Investigating the role of gut microbiome in the association between ambient air pollution and type-2 diabetes mellitus: a causal inference approach using review of evidence to date

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Pollutants in ambient air have been linked with type-2 diabetes mellitus (T2DM) in low as well as high pollution scenarios. Mechanisms of action include disruption of endothelial function, imbalance in the autonomic nervous system and direct translocation. Although reductions in exposure to ambient air pollution (AP) could translate to meaningful clinical and public health benefits, policy changes targeting AP are usually at the population level, multisectoral, and time consuming. The human gut microbiome (GM) is an ecosystem within individuals which has been linked with health in both beneficial and detrimental ways. During the last decade, mechanistic and epidemiological research on GM suggests altered microbial diversity and differential composition influencing T2DM through inflammation, metabolites, and microbial functions. This offers a scope to design individual level interventions to target AP related T2DM through GM. In this paper, we presented a combination approach of evidence synthesis by literature review and application of causal inference framework to investigate the role of GM in the association of AP and T2DM, to help design epidemiological studies and direct data analysis. We formulated Directed Acyclic Graphs with methodological considerations for mediatory, interacting, or effect modification role of GM in the association of AP and T2DM. Additionally, we considered the emerging links between gut and oral microbiome, the different T2DM disease patterns in South Asia, and unique co-exposures in these settings (for example, indoor air pollution).

KEYWORDS

gut microbiome, air pollution, chronic diseases, type-2 diabetes, directed acyclic graph

1 Introduction

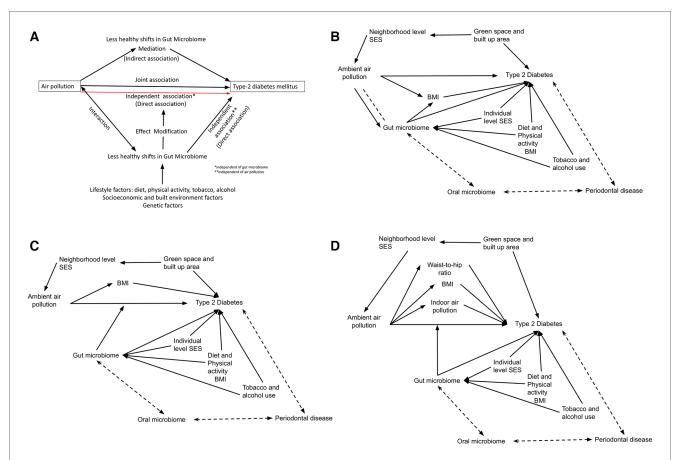There are 437 million adults (95% uncertainty 402–477 million) living with type-2 diabetes mellitus (T2DM) globally in 2019 (1) which is projected to rise to 643 million by 2030 and 783 million by 2045 (1, 2). Air pollutants, specifically fine particulate matter (PM) from anthropogenic activities have been shown to be a major risk factor for cardiometabolic diseases including T2DM. While reductions in

exposure AP could translate to meaningful clinical and public health outcomes, policy changes targeting AP are usually at the population level and multi-sectoral and thus time consuming. Host-associated microbial diversity, composition, and functions, supported by strong mechanistic evidence from animal models (3, 4) have been associated with beneficial as well as harmful health outcomes in human beings (5). Specifically, human gut microbiome (GM) has been emerging as a novel factor in the pathophysiology of several chronic disease outcomes (6, 7). Given the links between AP influencing unhealthy shifts in the GM and the associations of less healthy shifts in GM with T2DM, GM could be visualized as a mediator, an interacting factor, and/or as an effect modifier in a causal framework linking AP and T2DM (Figure 1A). This evidence, although largely from low AP exposure scenarios from developed country settings, gives rise to the potential of minimizing the harmful effects of AP on T2DM at an individual level by modulating GM or factors that influence it. Furthermore, the interactions between the gut and oral microbiome- the Gut-Oral axis- is gaining evidence (8). The Gut-Oral axis is particularly relevant in T2DM where periodontal disease, a chronic inflammatory

disease of the soft tissues and bone of the oral cavity driven by aberrant host response to oral microbial pathogens, is classified as the sixth major complication of T2DM with established bidirectional associations (9).

