we assigned exposure levels on the basis of the nearest air monitoring station within 30 miles, 10 miles, and 5 miles; assessed the relationship between $PM_{2.5}$ and risk of all-cause mortality as a positive control;^{1,32} assessed the relationship between ambient air sodium concentrations and risk of diabetes as a negative exposure control;³³ assessed the relationship between ambient air sodium concentrations and risk of all-cause mortality; and assessed the relationship between $PM_{2.5}$ and the risk of lower limb fracture. Further details on these sensitivity analyses are provided in the appendix (pp 5–11).

The use of a negative control is a valuable complement to other epidemiological methods and serves to identify and resolve both suspected and unsuspected sources of spurious causal inference including confounding, mismeasurements, and other biases, as well as design or analytic flaws.³⁴ Ambient air sodium concentration is measured by air monitoring stations; however, there is no biological basis to support an association between sodium concentrations in the air and the risk of diabetes. Therefore, ambient air sodium is an appropriate negative exposure control.³⁴ The negative outcome control was selected on the basis of the criteria outlined by Lipsitch and colleagues.³⁴ There is no previous knowledge of and no biological or mechanistic plausibility to explain an association between $PM_{2.5}$ and the risk of lower limb fracture. We therefore considered it a suitable negative outcome control.

Integrated exposure response function

An integrated exposure response function based on GBD methodologies was built to assess the risk of diabetes due to $PM_{2.5}$ across the spectrum of $PM_{2.5}$ exposure concentrations around the world.^{4,35,36} A literature review was done, where we evaluated currently available literature on the associations between risk of diabetes and $PM_{2.5}$, passive smoking, and active smoking for the use in building an integrated exposure response function.^{5–11,37–60} Passive smoking and active smoking were used as proxy exposures for high concentration of $PM_{2.5}$, because published literature on $PM_{2.5}$ tends to be from developed countries with these values on the lower

end of the spectrum, therefore, leaving a scarcity of evidence on the relationship at higher concentrations of exposure.^{4,35,36,61} Exposure attribution, as estimated by previous studies,^{32,35} is derived from breathing rate (ie, average volume of air breathed per minute), and the $PM_{2.5}$ mass per cigarette, or ambient exposure due to living with someone who smokes.

Studies were included in the building of the integrated exposure response function if they scored at least a four on the Newcastle-Ottawa Quality Assessment Scale^{10,62}—a nine-point scale for assessing quality of cohort studies—and were only included if the outcome was type 2 diabetes or all types of diabetes. Active smoking studies were only included if they contained a recorded dose-response of cigarettes per day, which was necessary for assigning a corresponding $PM_{2.5}$ exposure value, and if the reference group consisted of those who had never smoked. Passive smoking studies were included if the reference group had never smoked and were not exposed to passive smoke. Passive smoke was assigned a $PM_{2.5}$ exposure of 35 $\mu g/m^3$, and active smoking 667 $\mu g/m^3$ per cigarette per day.^{4,35,36} Selected studies, along with the Veterans Affairs longitudinal cohort study presented here, were included in building the integrated exposure response function; details on included studies are presented in the appendix (pp 12, 19–28).

The integrated exposure–response function fits available epidemiological data using a Bayesian hierarchical modelling approach, and is based on GBD methodology, which has been described elsewhere in detail.^{4,35,36} The theoretical minimum risk exposure level (TMREL) was assigned on the basis of a uniform distribution of $PM_{2.5}$ from 2.4 $\mu g/m^3$ to 5.9 $\mu g/m^3$, representing exposure values between the minimum and fifth percentiles of exposure distributions from outdoor air pollution cohort studies.^{4,35,63} TMREL by its definition should minimise individual-level and population-level risk and be theoretically possible to achieve, but not necessarily affordable or feasible to achieve.⁶³ Studies were weighted using the quality effects approach.⁶⁴ Results were obtained from 1000 sets of simulated values.^{4,35,36} The mean and 95% uncertainty intervals (UIs) are presented.

Estimation of the burden of diabetes due to $PM_{2.5}$

National annual $PM_{2.5}$ exposure estimates, which are population weighted and derived from the integration of satellite data, surface measurements, geographical data, and a chemical transport model, were obtained from GBD 2015.^{4,65} Estimates are population weighted. Incident rates, years of life lived with disability (YLD), years of life lost (YLL), and disability-adjusted life-years (DALYs) of diabetes and all causes, and their UIs were obtained from GBD 2016.^{66,67} The GBD methodology, explained elsewhere in detail,^{36,68} estimates these measures by using data from specific published literature on diabetes

For the Moderate Resolution Imaging Spectroradiometer see <https://modis.gsfc.nasa.gov/about/>

For the Multi-angle Imaging Spectroradiometer see <https://www-misr.jpl.nasa.gov/>

For the Sea-Viewing Wide Field-of View Sensor see <https://eosps.nasa.gov/missions/sea-viewing-wide-field-view-sensor>

and mortality in hierarchical models.^{66,68–71} The GBD Population Estimates dataset provided population size.⁷² Country income classifications were obtained from the World Bank.⁷³

The population attributable fraction (PAF) of diabetes due to PM_{2.5} represents the proportion of diabetes that would be eliminated if the PM_{2.5} exposure was reduced to concentrations equal to or less than the TMREL. The PAF of diabetes due to PM_{2.5} exposure above the TMREL was calculated with a GBD 2016 equation,⁷¹ using risk estimates from the integrated exposure response function. The TMREL was set as a uniform distribution between 2.4 µg/m³ and 5.9 µg/m³, for which levels under the TMREL were treated as contributing no risk.⁴ The attributable burden of disease (ABD), defined as the number of incident cases of diabetes per year attributable to PM_{2.5} exceeding the TMREL, was calculated using estimates of diabetes from the GBD 2016 study⁶⁸ multiplied by the PAF of diabetes due to PM_{2.5} exceeding the TMREL.

YLD due to diabetes is a measure of the burden placed on a population due to the ill-effects of living with diabetes. YLL due to diabetes is a measure of the burden placed on a population due to dying prematurely from diabetes. The DALY due to diabetes is a summary measure of YLD and YLL, and represents the total years of healthy life lost due to ill-health, disability, or early death due to diabetes.⁷⁴ YLD, YLL, and DALYs of diabetes due to PM_{2.5} were estimated by multiplying the diabetes-specific GBD values of the corresponding measure by the PAF of diabetes due to PM_{2.5} exceeding the TMREL.^{36,68} Details of these measures are discussed in the appendix (pp 13–15).

Uncertainty in measurements was factored in our estimations through the generation of measures from a distribution of 10000 estimates, and the median and 95% UIs are reported. Further details on estimation and UIs are presented in the appendix (pp 14, 15). Burden measures are reported as values, rates per 100000 population, and age-standardised rates per 100000 population. World maps of age-standardised ABD, YLD, YLL, and DALY rates are presented. Age-standardised DALY rates were additionally analysed by World Bank income classification and the socio-demographic index quintile.

