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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 1 729 108 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.

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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* Commission[12] 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

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.

See Online for appendix

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

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 μg/m³, and active smoking 667 μg/m³ 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 μg/m³ to 5·9 μg/m³, 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://eospso.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 study[68] 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 10 000 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 100 000 population, and age-standardised rates per 100 000 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 7.1). 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 1729 108 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/m³	$PM_{2.5}$* (EPA)	Diabetes	446334	94564 (21·2%)	3087·6	1·00 (Ref)
10·2–11·8 μg/m³	$PM_{2.5}$* (EPA)	Diabetes	442939	102456 (23·1%)	3431·4	1·08 (1·05–1·12)
11·9–13·6 μg/m³	$PM_{2.5}$* (EPA)	Diabetes	408580	98439 (24·1%)	3604·6	1·13 (1·07–1·18)
13·7–22·1 μg/m³	$PM_{2.5}$* (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, 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-

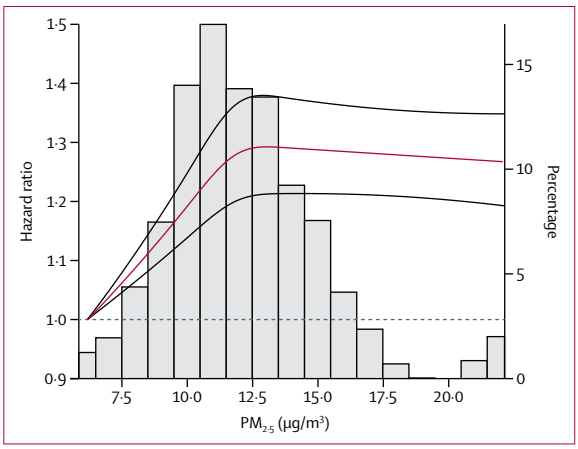


Figure 1: **Spline analysis of $PM_{2.5}$ and the risk of diabetes**
The red line is the hazard ratio. The black lines are the 95% CIs. A histogram of the distribution of $PM_{2.5}$ exposure is presented in the background in grey. The lowest $PM_{2.5}$ value included in the analysis was 6·2 μg/m³ and it served as the reference.

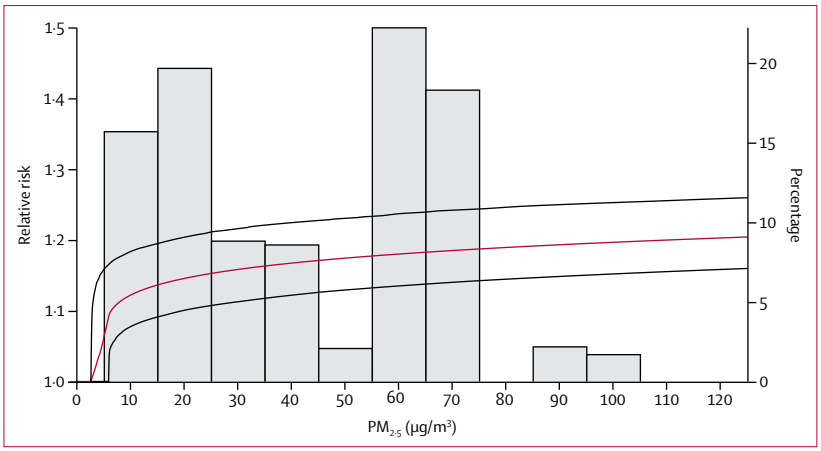


Figure 2: **Integrated exposure response function of the association between $PM_{2·5}$ and diabetes**
A histogram of the distribution of $PM_{2·5}$ exposure among the countries is presented in the background in grey. The red line is the mean estimated relative risk. The black lines are 95% uncertainty intervals.

	$PM_{2·5}$ exposure concentration (μg/m³)	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 homoeostasis 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)	YLL in 1000s (95% UI)	YLL 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)	13·3 (8·7–17·7)	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**

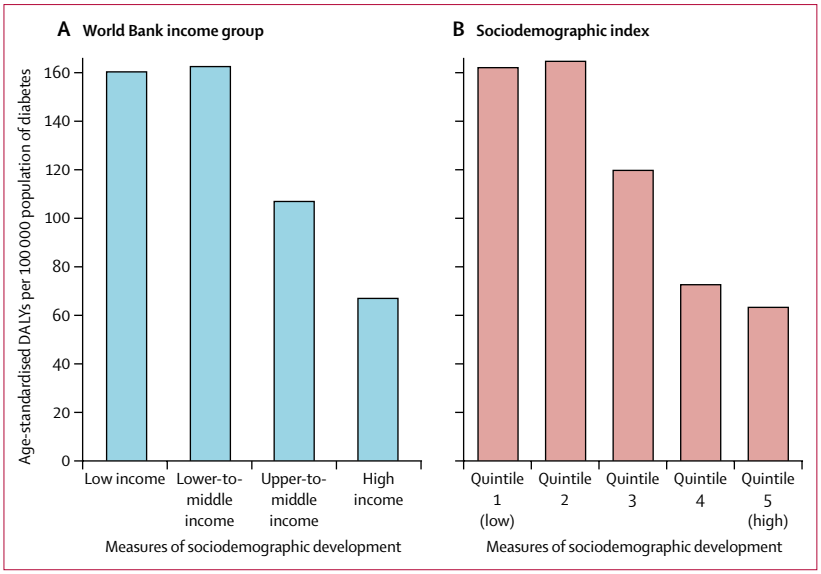


Figure 3: **Age-standardised DALYs per 100 000 population of diabetes by World Bank income group (A) and sociodemographic index quintile (B)**
DALYs=disability-adjusted life-years.

