**PM$_{2.5}$ exposure, glycemic markers and incidence of type 2 diabetes in two large Indian cities**

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**ABSTRACT**

**Introduction** Exposure to fine particulate matter has been associated with several cardiovascular and cardiometabolic diseases. However, such evidence mostly originates from low-pollution settings or cross-sectional studies, thus necessitating evidence from regions with high air pollution levels, such as India, where the burden of non-communicable diseases is high. **Research design and methods** We studied the associations between ambient PM$_{2.5}$ levels and fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) and incident type 2 diabetes mellitus (T2DM) among 12,064 participants in an adult cohort from urban Chennai and Delhi, India. A meta-analytic approach was used to combine estimates, obtained from mixed-effects models and proportional hazards models, from the two cities. **Results** We observed that 10 μg/m$^3$ differences in monthly average exposure to PM$_{2.5}$ was associated with a 0.40 mg/dL increase in FPG (95% CI 0.22 to 0.58) and 0.021 unit increase in HbA1c (95% CI 0.009 to 0.032). Further, 10 μg/m$^3$ differences in annual average PM$_{2.5}$ was associated with 1.22 (95% CI 1.09 to 1.36) times increased risk of incident T2DM, with non-linear exposure response. **Conclusions** We observed evidence of temporal association between PM$_{2.5}$ exposure, and higher FPG and incident T2DM in two urban environments in India, thus highlighting the potential for population-based mitigation policies to reduce the growing burden of diabetes.

**INTRODUCTION**

Global evidence linking ambient air pollution to non-communicable diseases is mostly based on studies from high-income countries with low concentrations of particulate matter. Evidence from low-income and middle-income countries, such as India, is scarce with research gaps in both exposure assessment and health studies. Air pollution exposure assessments in India have relied primarily on the sparse monitoring network located in major cities, spatiotemporal models with a coarse resolution or based only on satellite observations. Additionally, studies of fine particulate matter of diameter less than 2.5μm (PM$_{2.5}$) and diabetes are scarce in highly polluted regions like India, with limitations including cross-sectional design and self-reported outcome assessment. Given the high burden of cardiometabolic diseases in India and the unique pathophysiologic characteristics of the South Asian population, including low lean mass and propensity for higher hepatic fat deposition leading to reduced pancreatic beta cell function and impaired insulin action, it is important to generate robust evidence.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

- Current epidemiological evidence suggests that exposure to PM$_{2.5}$ is associated with incidence of type 2 diabetes through multiple mechanistic pathways.
- However, studies mostly originate from countries with low concentrations of PM$_{2.5}$ and with a Caucasian population, with few recent studies from China.
- There exists a major research gap due to the lack of robust exposure assessment and longitudinal studies in the large South Asian population which experiences a high burden of disease due to diabetes.

**WHAT THIS STUDY ADDS**

- This study provides evidence linking short-term, medium-term and long-term exposure to PM$_{2.5}$ assessed from locally developed high-resolution spatiotemporal models, glycemic markers and incidence of diabetes from a highly polluted region with a high burden of diabetes, thus adding to the existing evidence from low-pollution scenarios in the Western population.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

- The combined evidence provides directions for devising and implementing region-specific and population-specific policies targeted towards reducing ambient air pollution to counter the high burden of diabetes in order to achieve significant population-level public health gains.

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Epidemiological evidence linking particulate matter with type 2 diabetes mellitus (T2DM) suggests increased risk of diabetes, an increase in intermediate risk factors like Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), insulin, fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c), and increased diabetes-associated mortality. Studies from high-income countries showed a 10 μg/m³ increase in PM$_{2.5}$ exposure was associated with a 7%–11% increased risk of developing T2DM and an estimated 19% increased risk of diabetes mortality. However, the levels of annual average PM$_{2.5}$ in these countries are at the lower end of the spectrum, ranging between 2.8 μg/m³ to 21.2 μg/m³. In more polluted areas of China, Hong Kong, and Taiwan, studies have reported associations between PM$_{2.5}$ and increased prevalent and incident T2DM, fasting glucose and HbA1c. Evidence from studies in India has been inconclusive with major limitations in the PM$_{2.5}$ exposure assessment. Specifically, Curto et al reported no association between ambient air pollution and T2DM although the possible limitations of the study were noted as the potential confounding of personal exposure and measurement of exposure after health outcomes were ascertained.

We used PM$_{2.5}$ exposure data from recently developed machine learning based models for daily PM$_{2.5}$ concentrations at 1 km × 1 km spatial resolution over two major Indian cities, Chennai (South India) and Delhi (North India) between January 2010 to December 2016. We used an ongoing large prospective population-based cohort study in these two cities with 7 years or more of follow-up and rigorous cardiometabolic phenotyping to assess the association between short-term and long-term exposure to PM$_{2.5}$ with glycemic markers and incident T2DM in highly polluted regions.