Statistical analysis

We did all analyses in SAS (version 71). We generated maps using ArcMap (version 10.5). The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System (Saint Louis, MO, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We examined the relationship of PM_{2.5} and the risk of incident diabetes in a longitudinal cohort of 1729108 participants followed up for a median of 8.5 years (IQR 8.1–8.8). The demographic and health characteristics of the cohort participants are detailed in the appendix (pp 16–17). PM_{2.5} concentrations obtained from EPA ranged from 5.0 µg/m³ to 22.1 µg/m³. In models adjusted for individual-level sociodemographic and health characteristics, a 10.0 µg/m³ increase in PM_{2.5} exposure was associated with increased risk of diabetes (HR 1.15, 95% CI 1.08–1.22; table 1). Because characteristics of geographies might confound the association between PM_{2.5} and the risk of diabetes,⁷⁵ we curated the US County Health Rankings' datasets^{27,28} and built analyses additionally controlling for 55 US county-level variables in the six domains aforementioned. Models additionally adjusting for US county characteristics yielded consistent results in that an increase in PM_{2.5} was associated with increased risk of diabetes (HR 1.12, 95% CI 1.02–1.24; table 1). A spline analysis suggested that the relationship between PM_{2.5} concentrations and the risk of incident diabetes increased with increased concentrations of PM_{2.5} and then nearly plateaued at concentrations exceeding 12.0 µg/m³ (figure 1). The results were consistent in analysis considering PM_{2.5} in quartiles; in that compared with quartile 1 (5.0–10.1 µg/m³), the risk was increased in quartile 2 (consisting of PM_{2.5} concentrations of 10.2–11.8 µg/m³; HR 1.08, 95% CI 1.05–1.12) and then nearly plateaued in quartiles 3 and 4 (consisting of PM_{2.5} concentrations ≥11.9 µg/m³; HR 1.13 [95% CI 1.07–1.18] for quartile 3, and 1.14 [1.10–1.19] for quartile 4; table 1). Results were consistent when exposure was treated as time varying (HR 1.18, 95% CI 1.10–1.25), where it was updated as cohort participants moved from one location to another and as PM_{2.5} estimates changed over the duration of follow-up (table 1).

We additionally considered PM_{2.5} estimates derived from NASA's spaceborne satellite sensors as an alternative data source to define ambient PM_{2.5} exposure concentrations. Analyses considering these data yielded results consistent with those shown using exposure data obtained from the EPA ground-based air monitoring stations (HR 1.13, 95% CI 1.11–1.15; table 1). Results were consistent in models where exposure concentrations were assigned on the basis of the nearest air monitoring station within 30 miles, 10 miles, and 5 miles (appendix p 18).

We examined the association of PM_{2.5} and risk of all-cause mortality where a priori observations suggest that an association is expected (ie, the positive outcome control).^{1,76} Our results showed a significant association between PM_{2.5} concentrations and the risk of death (HR 1.08, 95% CI 1.03–1.13; table 1). We tested the association between ambient air sodium concentrations and the risk of diabetes (ie, a negative exposure control);

	Exposure (data source)	Outcome	Sample size	Event rate	Incident rate per 100 000 person-years	HR (95% CI)
Primary model	PM _{2.5} * (EPA)	Diabetes	1729108	397966 (23.0%)	3414.9	1.15 (1.08–1.22)
Additionally controlled for US county characteristics	PM _{2.5} * (EPA)	Diabetes	1301070	300500 (23.1%)	3426.2	1.12 (1.02–1.24)
Exposure as quartiles						
5.0–10.1 µg/m ³	PM _{2.5} * (EPA)	Diabetes	446334	94564 (21.2%)	3087.6	1.00 (Ref)
10.2–11.8 µg/m ³	PM _{2.5} * (EPA)	Diabetes	442939	102456 (23.1%)	3431.4	1.08 (1.05–1.12)
11.9–13.6 µg/m ³	PM _{2.5} * (EPA)	Diabetes	408580	98439 (24.1%)	3604.6	1.13 (1.07–1.18)
13.7–22.1 µg/m ³	PM _{2.5} * (EPA)	Diabetes	431255	102507 (23.8%)	3566.1	1.14 (1.10–1.19)
Time-varying exposure	PM _{2.5} * (EPA)	Diabetes	1729108	397966 (23.0%)	3414.9	1.18 (1.10–1.25)
Alternative exposure data source	PM _{2.5} * (NASA)	Diabetes	1670031	383894 (23.0%)	3410.9	1.13 (1.11–1.15)
Positive outcome control	PM _{2.5} * (EPA)	All-cause mortality	1729108	368387 (21.3%)	2740.7	1.08 (1.03–1.13)
Negative exposure control	Sodium† (EPA)	Diabetes	820160	191826 (23.4%)	3484.8	1.00 (0.99–1.00)
Negative exposure control	Sodium† (EPA)	All-cause mortality	820160	173240 (21.1%)	2718.8	1.00 (1.00–1.01)
Negative outcome control	PM _{2.5} * (EPA)	Lower limb fracture	1729108	96165 (5.6%)	740.0	1.00 (0.91–1.09)

*HRs for every 10 µg/m³ increase in PM_{2.5}. †HRs for every IQR increase (0.045 µg/m³) in sodium. HR=hazard ratio. EPA=US Environmental Protection Agency. NASA=National Aeronautics and Space Administration.

Table 1: Analyses of the Veterans Affairs longitudinal cohort study of the association of PM_{2.5} and diabetes

the results showed a non-significant association (HR 1.00, 95% CI 0.99–1.00; table 1). There was also no significant association between air sodium concentrations and the risk of all-cause mortality as a negative exposure control (HR 1.00, 95% CI 1.00–1.01) and no significant association between PM_{2.5} and risk of lower limb fracture as a negative outcome control (1.00, 0.91–1.09; table 1).

A summary table listing the studies used in the analysis of synthesising the integrated exposure response function is provided in the appendix (pp 19–28). The integrated exposure response function showed that the risk of diabetes increased substantially for PM_{2.5} concentrations above the lower bound of the TMREL of 2.4 µg/m³ then exhibited a more moderate increase in risk at concentrations above 10 µg/m³ (figure 2).

In 2016, the global burden of incident diabetes attributable to PM_{2.5} was, in 1000s, 3002.9 (95% UI 2208.6–3798.9). Globally, ABD per 100 000 population was 40.62 (95% UI 29.9–51.4), and age-standardised ABD per 100 000 population was 40.4 (29.7–51.1; table 2). Global diabetes DALYs attributable to long-term exposure to PM_{2.5} were 8.2 million (95% UI 5.8–11.0), consisting of 4.1 million (2.4–6.2) YLD and 4.1 million (3.1–5.1) YLL. The 2016 global YLD, YLL, and DALYs of diabetes attributable to PM_{2.5} in 1000s, in rate per 100 000 population, and age-standardised rate per 100 000 population are reported in table 3. Age-standardised DALY rates per 100 000 population increased as World Bank income classification decreased, and also as sociodemographic index decreased (figure 3).