High levels of ambient air pollution (AP) and a high burden of type-2 diabetes mellitus (T2DM) are two major public health hazards faced by several low- and middle-income countries (LMICs). Asia, with the most populous countries of the world (i.e., China and India), is at the epicenter of T2DM burden accounting for 40% of total global burden. Specifically in India, the prevalence of T2DM increased from 26·0 million in 1990 to 81·0 million in 2019 with an annual rate of change at 2.9% during this period (vs. 1.9% globally and 1.5% in China) (2). The GBD 2019 study reports 14.3% deaths due to T2DM and 15% of disability-adjusted life-years (DALYs) being attributable to AP in Southeast Asia (vs. 13.4% of all deaths and 13.6% of DALYs globally) (10).

The causal links between AP, GM and T2DM are complicated by multiple lifestyle and environmental factors that regulate GM that may confound associations with T2DM, a complex multifactorial disease. This further limit the ability to investigate

FIGURE 1
(A) Conceptual diagram for the role of gut microbiome in the associations between ambient air pollution and type-2 diabetes mellitus. Directed acyclic graphs showing the conceptual framework linking ambient air pollution (AP) with Type 2 diabetes (T2D) under three scenarios: (B) Mediation through gut microbiome (GM), (C) effect modification by GM, (D) South Asian scenario with co-exposures, with effect modification by GM. Biological interactions between AP and GM is represented by a dashed line in 1B. Other major confounders for each association are also shown for each main association, including neighborhood and individual level socioeconomic status (SES), green space, diet, physical activity, tobacco and alcohol use. Additionally, the gut-oral-periodontal disease pathway is shown as a bidirectional association.

the precise less healthy shifts in GM that may be causally associated with T2DM (11). The aim of this paper was to address whether GM was a potential modifiable factor in the causal association of AP and T2DM. We synthesized the evidence to date by summarizing systematic reviews and meta-analysis in the selected topic published until December 2023. We quantified the summary findings as appropriate and identified the research gaps. We then applied a causal inference framework, to help design future epidemiological studies and direct data analysis, to investigate the role of GM in the association of AP and T2DM. We utilized the combination approach of "Evidence Synthesis for Constructing Directed Acyclic Graphs" framework, proposed by Ferguson et al., in 2020 (12).

2 Methods

2.1 Evidence synthesis

First, using PubMed searches and limiting the keywords to the exposure and outcome we summarized the published systematic reviews and meta-analysis for the association between AP and T2DM stratified by high and low pollution scenarios. We also summarized systematic reviews for the association between AP and GM, and GM and T2DM. We extracted information on exposures, outcome, summary estimates of associations, and corresponding 95% confidence interval (CI), and heterogeneity measure, and covariates or confounders assessments. Second, we summarized all published evidence (reviews and original studies) investigating the mediating role of GM in the association between AP and T2DM with information on exposures, outcome, magnitude of associations, and covariates or confounders assessments. Further, for meta-analytical reviews on AP and T2DM, the effect estimates and CIs were converted to percentage excess risk of odds ratio (OR)/relative risk (RR)/ hazard ratio (HR); % excess risk = $(OR/HR/RR - 1) \times 100$ per $10 \, \mu g/m^3$ increase of AP (13). For meta-analytical reviews on GM and T2DM, we summarized the meta-analytic mean difference of the outcome. For all systematic reviews, we summarized the statistically significant associations. Overall, we classified the strength of the evidence as sufficiently conclusive (consistent positive association in ≥50% of meta-analysis), limited positive (consistent positive association <50% of meta-analysis or dose-response evidence in systematic review), limited suggestive (consistent positive association in original studies) or no association.