**METHODS**

**The CARRS cohort**

The Center for Cardiometabolic Risk Reduction in South Asia (CARRS) Surveillance Study is a cohort study in two Indian cities (https://www.carrsprogram.org/), Chennai and Delhi, based on representative (of the respective urban locations) samples of adult residents aged 20 years or more. A population-based, multistage, cluster random sampling design based on municipal wards was used to recruit the participants in each city. Pregnant women and seriously ill bedridden individuals were excluded from the study due to difficulties in obtaining anthropometric measurements. Two individuals, one male and one female, from each household were recruited. This resulted in 12271 (6906 in Chennai and 5365 in Delhi) adult participants (permanent members of the household). A total of 12604 individuals, that is, 6722 individuals from Chennai and 5342 individuals from Delhi were included in this study, who had geocoded household information as well as questionnaire-based survey responses. Out of these participants, 10031 had provided blood samples at baseline and at least one measured glycemic marker (FPG and HbA1c) between January 2010 and December 2016 (online supplemental figure 1). Assessment of glycemic markers was carried out irrespective of diabetes status in the entire cohort.

The baseline in-person questionnaire-based survey (administered by trained field workers) and biospecimen collection were performed during 2010 to 2012, with subsequent follow-ups (with both questionnaire interviews and biospecimen collections) from 2013 to 2014 and 2016 to 2017. In addition, two intermediate follow-ups with only short questionnaire-based interviews were conducted in 2011–2013 and 2014. Measures, methods and validated instruments (adapted from existing studies) for recording demographic indicators, behavioral, physiological and biochemical risk factors, along with laboratory techniques, are described in detail in the study by Nair et al. All participants in the study provided written informed consent for participation and the study was approved by the respective institutional ethics committees.

**Exposure data**

A satellite-based hybrid exposure model was used to assess daily average ambient PM$_{2.5}$ concentrations at 1 km × 1 km in Delhi and Chennai for each day from January 1, 2010 to December 31, 2016. These models used satellite observations, such as aerosol optical depth, meteorological parameters, land use variables, and emission inventories, while calibrating against ground monitoring observations obtained from real-time and manual stations of the Central Pollution Control Board, India and embassies of the USA at each city. Ground monitoring based daily average PM$_{2.5}$ across 2010–2016 were available from 19 (6752 observations) and 24 stationary monitors (17152 observations) in Chennai and Delhi, respectively. In addition, 62 observations of daily PM$_{2.5}$ collected as part of the Tamil Nadu Air Pollution and Health Effects (TAPHE) Study from 42 locations were also used in the development of the model at Chennai. In Chennai and Delhi, 48% and 39% of the observations were from 2015 to 2016, respectively. The variables used in building the models were similar in both cities, except proximity to shore which was specific to Chennai. The machine learning-based models were developed separately for each city using the same ensemble averaging based methodology. However, training and testing of the algorithms were carried out by calibrating to the ground monitoring-based daily PM$_{2.5}$ measurements from each city. Therefore, the model parameters were different in each city, as was the importance of predictor variables. Predictions from machine learning algorithms (such as random forests, gradient boosting, and support vector regression) were combined under a generalized additive model framework to obtain the final predictions. The daily predictions were validated against ground
measurements in a left-out data set with an overall cross-validated prediction accuracy of 84% and 80% at Chennai and Delhi, respectively. Online supplemental figure 2 shows the average PM$_{2.5}$ concentrations across time in the two cities based on the prediction models.

Notably, the annual average concentrations in both cities were higher than the monthly averages due to a higher number of participant interviews during summer and monsoon months (March to August) compared with fall and winter, in both cities. The difference was more prominent in Delhi, where pollution is much higher during October to January. Within Delhi, the difference was higher in the last follow-up because of extreme pollution in October and November of 2016, as shown in the maps of monthly average PM$_{2.5}$ (online supplemental figure 2).

To assess time-varying exposure for individuals in the study, we assigned each participant to a particular 1 km × 1 km grid based on the proximity of the household (as determined by their geocodes), (online supplemental figure 3) to the grid centroid. For a participant with a date of blood collection $d$, average exposure of duration $t$ was calculated as the average of daily ambient PM$_{2.5}$ at the household geocode spanning from $d$-$t$ to $d$-$1$. In case of exposures for incident T2DM, an additional 3 months were removed prior to the date of collection (average spanning from $d$-$1$ to $d$-$1$). In case of exposures for incident T2DM, an additional 3 months were removed prior to the date of collection (average spanning from $d$-$1$-$90$ to $d$-$1$-$90$) to allow for potential gap between actual incidence and date of sample collection. Based on different durations, short-term (1 month), medium-term (6 months) and long-term (≥1year) time-varying exposures for each participant were constructed based on time-updated follow-up.