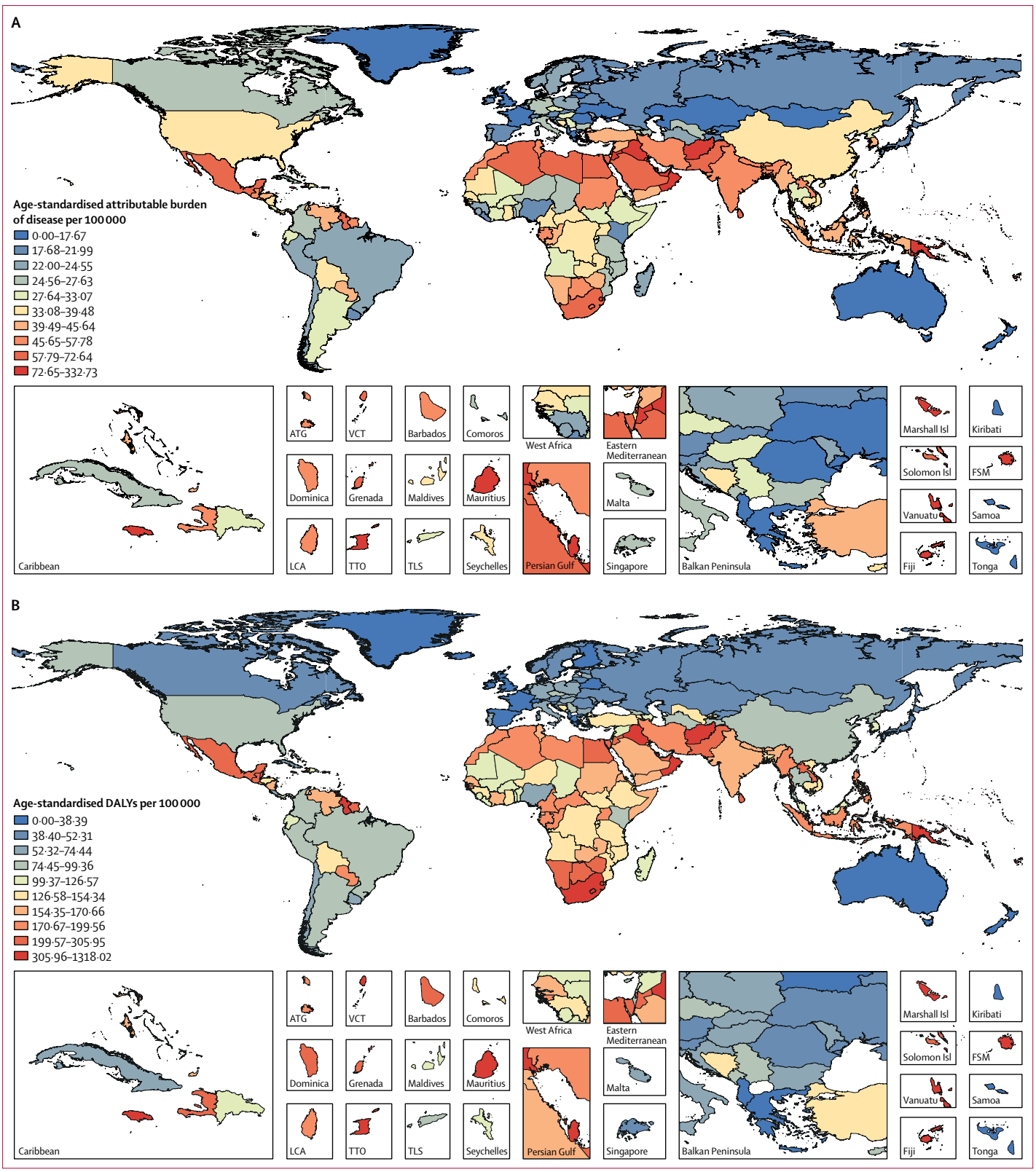
more prominent as major causes of disease and death, and the contribution of air pollution to non-communicable diseases in general, and specifically to diabetes will probably become even more pronounced. The forces of demographic expansion, ageing, epidemiological transition, and rapid industrialisation 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.


A
Age-standardised attributable burden of disease per 100 000
0·00–17·67
17·68–21·99
22·00–24·55
24·56–27·63
27·64–33·07
33·08–39·48
39·49–45·64
45·65–57·78
57·79–72·64
72·65–332·73
Caribbean
ATG
VCT
Barbados
Comoros
West Africa
Eastern Mediterranean
Dominica
Grenada
Maldives
Mauritius
Malta
Marshall Isl
Kiribati
Solomon Isl
FSM
Vanuatu
Samoa
LCA
TTO
TLS
Seychelles
Persian Gulf
Singapore
Balkan Peninsula
Fiji
Tonga
B
Age-standardised DALYs per 100 000
0·00–38·39
38·40–52·31
52·32–74·44
74·45–99·36
99·37–126·57
126·58–154·34
154·35–170·66
170·67–199·56
199·57–305·95
305·96–1318·02
Caribbean
ATG
VCT
Barbados
Comoros
West Africa
Eastern Mediterranean
Dominica
Grenada
Maldives
Mauritius
Malta
Marshall Isl
Kiribati
Solomon Isl
FSM
Vanuatu
Samoa
LCA
TTO
TLS
Seychelles
Persian Gulf
Singapore
Balkan Peninsula
Fiji
Tonga

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.

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