2.2 Constructing directed acyclic graphs

Directed acyclic graphs (DAGs), a causal inference method, are diagrammatic representation of causal relationships between exposure, outcome, and co-factors based on evidence in the existing literature. DAGs help to distinguish the types of factors such as mediators (factors associated with both exposure and outcome in the causal pathway), confounders (factors associated

with both exposure and outcome but not in the causal pathway), and colliders (factors caused by exposure and outcome independently), and identify an appropriate adjustment set for confounders, to direct data analysis (14–16). We formulated DAGs to design studies to investigate the role of GM in the association of AP and T2DM. We mapped exposure (AP) and outcome (T2DM) with all reported covariates in the literature; translated the information after considering temporality, plausibility of associations, and the strength of the supporting evidence and integrated the evidence to synthesise DAGs. The methodological considerations for the role of GM in the association of AP and T2DM included mediation (i.e., GM is the intermediate factor in the causal pathway between AP and T2DM) or effect modification (i.e., GM in a subgroup influences the association between AP and T2DM) or interaction (i.e., joint association of GM and AP with T2DM) (15, 16). Additionally, we considered the emerging links between gut and oral microbiome, the different T2DM disease patterns in South Asia, and unique co-exposures in these settings (for example, indoor air pollution).

3 Results

3.1 Evidence synthesis

3.1.1 Ambient air pollution and type-2 diabetes mellitus

A PubMed search using the keywords "air pollution" AND "diabetes mellitus" in combination with filter for review and manual searches of the reference list showed a result of 10 meta-analysis (2014–2023), 2 systematic reviews (2014–2018), and 10 reviews (2018–2021). Published systematic reviews (n = 2) (17, 18) and meta-analysis (n = 9; full-text was unavailable for one) (19–27) examining the associations between AP and T2DM are summarized in Supplementary Table S1 by low- and high-pollution scenarios. Exposure to various air pollutants, including particulate matter [$PM_{2.5}$, PM_{10}, elemental carbon (EC), Black Carbon (BC)], and gaseous pollutants such as O_3 (ozone), CO (carbon monoxide), SO_2 (sulphur dioxide), NO/NO_2 (nitrogen oxides), and traffic-related pollutants, have been investigated with incident or prevalent T2DM. Evidence linking AP with T2DM mostly arises from developed countries with low levels of AP (for example, with annual mean of $PM_{2.5}$: $7.7–28.5 \, \mu g/m^3$ vs. $33.7–147.0 \, \mu g/m^3$ in developing countries). Percent excess risk for long-term AP exposures on incident T2DM ranged between 10.0 (02.0, 18.0) and 39.0 (14.0, 68.0) for $PM_{2.5}$; 11.0 (00.0, 22.0) and 34.0 (22.0, 47.0) for PM_{10}; and 11.0 (07.0–16.0) and 13.0 (04.0, 22.0) for nitrogen oxides. The evidence was sufficiently conclusive for temporal associations of $PM_{2.5}$ (n = 7 meta-analysis) but limited for PM_{10} and nitrogen oxides (n = 2 meta-analysis). While the associations weakened for prevalent T2DM, it became insignificant for T2DM mortality. The evidence for long-term exposure for other pollutants were inconclusive. Short-term exposures to $PM_{2.5}$ was associated with 6%–49% increase in diabetes related mortality and 1%–3% increase in hospitalizations

per 10 µg/m^3 (22, 27). A detailed set of confounders and effect modifiers reported in these studies are summarized in Supplementary Table S1.

The plausible mechanisms underlying the association between AP and T2DM involve chronic inflammation, and insulin resistance, but also oxidative stress, alterations in insulin signaling, dysregulated glucose metabolism, and beta (β)-cell function (25–27). The exposure-response function of AP with chronic diseases indicates a steep increase in risk from 0 to 50 µg/m^3 and a subsequent plateauing or non-linear associations (28). Although the number of studies at higher levels were much fewer than those at lower levels, systematic evidence suggests similar magnitude of associations between low- and high-pollution regions (26).