Tables 2 and 3 also report the ABD, YLD, YLL, and DALYs for the ten most populated countries. ABD, YLD,

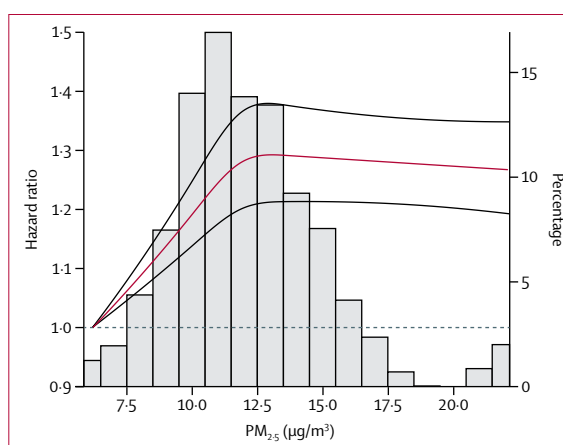


Figure 1: Spline analysis of PM_{2.5} and the risk of diabetes

The red line is the hazard ratio. The black lines are the 95% CIs. A histogram of the distribution of PM_{2.5} exposure is presented in the background in grey. The lowest PM_{2.5} value included in the analysis was 6.2 µg/m³ and it served as the reference.

YLL, and DALYs for the 194 countries and territories are provided in the appendix (pp 29–53). Among the ten most populated countries, China had the highest ABD of 600.3 (95% UI 447.2–757.3), followed by India with an ABD of 590.5 (447.0–737.1), and then the USA, with an ABD of 149.5 (85.2–210.3) in 1000s (table 2). Pakistan had an ABD per 100 000 population of 58.8 (95% UI 44.1–74.3), followed by the USA with an ABD per 100 000 population of 46.3 (26.4–65.1), and then India with an ABD per 100 000 population of 44.9 (34.0–56.0). Age-standardised ABD showed that Pakistan had the highest with 72.6 (95% UI 54.4–91.8), followed by India with 48.7 (36.9–60.8), and then Bangladesh with 48.6 (37.2–60.2) incident cases of diabetes per 100 000 population. There was substan-

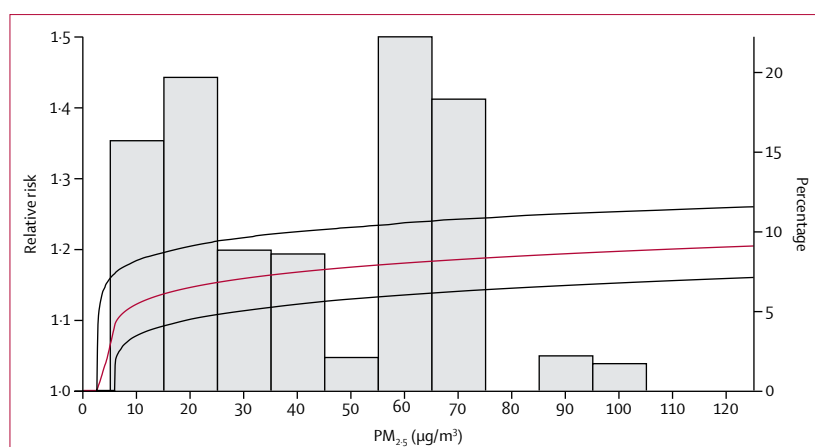


Figure 2: Integrated exposure response function of the association between $PM_{2.5}$ and diabetes
A histogram of the distribution of $PM_{2.5}$ exposure among the countries is presented in the background in grey. The red line is the mean estimated relative risk. The black lines are 95% uncertainty intervals.

	$PM_{2.5}$ exposure concentration ($\mu g/m^3$)	Attributable burden of disease in 1000s (95% UI)	Attributable burden of disease per 100 000 population (95% UI)	Age-standardised attributable burden of disease per 100 000 population (95% UI)
Global	42.3	3002.9 (2208.6–3798.9)	40.6 (29.9–51.4)	40.4 (29.7–51.1)
China	57.2	600.3 (447.2–757.3)	43.9 (32.7–55.4)	37.1 (27.8–46.6)
India	72.6	590.5 (447.0–737.1)	44.9 (34.0–56.0)	48.7 (36.9–60.8)
USA	8.3	149.5 (85.2–210.3)	46.3 (26.4–65.1)	37.4 (21.3–52.5)
Indonesia	15.0	104.8 (69.1–141.0)	40.7 (26.8–54.7)	41.3 (27.3–55.4)
Brazil	11.1	49.8 (31.0–68.6)	23.8 (14.8–32.7)	23.6 (14.7–32.5)
Pakistan	63.0	112.4 (84.2–141.9)	58.8 (44.1–74.3)	72.6 (54.4–91.8)
Nigeria	36.9	24.6 (17.7–31.6)	13.3 (9.6–17.1)	21.1 (15.2–27.1)
Bangladesh	87.0	69.8 (53.4–86.5)	43.1 (33.0–53.5)	48.6 (37.2–60.2)
Russia	15.8	36.17 (23.9–49.0)	24.8 (16.3–33.6)	19.9 (13.2–27.0)
Japan	13.1	34.9 (22.2–48.3)	27.7 (17.7–38.4)	21.8 (14.0–29.7)

UI=uncertainty interval.

Table 2: Attributable burden of diabetes associated with $PM_{2.5}$ exposure globally and for the top ten most populous countries

tial geographical heterogeneity in age-standardised ABD per 100 000 population; the burden was high in several geographical regions including Central America, north Africa and the Middle East, southern sub-Saharan Africa, south Asia, Oceania, and several countries in southeast Asia (figure 4A; appendix pp 29–35). By contrast, several countries had low age-standardised ABD per 100 000 population, including Australia, New Zealand, and Greenland, as well as some of those in central Europe and central Asia (figure 4A; appendix pp 29–35).

Among the ten most populated countries, India had the highest DALYs (1625.8, 95% UI 1193.7–2104.8), followed by China (1251.5, 828.5–1753.3), and then Indonesia (400.0, 261.7–544.5), in 1000s (table 3). DALYs per 100 000 population showed Indonesia as the highest with

155.1 DALYs (95% UI 101.5–211.1), followed by India with 123.4 (90.7–159.9), and then the USA with 108.5 (59.3–163.9). Age-standardised DALYs per 100 000 population showed Pakistan as the highest with an age-adjusted DALY rate of 221.7 (95% UI 159.0–291.6), followed by Indonesia with 189.4 (124.4–255.7), and then India with 165.5 (122.5–212.3; table 3).