**Diabetes assessment**

Venous FPG and HbA1c were measured in the blood samples collected from each participant at baseline and at the follow-ups. FPG was assessed using hexokinase/kinetic methods while HbA1c was quantified using high-performance liquid chromatography, as described in Deepa et al. Using these continuous markers, T2DM was defined as FPG ≥126 mg/dL, or HbA1c ≥6.5, or self-reported physician-diagnosed diabetes, or being on medication for diabetes. Prediabetes was defined by FPG between 100 mg/dL and 125 mg/dL or HbA1c between 5.7 to 6.4 for each participant at each follow-up.

**Confounders and covariates**

We considered calendar time, socioeconomic status, proximity to major roads and average monthly temperature before measurement (only for short-term exposures) as confounders in the models associating PM$_{2.5}$ exposure with glycemic markers and incident T2DM. Additionally, age, sex, current tobacco consumption, alcohol consumption, physical activity and diet were included as covariates in the models.

Out of these variables, calendar time, age, monthly temperature, tobacco, and alcohol consumption were time-varying variables. Details of these variables are provided in the online supplemental material. Anthropometric measurements including height, weight, waist circumference, and hip circumference, and measures such as systolic and diastolic blood pressure were measured in the CARRS Surveys, according to methodologies described in previous publications. A directed acyclic graph is shown in online supplemental figure 4 describing the relationships between the exposures, confounders, and outcomes.

**Statistical methods**

To study the effect of time-varying PM$_{2.5}$ exposure on the continuous outcomes, we analyzed the longitudinal associations between PM$_{2.5}$ exposure and FPG (and HbA1c) using linear mixed-effects models, stratified by city. Transformations were not used to modify the outcomes. Random intercepts for each participant were included to account for individual variation in the models, while inverse treatment probability weighting was used to account for loss to follow-up. For each city, the probability of study dropout for each participant at each follow-up ($π_i$) was modeled using logistic regression models against age at entry into the study, sex, years of education, socioeconomic status, body mass index (BMI), hypertension status, and diabetes status at baseline. Predicted probabilities for the participant still being part of the study at follow-up k were computed as $v_k = (1−π_i) \times \ldots \times (1−π_{ik})$, $k=1,2$ from these models. Inverse of these weights ($w_k = 1/v_k$) were used to weight the observations corresponding to each participant in the longitudinal models of association.

The association between long-term PM$_{2.5}$ exposure and incident diabetes in each city was analyzed using Cox proportional hazards models within individuals who did not have diabetes at baseline. In both cases, using the estimates obtained from the longitudinal models (or Cox proportional hazards models), we employed a random-effects meta-analysis approach to obtain pooled estimates, which combined effect estimates from Chennai and Delhi assuming that the observed studies are a random sample from a larger population of studies. Therefore, the true effects are normally distributed with the average true effect as mean and variance being the sum of the stochastic variance and the variance (if any) of the true effects across locations, referred to as the amount of heterogeneity in the true effects/outcomes. We also computed the I$^2$ statistic (total heterogeneity/total variability) and tested for residual heterogeneity using Cochran’s $Q$ for each exposure duration and glycemic marker.

To assess the non-linearity of the HRs across the range of exposures in each city, we first categorized all participants into deciles of exposure (within each city). Continuous exposure to PM$_{2.5}$ was modeled against baseline covariates (sex, age, occupation, years of education, tobacco, and alcohol consumption, socioeconomic status, BMI, and proximity to major roads) as well as month of measurement and calendar time, using a generalized linear model. Using these models, we computed
generalized propensity scores for each observation using Gaussian density functions evaluated at the corresponding exposure value, with the predictions from the propensity score model as the mean and variance of the residuals as the variance. The weights were stabilized using a Gaussian density evaluated at the individual exposure with mean and variance of the exposure in the whole sample. Subsequently, we carried out a Cox proportional hazards model with the penalized splines of exposure as the explanatory variable, using inverse probability treatment weighting by generalized propensity scores from the propensity score models.

Effect modification by factors such as hypertension at baseline, sex, age at entry into study, waist-to-hip ratio and high sensitivity C-reactive protein (hsCRP) levels (in a subset) was tested using stratified models, while mixed-effects models with multiplicative interaction terms between the exposure and the effect modifier were implemented to obtain the associated p value for the interaction of interest. Details of the methods for each analysis are provided in the online supplemental material.