3.1.2 Indoor air pollution and type-2 diabetes mellitus

Long-term exposure to indoor air pollution (IAP) has similar effects as ambient AP, wherein a 6.5% of T2DM deaths and 5.9% of DALYs were attributed to household PM$_{2.5}$ (10). Nevertheless, while the age-standardized rate of DALYs due to ambient air pollution increased by over 85%, it decreased by 37.9% for IAP during this period. This is found to affect the elderly, women and people of low social status disproportionately (29, 30). For example, long-duration cooking with solid fuel was associated with decreased insulin level among women, which was more pronounced among women of low monthly income (30). According to the Health Effect Institute, long-term exposure to IAP through household burning of solid fuels for cooking contributed to 2.31 million deaths (4% of total global deaths) and 91.5 million DALYs in 2019 (31). Nearly 95% of this burden is from South Asia, Sub-saharan Africa, Southeast Asia, East Asia and Oceania Asia (31).The prevalence of solid fuel use for cooking in these regions is as high as >30%–95%, although there is considerable decrease over time (31).

3.1.3 Gut microbiome and type-2 diabetes mellitus

A PubMed search using the keywords "gut microbiome" OR "gastrointestinal microbiome" AND "diabetes mellitus" in combination with filter for review and manual searches of the reference list revealed 75 review papers (2011–2023) and eight systematic reviews and meta-analysis (2018–2023). Published systematic reviews (N = 4; full-text unavailable for one) (32–35) and meta-analysis (N = 3) (36–38) examining the associations between GM and T2DM are summarized in Supplementary Table S2. Limited but high-quality randomized control trials (RCTs; n = 2 meta-analysis) in diabetic patients showed dietary intervention with high-fibre diet and probiotics *Lactobacillus sp., Bifidobacterium sp.* and *Actinoplanes* lowered glycated hemoglobin levels (HbA1c) and improved insulin sensitivity. Moderate quality RCTs (n = 2 meta-analysis) also showed that dietary intervention with low-fat, low-carbohydrate, and high-fibre diets lowered fasting blood glucose and HbA1c levels by increasing diversity and abundances of beneficial bacteria such as *Roseburia, Ruminococcus, Lactobacillus, Bacteroides, Lachnospira, Fusobacterium prausnitzii,* Eubacterium *rectale, Akkermansia*

muciniphilia. Further, limited but suggestive evidence from mechanistic studies in animals indicated probiotic supplementation with *Bacteroides* sp. reduced insulin resistance (n = 1 meta-analysis). However, the findings from observational studies yielded mixed results with conflicting reports on specific bacterial species (n = 2 meta-analysis). The set of covariates assessments reported in these studies are summarized in Supplementary Table S2. The plausible mechanisms include modulating inflammation, interactions with dietary components, influencing gut permeability, glucose and lipid metabolism, insulin sensitivity and thus the overall energy homeostasis (32, 35). Standard definitions of microbial features described in this paper are outlined in Supplementary Figure S1.

3.1.4 Gut-oral axis in T2DM

The bidirectional association between oral diseases, specifically the periodontal disease, and T2DM is well established and periodontal disease is classified as a major sixth complication of T2DM (9, 39, 40) Systematic reviews and meta-analysis of epidemiological studies strongly support the bi-directional relationship of periodontal disease and T2DM, leading to the formulation of European Federation of Periodontology/American Academy of Periodontology (EFP/AAP, 2013) and the EFP and the International Diabetes Federation consensus reports (2018). The consensus statements include (1) poor glycemic control is associated with poorer periodontal outcomes. (2) periodontal disease is associated with hyperglycemia and increased insulin resistance in diabetes, increased risk for incident diabetes and diabetic complications such as retinopathy, neuropathy, and cardiovascular complications (OR: 1.2–6.6) and mortality (HR: 3.5–4.5). Periodontal therapy improves serum HbA1C levels (0.27%–0.48% after 3 months) (39, 40). The suggested mechanistic pathways for these associations include shared disease progression through chronic inflammation, acetylated glycated end-products, and oral pathogens (9). Periodontal pathogens such as T*anerella forsythia, Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans* are few well studied oral microbiome (41). The concept of enteral and systemic entry of oral pathogens into the gastrointestinal tract and the interaction between oral and gut microbiome has plausible mechanistic evidence (8). The gut-oral axis contributing to the disease progression through shared pathways of chronic inflammation and dysregulated metabolic factors is rapidly emerging and strongly suggestive for T2DM (8).