Mapping of the geographical distribution of age-standardised DALYs across the world showed populations in Central America, north Africa and the Middle East, southern sub-Saharan Africa, south Asia, and several countries in southeast Asia exhibited high age-standardised DALYs (figure 4B; appendix pp 36–51). Canada, Greenland, several countries in central and eastern Europe as well as central Asia, Russia, and Australia and New Zealand had low estimates of age-standardised DALYs (figure 4B; appendix pp 36–51). Finally, our estimates suggest that in 2016 there were 206 105 (95% UI 153 408–259 119) global deaths from diabetes attributable to $PM_{2.5}$ exposure.

Discussion

Our results suggest that there is a significant association between increased $PM_{2.5}$ exposure and the risk of diabetes. Additionally, our integrated exposure response function suggests that risk is significant at concentrations below those recommended by regulatory agencies. Finally, we observed substantial geographical variation in the burden of diabetes attributable to air pollution, for which we estimated that in 2016, there were about 3.2 million cases of incident diabetes and about 8.2 million years of healthy life lost due to diabetes attributable to elevated concentrations of $PM_{2.5}$.

The association of $PM_{2.5}$ pollution and the risk of diabetes is remarkably consistent across a number of studies from different populations; it is consistent when using EPA or NASA data to define exposure, and it passed the scrutiny of application of both positive and negative controls. The application of negative exposure and outcome controls is especially important to identify non-causal associations and serves as an important complement to other epidemiological methods for improving causal inference.³⁴ The biological mechanism underpinning the association is based on the premise that pollutants enter the bloodstream where they might interact with tissue components to produce pathological effects. This mechanism is now supported by evidence both in experimental models and humans that inhaled nanoparticles, which when sufficiently small can enter the bloodstream and interact with distant organs—including liver tissue—and exhibit affinity to accumulate at sites of vascular inflammation.^{77,78} Furthermore, experimental and human evidence suggests that exposure to ambient air pollutants can lead to clinically significant disturbances in the autonomic nervous

system, oxidative stress, inflammation, endoplasmic reticulum stress, apoptosis, and broad metabolic derangements in glucose and insulin homeostasis including glucose intolerance, decreased insulin sensitivity and impaired secretion, and increased blood lipid concentrations, thus providing biological mechanistic plausibility to the association of PM_{2.5} exposure and the risk of diabetes.^{79–87}

Our integrated exposure response function suggests that the risk of diabetes increased substantially between the TMREL and the air quality standards recommended by WHO (10 µg/m³) and the EPA (12 µg/m³); there was a more moderate increase in the risk at PM_{2.5} concentrations greater than 10 µg/m³. The findings are consistent with recent data^{2,3,88} suggesting that even low concentration of air pollution might be unsafe, in which the unfortunate effect of air pollution becomes obvious at relatively low concentrations below those currently considered safe by regulatory agencies. The morphology of our integrated exposure response function is congruent with observations from other studies that examined the effect of PM_{2.5} and other non-communicable diseases,⁴ in which following an initial sharp increase the risk also nearly plateaued and subsequently exhibited minimal increase in risk.⁴ The non-linear integrated exposure response function implies that in the most polluted countries a modest reduction in PM_{2.5} will yield small reduction in risk; however, given the large populations living in heavily polluted geographies, even small incremental reductions in PM_{2.5} will yield substantial reduction in the burden of diabetes.

The toll of diabetes attributable to PM_{2.5} pollution is substantial; long-term exposure to PM_{2.5} contributed to about 3·2 million cases of diabetes in 2016, representing 14% of total incident diabetes globally. It contributed to about 8·2 million DALYs representing 14·4% of DALYs due to diabetes and 0·3% of the overall global toll of DALYs due to all diseases. The high toll is driven in part by the fact that more people breathe polluted air than ever before, as average population-weighted PM_{2.5} exposure has increased by 11·2% from 39·7 µg/m³ in 1990 to 44·2 µg/m³ in 2015. Estimates of PM_{2.5} attributable diabetes at the global and national levels reflect the influence not only of the increase in population-weighted PM_{2.5} exposure, but also of demographic expansion and underlying epidemiological trends of increased burden of non-communicable disease in general, and more specifically diabetes.

Our results suggest substantial geographical variation in the burden of diabetes attributable to air pollution and that the burden is more heavily skewed toward regions that are less developed (low-income and lower-to-middle-income countries, and countries with a lower sociodemographic index). As countries develop economically and undergo an epidemiological transition, non-communicable diseases are likely to become even

	YLD			YLL			DALYs			
	YLD in 1000s (95% UI)	YLD per 100 000 population (95% UI)	Age-standardised YLD per 100 000 population (95% UI)	YLD in 1000s (95% UI)	YLD per 100 000 population (95% UI)	Age-standardised YLL per 100 000 population (95% UI)	DALYs in 1000s (95% UI)	DALYs per 100 000 population (95% UI)	Age-standardised DALYs per 100 000 population (95% UI)	
Global	4081·6 (2364·6–6158·6)	55·2 (32·0–83·3)	57·0 (33·1–85·8)	4140·9 (3087·1–5136·1)	56·0 (41·8–69·5)	60·0 (44·8–74·5)	8217·4 (5778·1–10971·5)	111·2 (78·2–148·4)	116·9 (82·6–155·4)	
China	829·8 (455·0–1274·2)	60·7 (33·3–93·2)	50·1 (27·4–77·1)	423·4 (321·7–519·3)	31·0 (23·5–38·0)	27·1 (20·6–33·2)	1251·5 (828·5–1753·3)	91·6 (60·6–128·3)	77·1 (51·2–107·7)	
India	693·3 (396·7–1040·9)	52·7 (30·2–79·1)	63·2 (36·9–94·2)	933·3 (718·8–1140·9)	70·9 (54·6–86·7)	102·3 (78·7–125·1)	1625·8 (1193·7–2104·8)	123·4 (90·7–159·9)	165·5 (122·5–212·3)	
USA	216·2 (107·8–354·2)	67·0 (33·4–109·7)	50·0 (25·0–81·8)	134·4 (76·8–188·5)	41·6 (23·8–58·4)	30·7 (17·6–43·1)	350·4 (191·6–529·1)	108·5 (59·3–163·9)	80·7 (43·9–122·2)	
Indonesia	124·0 (65·5–198·1)	48·1 (25·4–76·8)	55·0 (29·2–87·7)	275·8 (183·4–363·4)	106·9 (71·1–140·9)	134·0 (89·1–176·6)	400·0 (261·7–544·5)	155·1 (101·5–211·1)	189·4 (124·4–255·7)	
Brazil	71·6 (36·8–116·1)	34·1 (17·5–55·4)	34·9 (18·0–56·4)	120·5 (75·6–162·7)	57·4 (36·1–77·5)	63·2 (39·6–85·3)	192·2 (117·9–271·5)	91·6 (56·2–129·4)	98·1 (60·3–138·0)	
Pakistan	120·0 (69·2–180·1)	62·9 (36·3–94·3)	93·5 (54·9–139·4)	132·1 (95·2–173·2)	69·2 (49·9–90·7)	127·7 (92·1–167·4)	252·5 (178·4–337·2)	132·2 (93·4–176·6)	221·7 (159·0–291·6)	
Nigeria	26·1 (14·9–39·7)	14·1 (8·1–21·5)	27·8 (16·0–42·1)	33·5 (22·3–46·7)	18·1 (12·1–25·3)	45·4 (30·1–63·5)	59·9 (41·1–81·1)	32·4 (22·3–43·9)	73·6 (50·6–99·6)	
Bangladesh	78·8 (45·0–118·3)	48·7 (27·8–73·1)	63·3 (36·8–94·2)	86·6 (65·5–108·9)	53·5 (40·4–67·2)	87·5 (66·2–109·9)	165·6 (120·5–215·9)	102·3 (74·4–133·4)	151·0 (111·6–194·4)	
Russia	64·6 (35·6–101·4)	44·3 (24·4–69·4)	32·3 (17·8–50·6)	28·2 (15·9–43·6)	19·3 (10·9–29·9)	14·3 (8·2–21·9)	93·2 (56·1–138·1)	63·8 (38·4–94·6)	46·8 (28·1–69·4)	
Japan	89·0 (45·7–144·3)	70·8 (36·3–114·8)	41·9 (21·4–68·0)	133 (87·1–177)	10·6 (6·9–14·1)	5·1 (3·3–6·8)	102·3 (56·2–159·8)	81·4 (44·7–127·1)	46·9 (25·4–74·0)	