RESULTS
Descriptive summaries
At baseline, the study population was 50% female with a median age of 44 years in Delhi, while in Chennai it was 56% female with a median age of 40 years (table 1). Median years of follow-up in the study was 4.84 years (IQR: 3.99–5.17 years). Median PM$_{2.5}$ (IQR) annual concentrations were 40.2 μg/m$^3$ (37.5–42.7) in Chennai and 101.5 μg/m$^3$ (92.2–119.8) in Delhi over the duration of the study. Concentrations in Chennai were four times the WHO recommended guidelines at that time (10 μg/m$^3$) and equal to the Indian National Ambient Air Quality Standards (40 μg/m$^3$) for annual average PM$_{2.5}$. In comparison, concentrations in Delhi exceeded WHO and Indian standards by 10 times and 2.5 times, respectively. Table 1 shows the average exposure to PM$_{2.5}$ for analysis of glycemic markers by city and follow-up, while online supplemental table 1 shows the average exposures for the incidence analysis and correlation among the different exposure metrics. Online supplemental table 2 shows the information on confounders and covariates in the study participants, while online supplemental table 3 describes the distribution of the characteristics by exposure quartiles. The association between loss to follow-up and participant characteristics at baseline is shown in online supplemental table 4.

Associations between short-term exposure to PM$_{2.5}$ and glycemic markers
We observed a significant increase in both FPG (0.39 mg/dL, 95% CI 0.21 to 0.58) and HbA1c (0.018, 95% CI 0.012 to 0.024) against 10 μg/m$^3$ change in monthly exposure in Delhi (figure 1 and online supplemental table 5). In Chennai, 10 μg/m$^3$ change in monthly exposure was associated with 0.51 mg/dL (95% CI -0.36 to 1.39) increase in FPG and 0.03 unit (95% CI 0.01 to 0.06) increase in HbA1c. Against medium-term exposure averages over 6 months, a 10 μg/m$^3$ change was associated with 0.68 mg/dL (95% CI 0.41 to 0.95) increase in FPG and 0.05 unit (95% CI 0.025 to 0.043) increase in HbA1c in Delhi, while the effects in Chennai were positive but not statistically significant (figure 1). Using a meta-analytic approach, we observed that average changes (and CIs) in FPG and HbA1c against monthly exposure to PM$_{2.5}$ were 0.40 mg/dL (95% CI 0.22 to 0.58) and 0.021 (95% CI 0.009 to 0.032), respectively (table 2). Against medium-term exposure of 6 months, the average changes in FPG and HbA1c were 0.69 mg/dL (95% CI 0.42 to 0.96) and 0.033 (95% CI 0.025 to 0.042), respectively. The values of the I$^2$ statistic were 0% and the Q test indicated that there was no true ‘between-city’ heterogeneity in the estimates justifying a focus on the combined measures.

Online supplemental table 6 indicates potential effect modification of the association between medium-term exposure to PM$_{2.5}$ by age at entry into the study (for FPG) and BMI (for both markers) in Delhi. Against short-term exposure, only hypertension status modified the association with HbA1c in Delhi. Further, the association between PM$_{2.5}$ and both glycemic markers were higher in the medication group specifically in Chennai, although the low sample size in the medication group resulted in wide CIs (online supplemental table 7). In a subset of 8796 individuals with measured hsCRP levels at baseline, we detected significant effect modification of the associations between monthly PM$_{2.5}$ exposure with FPG and HbA1c by hsCRP levels in Chennai at baseline (value of p for interaction <0.001), with increased levels of both glycemic markers in the participants with higher-than-average hsCRP levels (online supplemental table 8), while contrasting yet insignificant interaction effects were observed in Delhi. As a sensitivity analysis in 1310 participants with physician-diagnosed diabetes at baseline who were also on allopathic diabetes medication (783 in Chennai and 527 in Delhi), we analyzed the associations between 3 months and 6 months exposure to PM$_{2.5}$ with glycemic markers. The associations were positive irrespective of the marker or city, but the effects were significant only in Delhi (online supplemental table 9).