3.1.5 Air pollution and gut microbiome

A PubMed search using the keywords "air pollution" AND "gut microbiome" OR "gastrointestinal microbiome" in combination with filter for review revealed 1 systematic review (42) including human studies (N = 12) and animal studies (N = 36) and five review papers (2017–2020). The findings of the systematic review are shown in Good quality human studies across the life-course strongly indicated lower gut diversity and shifts in GM composition with dose-response function for PM exposure (average exposure in studies ranged from 8.4 µg/m^3–102 µg/m^3) (42). Prenatal and post-natal black carbon exposure explained

6%–17% of bacterial diversity among healthy children. Nitrogen oxides and ozone exposures explained 4%–11% variation of GM composition. These have also been linked to lower gut microbial diversity, gene functional pathways related to insulin release (43). AP exposure increased *Porphyromonadaceae*, *Mucisprillum*, and *Campylobacter*, and decreased *Akkermansia muciniphila*. While animal studies supported the findings in general, the reported bacterial taxa were different. Plausible biological mechanisms include increased gut damage, inflammation, oxidative stress, and gut permeability. The set of covariates assessments reported in these studies are summarized in Supplementary Table S3.

3.1.6 Air pollution, gut microbiome, and type-2 diabetes mellitus

Studies examining the role of GM in the associations between AP and T2DM are very limited to date (Supplementary Table S4). A PubMed search using the keywords ("air pollution"[MeSH Terms] OR ("air"[All Fields] AND "pollution"[All Fields]) OR "air pollution"[All Fields]) AND ("gastrointestinal microbiome"[MeSH Terms] OR ("gastrointestinal"[All Fields] AND "microbiome"[All Fields]) OR "gastrointestinal microbiome"[All Fields] OR ("gut"[All Fields] AND "microbiome"[All Fields]) OR "gut microbiome"[All Fields]) AND ("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields]) revealed a review of five animal studies (2013–2018) and three human studies (2015–2018) (44) and an additional two original research articles (45, 46). Limited evidence from prospective and population based studies from high pollution regions suggest a 4.3–37.8% of associations between PM exposure and impaired glucose metabolism and T2DM mediated through GM either directly or via lipid metabolism. Specifically, the abundance of *Oribacterium* and *Shuttleworthia*, reduction in *Firmicutes*, *Proteobacteria*, and *Verrucomicrobia* might explain the correlations between AP and T2DM (45, 46). Mechanistic evidence supports inflammatory pathway for the role of GM in the associations between AP and T2DM. The set of covariates assessments reported in these studies are summarized in Supplementary Table S4.

3.1.7 Pathophysiology of diabetes in South Asians

South Asian populations show certain distinct T2DM disease patterns compared to the Western populations and possibly to other Asian populations in the East and South-East Asia (47–52). For instance, systematic evidence reveals that South Asians exhibit a high prevalence of early-onset T2DM (≤55 years of age) and a high prevalence of T2DM at a lower BMI. They also have also have a higher risk for microvascular complications, possibly associated with earlier mortality compared to Western populations (47, 50). Different body fat distribution and lipid metabolism coupled with dysregulated metabolic pathways (i.e., poor insulin secretion and beta-cell dysfunction) are suggested to explain, at least in part, these differences in disease patterns in South Asians (47, 51). South Asians tend to have a low lean mass, visceral (abdominal) and ectopic (in skeletal muscles and liver) adiposity

leading to elevated triglycerides and possibly a pro-inflammatory high-density lipoprotein cholesterol (47, 53). Certain lifestyle factors (diet rich in saturated fat and low in omega-3 fatty acid with sedentary activity), genetic susceptibility (e.g., family history, specific genetic variants with high heritability) and evolutionary biology (historical undernourishment, low lean mass, visceral and ectopic adiposity) are suggested to influence this pattern among South Asians (47, 50, 51).