YLD=years of life lived with disability. UI=uncertainty interval. YLL=years of life lost. DALYs=disability-adjusted life-years.

Table 3: YLD, YLL, and DALYs of diabetes associated with PM_{2.5} exposure globally and for the top ten most populous countries

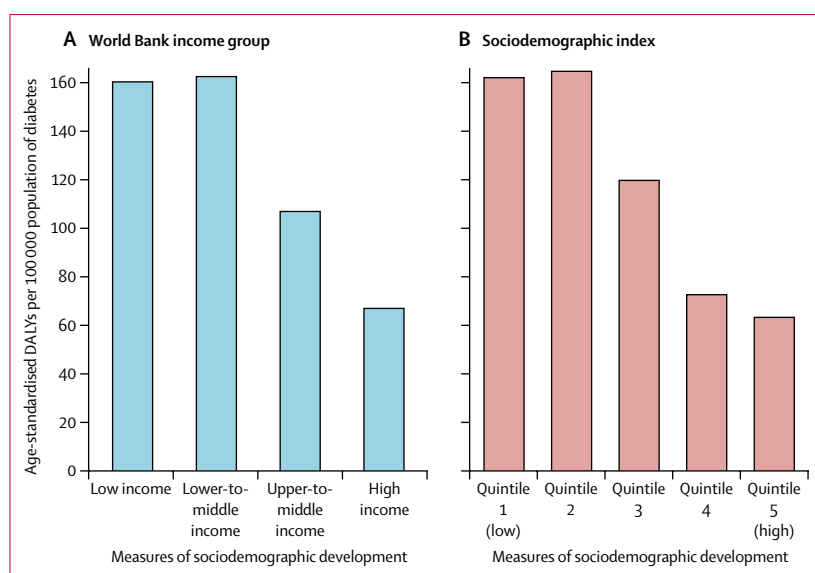


Figure 3: Age-standardised DALYs per 100 000 population of diabetes by World Bank income group (A) and sociodemographic index quintile (B)

DALYs=disability-adjusted life-years.

more prominent as major causes of disease and death, and the contribution of air pollution to non-communicable diseases in general, and specifically to diabetes will probably become even more pronounced. The forces of demographic expansion, ageing, epidemiological transition, and rapid industrialisation in low-income and lower-to-middle-income countries will probably increase the burden of health loss and death due to air pollution. The burden of health loss from diabetes attributable to $PM_{2.5}$ pollution is not insignificant in well developed countries and in geographies with relatively lower air pollution. Developing a better understanding of the effect of low concentrations of pollution (those currently considered safe) on health should be also be addressed by funding agencies and the scientific community.⁸⁸ Scientific evidence to define concentrations of particulate matter that are safe is needed to inform advocacy and guide policy making.