Association of long-term exposure to PM$_{2.5}$ with incidence of diabetes
We observed 360 and 383 incident cases of T2DM in Chennai and Delhi, respectively, over the entire study period. The total number of person-years was 25 670, which translated to 29 new cases of diabetes per 1000 person-years. According to city-specific models, irrespective of the duration, long-term exposure to PM$_{2.5}$ was associated with an increased risk of developing T2DM in both cities, although the pattern against different durations of exposure was different in the two cities (online supplemental table 10). In Chennai, the risk of developing T2DM increased with longer durations of exposure with the highest risk (HR: 1.46, 95% CI 1.04 to 1.98) against 75% increase in monthly exposure versus the reference group.
Table 1  Descriptive characteristics of participants in the CARRS cohort in Delhi and Chennai at baseline and two subsequent follow-ups with biospecimen collection. Categorical variables are summarized using numbers and percentages, while continuous variables are summarized using median and IQRs. Blank cells indicate that the variable was not measured at a particular follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Chennai Baseline</th>
<th>Follow-up 1</th>
<th>Follow-up 2</th>
<th>Delhi Baseline</th>
<th>Follow-up 1</th>
<th>Follow-up 2</th>
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<tbody>
<tr>
<td>Number of recruited participants with geocodes</td>
<td>6722</td>
<td>5342</td>
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<td>Number of geocoded individuals with measured glycemic traits (at least one of FPG and HbA1c) and with blood samples before 2017</td>
<td>5710</td>
<td>3928</td>
<td>3309</td>
<td>4148</td>
<td>3102</td>
<td>2698</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Female</td>
<td>3178 (55.7)</td>
<td>2236 (56.9)</td>
<td>1907 (57.6)</td>
<td>2097 (50.6)</td>
<td>1591 (51.3)</td>
<td>1401 (51.9)</td>
</tr>
<tr>
<td>Male</td>
<td>2532 (44.3)</td>
<td>1692 (43.1)</td>
<td>1402 (42.4)</td>
<td>2051 (49.4)</td>
<td>1511 (48.7)</td>
<td>1297 (48.1)</td>
</tr>
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<td>Median age (IQR), in years</td>
<td>40.1 (32.1–49.6)</td>
<td>42.3 (34.7–51.4)</td>
<td>45.2 (37.8–53.9)</td>
<td>44.6 (35.8–53.9)</td>
<td>47.3 (38.8–56.0)</td>
<td>49.8 (41.3–58.0)</td>
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<td>Self-reported diabetes mellitus, n (%)</td>
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<tr>
<td>Yes</td>
<td>748 (13.2)</td>
<td>132 (3.4)</td>
<td>844 (25.5)</td>
<td>479 (11.6)</td>
<td>41 (1.3)</td>
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<td>3796 (96.6)</td>
<td>2465 (74.5)</td>
<td>3651 (88.4)</td>
<td>3061 (98.7)</td>
<td>2180 (80.8)</td>
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<td>Median glucose (IQR), in mg/dL</td>
<td>94.0 (88.0–106.0)</td>
<td>97.0 (89.0–111.0)</td>
<td>97.0 (89.0–116.0)</td>
<td>101.0 (94.0–112.0)</td>
<td>112.0 (92.0–112.0)</td>
<td>103.1 (95.2–118.8)</td>
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<td>Median HbA1c (IQR), in %</td>
<td>5.8 (5.4–6.3)</td>
<td>5.6 (5.2–6.2)</td>
<td>5.7 (5.4–6.5)</td>
<td>6.0 (5.6–6.6)</td>
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<td>5.6 (5.2–6.3)</td>
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<td>Reported use of medication for diabetes, n (%)</td>
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<td>Yes</td>
<td>678 (11.6)</td>
<td>90 (2.3)</td>
<td>686 (20.6)</td>
<td>424 (9.9)</td>
<td>27 (0.9)</td>
<td>444 (16.6)</td>
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<td>3838 (97.6)</td>
<td>2623 (79.4)</td>
<td>3724 (90.1)</td>
<td>3075 (99.0)</td>
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<td>Diabetes mellitus (FPG ≥126 mg/dL and/or HbA1c ≥6.5 and/or self-reported physician-diagnosed diabetes mellitus and/or on medication for diabetes), n (%)</td>
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<td>1366 (23.9)</td>
<td>934 (23.8)</td>
<td>1053 (31.8)</td>
<td>1356 (32.7)</td>
<td>754 (24.3)</td>
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<td>2994 (76.2)</td>
<td>2256 (68.2)</td>
<td>2792 (75.7)</td>
<td>2348 (75.7)</td>
<td>1917 (71.1)</td>
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<td>Prediabetes (100 mg/dL ≤ FPG &lt;126 mg/dL and/or 5.7 ≤ HbA1c &lt; 6.5), n (%) at baseline</td>
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<tr>
<td>Yes</td>
<td>2734 (47.9)</td>
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<td>2976 (52.1)</td>
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<td>1521 (36.7)</td>
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<td>Hypertensive (Systolic blood pressure (SBP) ≥ 140 mm Hg and/or Diastolic blood pressure (DBP) ≥ 90 mm Hg and/or self-reported physician-diagnosed hypertension and/or on medication for hypertension), n (%) at baseline</td>
<td></td>
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<tr>
<td>Yes</td>
<td>1550 (27.1)</td>
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<td>1641 (39.6)</td>
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<td>2507 (60.4)</td>
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<tr>
<td>Median PM$_{2.5}$ exposure (IQR) in μg/m$^3$</td>
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<tr>
<td>1 month</td>
<td>35.8 (30.9–44.3)</td>
<td>35.7 (32.1–43.9)</td>
<td>33.3 (29.4–36.7)</td>
<td>82.4 (69.1–107.1)</td>
<td>1 (67.7–143.3)</td>
<td>91.9 (73.3–117.7)</td>
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<td>3 months</td>
<td>38.3 (32.5–43.4)</td>
<td>36.6 (33.1–41.6)</td>
<td>35.3 (31.5–39.6)</td>
<td>88.1 (69.4–110.1)</td>
<td>94.6 (76.5–106.4)</td>
<td>99.9 (82.7–133.3)</td>
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<td>6 months</td>
<td>38.5 (35.6–43.4)</td>
<td>37.8 (34.9–43.1)</td>
<td>37.7 (33.8–40.7)</td>
<td>98.7 (74.3–116.9)</td>
<td>92.3 (85.5–103.1)</td>
<td>128.2 (89.1–149.6)</td>
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<td>1 year</td>
<td>41.1 (38.7–43.4)</td>
<td>41.5 (38.8–44.3)</td>
<td>36.5 (34.5, 39.9)</td>
<td>92.1 (87.6–95.7)</td>
<td>98.7 (92.2–107.1)</td>
<td>121.5 (117.9–124.8)</td>
</tr>
</tbody>
</table>