3.2 Directed acyclic graph (DAG) approach

Table 1 summarizes the strength of evidence for the causal associations between AP-T2DM, GM-T2DM, AP-GM, and AP-GM-T2DM, with the reported set of confounders and effect modifiers. Interacting factors in any of these associations are little explored. (i) Considering causal associations of AP with T2DM and GM with T2DM wherein both AP and GM can be considered as independent exposures (i.e., independent of each other's influence) against T2DM as the outcome—GM could be an interacting factor in the association between AP and T2DM (i.e., joint effect of the causal effects of AP and GM on T2DM that could be more than the sum or product of their individual effects 14–16) (Figure 1B) (ii) Considering causal associations of AP with T2DM and GM with T2DM and moderate causal associations of AP with GM—GM could be a mediator in the association between AP and T2DM (i.e., AP exposure affecting GM in an intermediate pathway resulting in T2DM outcome 14–16) (Figure 1B). (iii) Epidemiological evidence indicates inequities in the health effect of AP, where individuals belonging to lower socioeconomic groups or vulnerable communities bear a larger impact from AP (54, 55). These same population subgroups are also likely to have dietary patterns or other lifestyle practices that promote less healthy GM shifts, higher adiposity and higher burden of cardiometabolic diseases (56). Thus, this could be hypothesized as an effect modification pathway wherein different levels of shifts in GM can influence variations in the causal associations of AP with T2DM 14–16) (Figure 1C). Further, in case of highly polluted LMIC settings, one needs to account for co-exposures such as indoor air pollution and pathophysiological characteristics such as low body mass index, but high visceral fat, related reduced beta cell dysfunction (Figure 1D). Further, indoor air pollution in LMICs is often affected by ambient levels due to open windows and lack of insulation, which creates a potential mediation pathway (ambient to indoor to outcome). Hence if the main exposure of the interest is ambient AP, indoor AP might be considered as a mediator. In contrast if indoor AP is the main exposure of interest, ambient AP needs to be treated as a confounder.

3.2.1 Quantitative study designs

Among commonly used study designs, a cross-sectional or a longitudinal design can be used to study these associations, depending on whether T2DM was assessed once or multiple times over time. In addition, AP could be treated as a time-varying exposure and GM could be assessed at one or more time

TABLE 1 Summary of evidence synthesis for ambient air pollution (AP), gut microbiome (GM) and type-2 diabetes mellitus (T2DM).

Causal associations	Strength of evidence	Confounders	Effect modifiers
AP-T2DM	Sufficiently conclusive: PM$_{2.5}$ Limited positive: PM$_{10}$ Limited positive: nitrogen oxides Plausible mechanisms	Demographics: age, sex, ethnicity, marital status, time-varying age Socioeconomic status (SES): education, occupation, income, members & income of household, residence location, neighborhood SES, population density, health insurance, contextual factors Lifestyle factors: smoking, alcohol, physical activity, diet, BMI/waist-hip ratio, time-varying lifestyle factors, passive tobacco Comorbidities: cardiovascular disease, hypertension, hyperlipidaemia, chronic respiratory conditions, asthma, time-varying hypertension Environmental & occupational exposures: latitude, seasons, weather, calendar year, workplace & indoor exposures, noise, annual mean PM2.5, location-specific long-term trends, co-pollutants Others: familial diabetes, inflammatory markers such as hs-CRP	Household income, chronic respiratory conditions, tobacco, physical activity, age, body fat, individual & neighborhood SES, waist-to-hip ratio, subclinical inflammation, <50/>65 years of age
GM-T2DM	Limited positive Plausible mechanisms	BMI, waist-hip ratio, inflammatory markers, lipids, age, gender, physical activity, diet, amino acids, miRNA, blood pressure, liver & kidney function tests, fatty acids, bile acids, inflammatory markers	None reported
AP-GM	Limited positive Dose-response across life course Plausible mechanisms	Sex, age, weight/body mass index, socio-economic status, diet, antibiotic use.	None reported
AP-GM-T2DM	Limited suggestive for mediation None for effect modification None for interaction Plausible mechanisms	Age, sex, race, education occupation, income, marital status, cooking fuel, smoking passive smoking, alcohol, BMI, weight change, blood lipid, blood pressure, physical activity, familial diabetes diet, gaseous pollutants, temperature, relative humidity	None reported