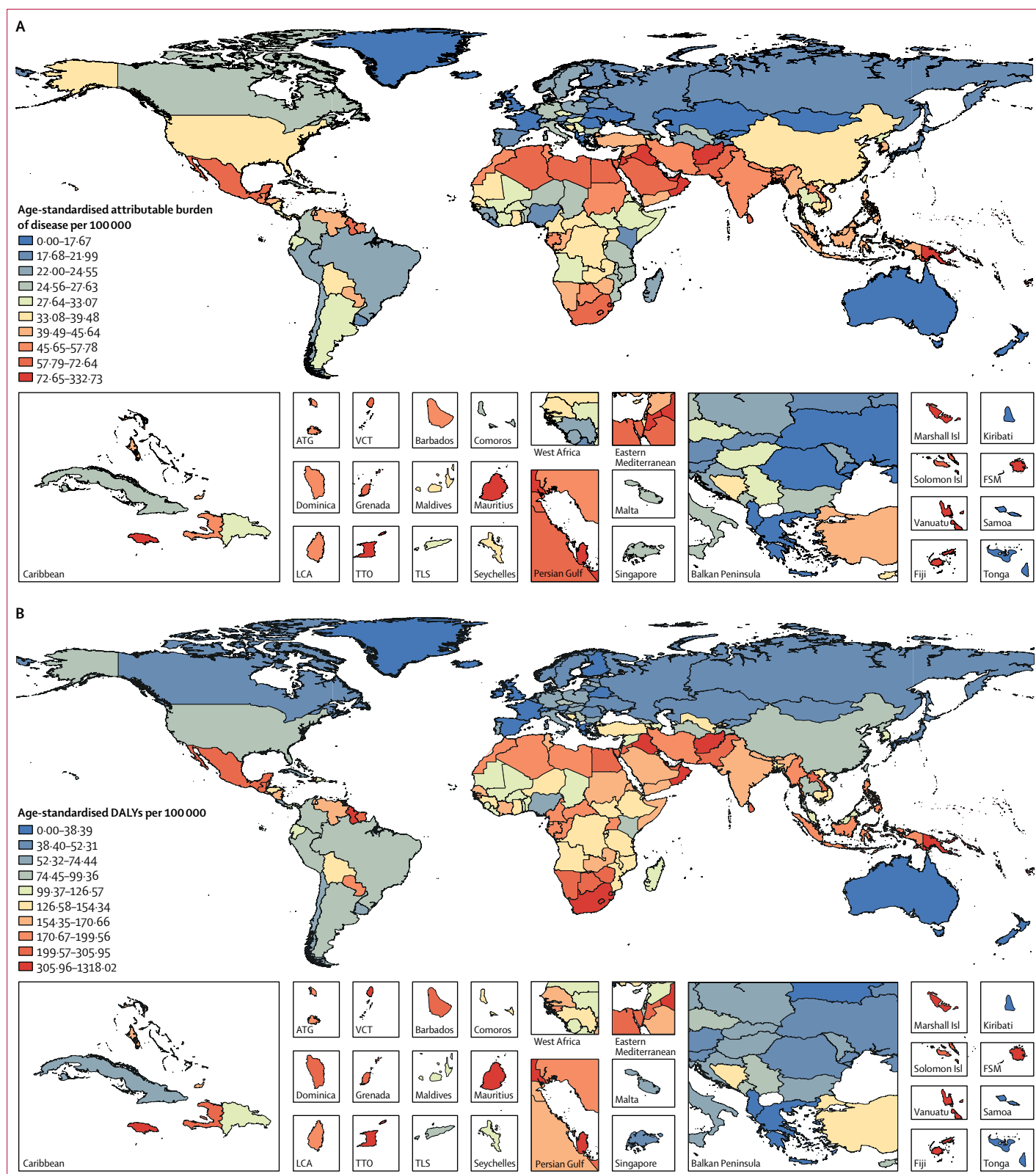
This study has several limitations. Our analyses neither considered the source of $PM_{2.5}$ nor the chemical composition and toxic content of $PM_{2.5}$, which might vary within and among countries; however, studies have shown that estimates using non-specific $PM_{2.5}$ biomass alone will underestimate the burden of disease attributable to $PM_{2.5}$ pollution.^{1,4,65} Our study focused on quantitating the burden of diabetes associated with $PM_{2.5}$ exposure (ie, the *Lancet* Commission on pollution and health research recommendation number two); however, evaluation of the burden of diabetes associated with exposure to other pollutants including carbon monoxide, nitrogen dioxide, and others should be undertaken in future research.^{86,89} Although we accounted for several individual-level and county-level health characteristics, used two different data sources to define exposure, and

took care to vary the spatial resolution of exposure definition, our analyses do not account for individual-level differences in socioeconomic status, physical activity,^{90–92} and $PM_{2.5}$ exposure; however, the successful application of both a negative exposure control and negative outcome control lessens the concern about residual confounding. Our analyses do not provide insight into the subnational level; this level is particularly important because several countries are especially large and there is likely to be substantial national geographical variation in both $PM_{2.5}$ and underlying morbidity and mortality rates related to diabetes (eg, in India and China) that is not captured in our analyses. In this study, we used estimates for incident diabetes generated by the GBD study group, and although these Bayesian estimates are considered robust, they are limited by the quality of the available data.⁹³ Furthermore, variability and inconsistency of data collection methods and tools across the countries could influence geographical variations.⁹³ Because data for the relationship of $PM_{2.5}$ and the risk of diabetes was primarily derived from studies done in countries with relatively lower $PM_{2.5}$ air pollution (eg, USA, Canada, and western Europe), we relied on active and passive smoking as proxies for exposure to higher concentrations of $PM_{2.5}$ pollution to build our integrated exposure response function;³⁵ this analytical strategy is well accepted, widely used, and represents the optimal methodological approach to quantitate the risk of disease associated with $PM_{2.5}$ exposure given the available data.^{1,4,35,65,94}

Our study also had key strengths, such as the examination of the relationship between $PM_{2.5}$ and the risk of diabetes in a longitudinal cohort for which we also tested a positive control, negative exposure control, and negative outcome control to resolve concerns about causal inference. We also leveraged the availability of data from GBD 2016, which is the most comprehensive compilation and analysis of global health information available. We use GBD methodologies including the concept of DALYs to comprehensively capture the burden of disease across the world and a measure of uncertainty.

In conclusion, we provided evidence for a relationship between $PM_{2.5}$ and the risk of diabetes, we synthesised available evidence and integrated it to build an exposure response function describing the risk of diabetes at each level of ambient $PM_{2.5}$ exposure, and we quantitated the burden of diabetes including the number of incident cases of diabetes per year, and the years of healthy life lost due to diabetes attributable to $PM_{2.5}$.

Figure 4: Age-standardised burden of incident diabetes attributable to $PM_{2.5}$ per 100 000 population (A) and age-standardised DALYs due to incident diabetes attributable to $PM_{2.5}$ per 100 000 population (B)
DALYs=disability-adjusted life-years. ATG=Antigua and Barbuda.
VCT=Saint Vincent and the Grenadines. LCA=Saint Lucia.
TTO=Trinidad and Tobago. Isl=Island. FSM=Federated States of Micronesia.
TLS=Timor-Leste.



Contributors

BB, YX, and ZA-A did the background research and study design. BB and YX collected the data. BB, YX, and ZA-A analysed and interpreted the data. BB and ZA-A drafted the manuscript. ZA-A supervised and provided mentorship. Each author contributed important intellectual content during manuscript drafting or revision. All authors accept accountability for the overall work.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by the US Department of Veterans Affairs. The contents do not represent the views of the US Department of Veterans Affairs or the US Government. Support for VA and Centers for Medicare and Medicaid Services (CMS) data are provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, and the VA Information Resource Center (project number or data use agreement identification, Al-Aly-01).