CARRS, Center for cArdiometabolic Risk Reduction in South Asia; FPG, fasting plasma glucose; HbA1c, Glycosylated hemoglobin.
Figure 1  Associations between short-term ambient PM$_{2.5}$ exposure and glycemic markers: (Left panel) Average changes in fasting plasma glucose levels (measured in mg/dL) and glycosylated hemoglobin (HbA1c) (measured in %) against 10 μg/m$^3$ change in PM$_{2.5}$ exposure averaged over 1 month, 3 months and 6 months, at Chennai and Delhi, using longitudinal mixed-effects modeling after adjusting for confounders and covariates. Black dots represent the point estimates and vertical bars represent the lower and upper 95% CIs.

Table 2  Meta-analytic estimates by combining city-specific estimates for associations between exposure to PM$_{2.5}$ and (A) glycemic markers and (B) incident T2DM, using a random-effects model

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>FPG</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>0.40 mg/dL</td>
<td>0.22 to 0.58</td>
</tr>
<tr>
<td>3 months</td>
<td>0.19 mg/dL</td>
<td>0.01 to 0.38</td>
</tr>
<tr>
<td>6 months</td>
<td>0.69 mg/dL</td>
<td>0.42 to 0.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident T2DM</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>1.22</td>
<td>1.09 to 1.36</td>
</tr>
<tr>
<td>1.5 years</td>
<td>1.23</td>
<td>1.12 to 1.37</td>
</tr>
<tr>
<td>2 years</td>
<td>1.23</td>
<td>1.01 to 1.50</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus.
In contrast, the risk in Delhi was observed to be highest for 1.5 years of exposure (HR: 1.24, 95% CI 1.12 to 1.38) while the risk against 2 years of exposure was lower (HR: 1.16, 95% CI 1.03 to 1.3). The pooled estimates using the meta-analytic approach indicated that average HR (and CIs) for developing T2DM against 1 year, 1.5 years, and 2 years were 1.22 (95% CI 1.09 to 1.36), 1.23 (95% CI 1.12 to 1.37), and 1.23 (95% CI 1.01 to 1.50), respectively (table 2). The corresponding values of the I² statistic were 0%, 0%, and 38.6% and the Q tests indicated that there was no true ‘between-city’ heterogeneity in the estimates. Further, hypertensive participants at baseline (value of p for interaction=0.09) were more susceptible to developing T2DM against long-term exposure to PM2.5 in Chennai. In contrast, younger participants were more susceptible to developing T2DM in Delhi (value of p for interaction=0.03) (online supplemental table 11).

Analysis for non-linear HRs
We computed the HRs of developing T2DM using penalized splines of exposures (figure 2), while using inverse probability treatment weighting based on generalized propensity scores. In Chennai, the risks of developing T2DM were maximized at 34 μg/m³ for 1 year, 34 μg/m³ for 1.5 years, and 40.7 μg/m³ for 2 years exposure, with the highest HRs being 2.98 (95% CI 2.24 to 3.96), 3.53 (95% CI 2.62 to 4.74), and 2.21 (95% CI 1.74 to 2.81), respectively. In comparison, the maximum risks in Delhi were 8.98 (95% CI 5.31 to 15.17), 3.59 (95% CI 2.42 to 5.33,) and 10.79 (95% CI 6.12 to 19.00) at 119 μg/m³ for 1 year, 116.5 μg/m³ for 1.5 years, and 112 μg/m³ for 2 years of exposure.

DISCUSSION
Using data from a large prospective population-based cohort study in India, we observed associations between exposure to ambient PM2.5 and FPG and HbA1c as well as increased risk of developing T2DM across a wide spectrum of exposure. In addition, we also observed non-linear exposure-response association in the two cities.