points. Within a cross-sectional design, to evaluate the potential role of GM in the epidemiological studies for the association of AP with T2DM, we would recommend first testing for mediation through GM if any, while adjusting for an appropriate set of neighborhood level and individual factors. Mediation analysis refers to a statistical analysis that assesses the amount of association between the exposure and outcome that is mediated through a mediator (57). We recommend using a causal mediation analysis with a counterfactual approach over a traditional mediation analysis (58, 59). This approach provides a segregation of the total effect of exposure (joint association) on outcome into direct (independent association) and indirect effects (mediated association). In case of mediation over time, recent approaches using two generalized mixed effect models for the mediator and the outcome can be used (60). If the joint or mediated associations are small in magnitude as well as statistically insignificant, we would recommend testing for effect modification, by stratifying across quartiles of microbial diversity and testing for significant interaction between AP and microbial diversity. For ease of exposition, we are considering "GM diversity" as a representative variable of GM composition as evidence on specific shifts in the composition is sparse. It is to be noted here, that for all the analyses described above, other confounders need to be appropriately controlled to avoid bias in estimations.

Propensity score-based methods can be utilized to account for measured confounders within each of the above approaches (61). If we consider AP or GM as the exposure, these can be modeled against measured confounders to construct scores that indicate the probability of being exposed given the confounders. Since AP (for e.g., annual average PM$_{2.5}$) and GM (for e.g., microbial alpha diversity) are inherently continuous variables, generalized propensity scores may be constructed and participants can either be a) weighted using an inverse of the scores or b) be matched based on deciles of these scores (62).

4 Conclusion

In this review, we have discussed the potential role of GM in the pathways linking ambient air pollution and T2DM, and which could lead to interventions or strategies at an individual level to reduce the risk of AP attributable T2DM. We have also discussed the causal inference framework to investigate the role of GM in the association of AP and T2DM, to help design studies and direct data analysis. We observed "sufficient evidence" linking AP to T2DM (10-39% excess risk for different pollutants for T2DM incidence), and 'limited yet positive evidence' linking AP with GM (4-17% of GM variation explained by different pollutants with dose-response). Further, although the evidence linking GM with T2DM is less quantified, it is supported through experimental studies. However, the evidence linking AP, GM and T2DM is at a nascent stage with five studies conducted with human participants and conflicting information on specific targetable GM composition influencing these associations. Studies investigating these links between AP, GM and T2DM in large cohort studies, particularly in LMICs would be of great clinical and public health significance, given the large burden of T2DM, diversity in exposure and unique pathophysiology of the population. Leveraging existing cohort studies with comprehensive repeated information on sociodemographic, lifestyle and environmental factors, to incorporate the aspect of GM would be advantageous if AP exposures are available at fine spatiotemporal resolution. Findings

from such studies could facilitate mechanistic studies to identify specific unhealthy GM shifts and to understand the progression of T2DM starting from non-diabetic to pre-diabetics to T2DM. These findings could inform potential interventions to tackle the high burden of T2DM, a significant portion of which is attributable to AP.

Author contributions

SM: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. SK: Data curation, Formal Analysis, Investigation, Software, Writing – review & editing. KS: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fenvh.2024.1339674/full#supplementary-material

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