References

- Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature* 2015; **525**: 367–71.
- Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 2017; **29**: 218–30.
- Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: a cohort study. *Lancet Planet Health* 2017; **1**: e267–76.
- Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; **389**: 1907–18.
- Puett RC, Hart JE, Schwartz J, Hu FB, Liese AD, Laden F. Are particulate matter exposures associated with risk of type 2 diabetes? *Environ Health Perspect* 2011; **119**: 384–89.
- Coogan PF, White LF, Jerrett M, et al. Air pollution and incidence of hypertension and diabetes in African American women living in Los Angeles. *Circulation* 2012; **125**: 767–72.
- Brook RD, Cakmak S, Turner MC, et al. Long-term fine particulate matter exposure and mortality from diabetes in Canada. *Diabetes Care* 2013; **36**: 3313–20.
- Chen H, Burnett RT, Kwong JC, et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ Health Perspect* 2013; **121**: 804–10.
- Hansen AB, Ravnskjaer L, Loft S, et al. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. *Environ Int* 2016; **91**: 243–50.
- He D, Wu S, Zhao H, et al. Association between particulate matter 2.5 and diabetes mellitus: a meta-analysis of cohort studies. *J Diabetes Investig* 2017; **8**: 687–96.
- Honda T, Pun VC, Manjourides J, Suh H. Associations between long-term exposure to air pollution, glycosylated hemoglobin and diabetes. *Int J Hyg Environ Health* 2017; **220**: 1124–32.
- Landrigan PJ, Fuller R, Acosta NJR, et al. The Lancet Commission on pollution and health. *Lancet* 2017; **391**: 462–512.
- Al-Aly Z, Edwards JC. Vascular biology in uremia: insights into novel mechanisms of vascular injury. *Adv Chronic Kidney Dis* 2004; **11**: 310–18.
- Al-Aly Z, Balasubramanian S, McDonald JR, Scherrer JF, O'Hare AM. Greater variability in kidney function is associated with an increased risk of death. *Kidney Int* 2012; **82**: 1208–14.
- Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 2016; **27**: 3153–63.
- Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. *Kidney Int* 2017; **91**: 1482–94.
- Xie Y, Bowe B, Xian H, Balasubramanian S, Al-Aly Z. Rate of kidney function decline and risk of hospitalizations in stage 3a CKD. *C J Am Soc Nephrol* 2015; **10**: 1946–55.
- Xie Y, Bowe B, Xian H, Balasubramanian S, Al-Aly Z. Estimated GFR trajectories of people entering CKD stage 4 and subsequent kidney disease outcomes and mortality. *Am J Kidney Dis* 2016; **68**: 219–28.
- Murphy PA, Cowper DC, Seppala G, Stroupe KT, Hynes DM. Veterans Health Administration inpatient and outpatient care data: an overview. *Eff Clin Pract* 2002; **5** (suppl 3): E4.
- Oddone EZ, Eisen S. Veterans Affairs Research and Development: using science to improve health care for veterans. *N C Med J* 2008; **69**: 35–37.
- US Department of Veterans Affairs. VIREC research user guide: Veterans Health Administration medical SAS outpatient datasets FY2006. Hines, IL: VA Information Resource Center, 2007.
- US Department of Veterans Affairs. VIREC research user guide: Veterans Health Administration medical SAS inpatient datasets FY2006. Hines, IL: VA Information Resource Center, 2007.
- US Department of Veterans Affairs. VIREC research user guide: Veterans Health Administration decision support system clinical national data extracts. Hines, IL: VA Information Resource Center, 2009.
- Vaidyanathan A, Dimmick WF, Kegler SR, Qualters JR. Statistical air quality predictions for public health surveillance: evaluation and generation of county level metrics of PM_{2.5} for the environmental public health tracking network. *Int J Health Geogr* 2013; **12**: 12.
- CDC. National environmental public health tracking network. 2016. www.cdc.gov/ephrtracking (accessed Sept 20, 2016).
- Xie Y, Bowe B, Xian H, Balasubramanian S, Al-Aly Z. Renal function trajectories in patients with prior improved eGFR slopes and risk of death. *PLoS One* 2016; **11**: e0149283.
- Remington PL, Catlin BB, Gennuso KP. The County Health Rankings: rationale and methods. *Popul Health Metr* 2015; **13**: 11.
- County Health Rankings & Roadmaps. Rankings data and documentation. 2016. <http://www.countyhealthrankings.org/rankings/data> (accessed June 9, 2016).
- Heinzel H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed* 1997; **54**: 201–08.
- van Donkelaar A, Martin RV, Brauer M, Boys BL. Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. *Environ Health Perspect* 2015; **123**: 135–43.
- van Donkelaar A, Martin RV, Brauer M, Boys BL. Global annual PM_{2.5} grids from MODIS, MISR and SeaWiFS Aerosol Optical Depth (AOD), v1 (1998–2012). Palisades, NY: NASA Socioeconomic Data and Applications Center (SEDAC), 2015.
- Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002; **287**: 1132–41.
- Lipsitch M, Tchetgen ET, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21**: 383–88.
- Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21**: 383–88.
- Burnett RT, Pope CA 3rd, Ezzati M, et al. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. *Environ Health Perspect* 2014; **122**: 397–403.
- GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1659–724.
- Cho NH, Chan JC, Jang HC, Lim S, Kim HL, Choi SH. Cigarette smoking is an independent risk factor for type 2 diabetes: a four-year community-based prospective study. *Clin Endocrinol* 2009; **71**: 679–85.
- Hayashino Y, Fukuhara S, Okamura T, et al. A prospective study of passive smoking and risk of diabetes in a cohort of workers. *Diabetes Care* 2008; **31**: 732–34.
- Hilawe EH, Yatsuya H, Li Y, et al. Smoking and diabetes: is the association mediated by adiponectin, leptin, or C-reactive protein? *J Epidemiol* 2015; **25**: 99–109.