To our knowledge, most studies from low pollution settings, such as the USA or Europe, have observed a positive association between ambient PM2.5 and incident T2DM. A meta-analysis of five prospective cohort studies from Denmark, Canada, and the USA reported a pooled relative risk of 1.10 (95% CI 1.02 to 1.18) for developing T2DM per 10 μg/m³ change in average PM2.5 exposure. A recent cohort study in Taiwan reported a 1.28 times (95% CI 1.18 to 1.39) risk of incident diabetes in the second quartile of exposure (mean PM2.5: 26.5 μg/m³,
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IQR: 21.7–28.0 μg/m³), which is close to our findings in the combined study population in both cities at a lower concentration. Recently, Liang et al reported an HR of 1.15 (95% CI 1.06 to 1.25) per 10 μg/m³ increase in PM2.5 for incident T2DM in China. In comparison, evidence from India linking air pollution with glycemic markers and diabetes has been limited and the findings have been inconclusive.

We observed increases in FPG and HbA1c levels in both cities against short-term to medium-term exposure to PM2.5. At a population level, reducing the monthly average exposures to the first quartile from the third quartile of exposure in each city would potentially reduce the prevalence of diabetes by 1%–2%. We observed increased risk for developing diabetes in both cities against long-term exposure to PM2.5, although the largest effects were observed against 2 years and 1.5 years in Chennai and Delhi, respectively. Using the pooled estimate for the risk of developing T2DM against changes in annual exposure, we obtained the percentage of T2DM attributable to PM2.5 as 56% for a 40 μg/m³ change (change from annual average levels in the study population in 2016 to the national air quality standards of 40 μg/m³) in annual PM2.5 levels. Similar magnitudes of increase might be more hazardous in moderately polluted regions compared with extremely polluted regions, which is partly supported by our analysis of non-linear dose response. From our pooled analyses, we observed a 29% increased risk of developing T2DM, against a 10 μg/m³ change in long-term exposure to PM2.5, which is higher than the reported risks from developed countries and indicates the relevance of reducing PM2.5 exposures across the country to reduce the burden of diabetes and related diseases in India.

For non-linear exposure-response we observed an initial increase in risk and subsequent decrease of risk depending on exposure durations. A longitudinal cohort study from Taiwan reported non-linear exposure-response across deciles of exposure with maximum risk at the fifth decile of exposure and subsequent decrease of risks. Further, in a study involving US veterans, evidence of non-linear increase in risk of T2DM was reported with PM2.5 above 2.4 μg/m³, and a moderate increase at concentrations above 10 μg/m³. The participants in the current study had higher exposures than reported exposures in the existing studies. Further, the maximum annual exposure in Chennai was 27 μg/m³ lower than the minimum exposure in Delhi. Thus, it may be hypothesized that the risk of developing T2DM in high-exposure scenarios increases steeply across exposures experienced in Chennai and Delhi, while the additional risk is small with increasing long-term exposure. Given the difference in exposure ranges, future studies need to be conducted with a larger number of participants exposed to the complete range of exposures.

There have been several animal and human studies on the mechanistic action of PM2.5 on cardiometabolic health. One of the hypothesized pathways of association between ambient air pollution and diabetes is through chronic inflammation and oxidative stress leading to lipid deposition, insulin resistance, and endothelial dysfunction. PM2.5-associated decrease in endothelial function was higher in patients with high HbA1c, and low adiponectin and myeloperoxidase level. Experimental evidence also indicated that exposure to PM2.5 in conjunction with a high fat diet led to a proinflammatory insulin-resistant state, decreased tyrosine phosphorylation of insulin receptor substrate (IRS-1) in the liver pathway, and an increase in HOMA-IR and postprandial glucose. Other reported mechanisms linking PM2.5 with T2DM include increased adipose tissue macrophages and innate immune cells in visceral adipose tissue, increase in intracapsular brown adipose tissue (BAT), oxidative stress within BAT and downregulation of pathways that modulate insulin sensitivity in adipose tissues, which are all markers of T2DM pathogenesis.

Apart from the inflammatory pathways, PM2.5 may affect insulin resistance by triggering imbalance in the autonomic nervous system, which is also a pathway towards future cardiovascular diseases. Experimental evidence also links pathways involving toll-like receptors and nucleotide-binding oligomerization domain-like receptors with obesity and T2DM, which are expressed in response to PM2.5 in alveolar macrophage and bronchial epithelial cells. Further, components of particulate matter differ by location depending on sources of PM2.5, and existing studies linking sulphates and black carbon with decreased flow-mediated vascular reactivity could explain spatial differences in the PM2.5-linked associations with T2DM. Our study indicated effect-modifying roles of hypertension and markers of obesity in increasing the risk of developing T2DM and that of inflammatory markers such as hsCRP on glycemic markers in moderately polluted Chennai, which could involve a multiple of these mechanisms. However, a more detailed study of mechanistic pathways with longitudinal data on inflammatory markers is necessary to confirm these findings in India.

Limitations
A few limitations of our study are as follows. First, our results are based on a cohort located in two urban environments in India, which limits the generalizability of the results across the country. Specifically, the rural population in India is exposed to different levels of ambient as well as indoor pollutants along with varying socioeconomic status and dietary practices, which were beyond the scope of this study. Further, lack of quantified indoor PM2.5, which also exists in urban environments, is a limitation in our study. Second, we lack detailed exposure assessments for other pollutants such as nitrogen dioxide (NO₂), which might also play a role in impaired glucose metabolism. However, we have incorporated proximity to roads to account for traffic-related emissions in our health association models. Further, although the exposure model used variables from multiple domains in a
predictive model, it lacked chemical transport model outputs for the region. Additionally, the varying composition of PM$_{2.5}$ in the two cities and intricacy variability due to differences in sources of emissions may also impact the associations. Third, we lacked repeated measurements of inflammatory markers and insulin across the cohort which could provide insights into the mechanistic pathways by which PM$_{2.5}$ affects glycemic markers and incidence of diabetes.

Strengths and conclusions

To the best of our knowledge, this is among the few studies from India that has linked high-resolution ambient PM$_{2.5}$ exposure with measured glycemic markers and incident T2DM in a prospective cohort. In terms of exposure assessment, we used an ensemble averaging based model that provides high spatial as well as temporal resolution and accuracy addressing a major research gap. This is an improvement towards obtaining robust evidence in air pollution epidemiology studies based in India with high PM$_{2.5}$ levels. The longitudinal nature of the study along with the 7 years of follow-up suggests that the findings reported here are not due to intermittent episodes of high pollution levels thereby improving on findings from cross-sectional studies.

In summary, our results suggest a link between long-term exposure to ambient PM$_{2.5}$ and T2DM, which may have potential public health significance as well as policy implications for India, a country with high levels of ambient pollution as well as high burden of cardiovascular and cardiometabolic diseases.

Acknowledgements The authors thank the wider GEOHealth Hub team and CARRS team from Center for Chronic Disease Control, Public Health Foundation of India, Harvard TH Chan School of Public Health and Rollins School of Public Health, Emory University for their inputs in carrying out this work. The authors also thank Prof Kalpana Balakrishnan from Sri Ramachandra University, Chennai for providing the ground monitoring data for PM$_{10}$ collected as part of the TAPHE Study. The authors also thank all individuals in the cohort for advancement of science through their wholehearted participation.

Contributors SM, DP, KMV and JDS formulated the research question and analyses plan. SJ conducted the literature search, helped in creating the DAG and the tables. SM and JDS carried out the statistical analyses. DP, KMV, NT, VM and DK were involved in conceptualizing and setting up the CARRS cohort, leading the science, and managing the data. KMW and DP contributed to interpreting the analysis and to reviewing and editing several versions of the manuscript. DP and JDS were involved in setting up the GEOHealth Hub research and training grant. SM and JDS were involved in implementing the exposure assessment used in this study. All authors were involved in writing and reviewing the manuscript. DP is responsible for the overall content of this paper as the guarantor.

Funding Research reported in this article was partly supported by the Fogarty International Center of the National Institutes of Health, National Institute of Environmental Health Sciences and National Cancer Institute, under the GEOHealth HUB research grant (Award Number U01 TW010097). The CARRS cohort has been funded in part with Federal funds from the USA, the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Department of Health and Human Services, under contract no. HHSN269200900002C, and the United-Health Group, Minneapolis, Minnesota, USA.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. For the CARRS Project, ethical approval was provided by the Institutional Review Boards (IRBs) of Public Health Foundation of India, New Delhi (IRB00006658), All India Institute of Medical Sciences (IECN-P-17/07.09.09), Madras Diabetes Research Foundation, Chennai, (MDRF/EC/ER/2009/10), Agna Khan University (1468-CHS-ERC-2010) and Emory University, Atlanta (IRB00044159). For the GEOHealth Hub project, ethics approval was obtained from Centre for Chronic Disease Control (CCDC-IEC_10_2017), All India Institute of Medical Sciences (IECN-P-401/09.10.2015) and the Health Ministry Screening Committee of India (HMSC:5/8/4-17/Env/Indo-foreign/15-NCD-1). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data used in the analyses for this study, including exposure, de-identified participant information and covariates, can be provided to others on a case-to-case basis. Investigators need to request access from the principal investigators of the CARRS cohort (https://www.carrsprogram.org/overview) along with a short proposal detailing the purpose of the request. An internal review will be conducted before data are provided.

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