- 40 Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C, Kiefe CI. Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. *BMJ* 2006; **332**: 1064–69.
- 41 Hunt K, Hansis-Diarte A, Shipman K, Korte J, Fowles S, Stern M. Impact of parental smoking on diabetes, hypertension and the metabolic syndrome in adult men and women in the San Antonio Heart Study. *Diabetologia* 2006; **49**: 2291–98.
- 42 Hur NW, Kim HC, Mo Nam C, Ha Jee S, Lee HC, Suh I. Smoking cessation and risk of type 2 diabetes mellitus: Korea Medical Insurance Corporation Study. *Eur J Cardiovasc Prev Rehabil* 2007; **14**: 244–49.
- 43 Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Effects of Smoking on the incidence of non-insulin-dependent diabetes mellitus: replication and extension in a Japanese cohort of male employees. *Am J Epidemiol* 1997; **145**: 103–09.
- 44 Ko K-P, Min H, Ahn Y, et al. A prospective study investigating the association between environmental tobacco smoke exposure and the incidence of type 2 diabetes in never smokers. *Ann Epidemiol* 2011; **21**: 42–47.
- 45 Kowall B, Rathmann W, Strassburger K, et al. Association of passive and active smoking with incident type 2 diabetes mellitus in the elderly population: the KORA S4/F4 cohort study. *Eur J Epidemiol* 2010; **25**: 393–402.
- 46 Laaksonen MA, Knekt P, Rissanen H, et al. The relative importance of modifiable potential risk factors of type 2 diabetes: a meta-analysis of two cohorts. *Eur J Epidemiol* 2010; **25**: 115–24.
- 47 Lajous M, Tondeur L, Fagherazzi G, de Lauzon-Guillain B, Boutron-Ruault M-C, Clavel-Chapelon F. Childhood and adult secondhand smoke and type 2 diabetes in women. *Diabetes Care* 2013; **36**: 2720–25.
- 48 Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med* 2000; **109**: 538–42.
- 49 Nagaya T, Yoshida H, Takahashi H, Kawai M. Heavy smoking raises risk for type 2 diabetes mellitus in obese men; but, light smoking reduces the risk in lean men: a follow-up study in Japan. *Ann Epidemiol* 2008; **18**: 113–18.
- 50 Nakanishi N, Nakamura K, Matsuo Y, Suzuki K, Tatara K. Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. *Ann Intern Med* 2000; **133**: 183–91.
- 51 Östenson C-G, Hilding A, Grill V, Efendic S. High consumption of smokeless tobacco (“snus”) predicts increased risk of type 2 diabetes in a 10-year prospective study of middle-aged Swedish men. *Scand J Public Health* 2012; **40**: 730–37.
- 52 Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015; **3**: 958–67.
- 53 Park CH, Ga H, Leem JH, Kwak SM, Kim HC, Choi JH. The effect of smoking status upon occurrence of impaired fasting glucose or type 2 diabetes in Korean men. *Journal of preventive medicine and public health*. *J Prev Med Public Health* 2008; **41**: 249–54.
- 54 Patja K, Jousilahti P, Hu G, Valle T, Qiao Q, Tuomilehto J. Effects of smoking, obesity and physical activity on the risk of type 2 diabetes in middle-aged Finnish men and women. *J Intern Med* 2005; **258**: 356–62.
- 55 Rasouli B, Grill V, Midtjell K, Ahlbom A, Andersson T, Carlsson S. Smoking is associated with reduced risk of autoimmune diabetes in adults contrasting with increased risk of overweight men with type 2 diabetes. *Diabetes Care* 2013; **36**: 604–10.
- 56 Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 1995; **310**: 555–59.
- 57 Shi L, Shu X-O, Li H, et al. Physical activity, smoking, and alcohol consumption in association with incidence of type 2 diabetes among middle-aged and elderly Chinese men. *PLoS One* 2013; **8**: e77919.
- 58 Teratani T, Morimoto H, Sakata K, et al. Dose-response relationship between tobacco or alcohol consumption and the development of diabetes mellitus in Japanese male workers. *Drug Alcohol Depend* 2012; **125**: 276–82.
- 59 Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care* 2001; **24**: 1590–95.
- 60 Zhang L, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. *Diabetes Care* 2011; **34**: 892–97.
- 61 Pope CA 3rd, Burnett RT, Krewski D, et al. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation* 2009; **120**: 941–48.
- 62 Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON, Canada: Ottawa Hospital Research Institute, 2013.
- 63 Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2224–60.
- 64 Doi SA, Thalib L. A quality-effects model for meta-analysis. *Epidemiology* 2008; **19**: 94–100.
- 65 Brauer M, Freedman G, Frostad J, et al. Ambient air pollution exposure estimation for the global burden of disease 2013. *Environ Sci Technol* 2016; **50**: 79–88.
- 66 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1211–59.
- 67 Institute for Health Metrics and Evaluation. GBD results tool. 2017. <http://ghdx.healthdata.org/gbd-results-tool> (accessed Oct 24, 2017).
- 68 GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1345–422.
- 69 GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1260–344.
- 70 GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1151–210.
- 71 GBD 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1084–150.
- 72 Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2015 (GBD 2015) population estimates 1970–2015. 2015. <http://ghdx.healthdata.org/record/global-burden-disease-study-2015-gbd-2015-population-estimates-1970-2015> (accessed Jan 9, 2018).
- 73 World Bank. World Bank country and lending groups: World Bank list of economies. 2017. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519> (accessed Oct 16, 2016).
- 74 Institute for Health Metrics and Evaluation. The global burden of disease: generating evidence, guiding policy. Seattle, WA: Institute for Health Metrics and Evaluation, 2013.
- 75 Bowe B, Xie Y, Xian H, Lian M, Al-Aly Z. Geographic variation and US county characteristics associated with rapid kidney function decline. *Kidney Int Rep* 2017; **2**: 5–17.
- 76 Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002; **287**: 1132–41.
- 77 Chin MT. Basic mechanisms for adverse cardiovascular events associated with air pollution. *Heart* 2015; **101**: 253–56.
- 78 Miller MR, Raftis JB, Langrish JP, et al. Inhaled nanoparticles accumulate at sites of vascular disease. *ACS Nano* 2017; **11**: 4542–52.
- 79 Wei Y, Zhang JJ, Li Z, et al. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing. *FASEB J* 2016; **30**: 2115–22.

- 80 Chen Z, Salam MT, Toledo-Corral C, et al. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. *Diabetes Care* 2016; **39**: 547–54.
- 81 Wolf K, Popp A, Schneider A, et al. Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation, and adipokines. *Diabetes* 2016; **65**: 3314–26.
- 82 Sun Q, Yue P, Deiluiis JA, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. *Circulation* 2009; **119**: 538–46.
- 83 Brook RD, Xu X, Bard RL, et al. Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. *Sci Total Environ* 2013; **448**: 66–71.
- 84 Alderete TL, Habre R, Toledo-Corral CM, et al. Longitudinal associations between ambient air pollution with insulin sensitivity, β -cell function, and adiposity in Los Angeles Latino children. *Diabetes* 2017; **66**: 1789–96.
- 85 Holmes D. Endocrine disruptors: air pollution linked to insulin resistance. *Nat Rev Endocrinol* 2016; **12**: 688.
- 86 Yang BY, Qian ZM, Li S, et al. Ambient air pollution in relation to diabetes and glucose-homoeostasis markers in China: a cross-sectional study with findings from the 33 Communities Chinese Health Study. *Lancet Planet Health* 2018; **2**: e64–73.
- 87 Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: mechanistic insights. *Diabetes* 2012; **61**: 3037–45.
- 88 Di Q, Wang Y, Zanobetti A, et al. Air pollution and mortality in the Medicare population. *N Engl J Med* 2017; **376**: 2513–22.
- 89 Meo SA, Memon AN, Sheikh SA, et al. Effect of environmental air pollution on type 2 diabetes mellitus. *Eur Rev Med Pharmacol Sci* 2015; **19**: 123–28.
- 90 Gill JM, Cooper AR. Physical activity and prevention of type 2 diabetes mellitus. *Sports Med* 2008; **38**: 807–24.
- 91 Sieverdes JC, Sui X, Lee DC, et al. Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men. *Br J Sports Med* 2010; **44**: 238–44.
- 92 Jefferis BJ, Whincup PH, Lennon L, Wannamethee SG. Longitudinal associations between changes in physical activity and onset of type 2 diabetes in older British men: the influence of adiposity. *Diabetes Care* 2012; **35**: 1876–83.
- 93 Thomas B, Matsushita K, Abate KH, et al. Global cardiovascular and renal outcomes of reduced GFR. *J Am Soc Nephrol* 2017; **28**: 2167–79.
- 94 Zhang Q, Jiang X, Tong D, et al. Transboundary health impacts of transported global air pollution and international trade. *Nature* 2017; **543**: 705–09.