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Effects of particulate matter exposure on the risk of type 2 diabetes: a Mendelian randomization study

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Abstract. – OBJECTIVE: The impact of particulate matter (PM) on the risk of type 2 diabetes (T2D) remains inconclusive. The purpose of this study was to assess the causal relationship between PM and T2D using Mendelian randomization (MR) analysis.

MATERIALS AND METHODS: Single nucleotide polymorphisms (SNPs) for $PM_{2.5}$, PM_{10}, and T2D were obtained from the UK Biobank and FinnGen datasets. Inverse variance weighted, MR-Egger, and weighted median were utilized to examine the causal relationship between exposure and outcome. MR-Egger intercept analysis, Cochran's Q test, and leave-one-out sensitivity analysis were used to assess horizontal pleiotropy, heterogeneity, and robustness of the results, respectively.

RESULTS: The MR analysis revealed a significant association between $PM_{2.5}$ and increased risk of T2D (OR: 1.159, 95% CI: 1.003 to 1.339, $p = 0.045$), while no significant association was found between PM_{10} and T2D risk (OR: 1.031, 95% CI: 0.788 to 1.350, $p = 0.822$). MR-Egger intercept analysis and Cochran's Q test indicated no evidence of horizontal pleiotropy or heterogeneity in these results. Sensitivity analysis demonstrated the robustness of the results.

CONCLUSIONS: This MR analysis suggests that $PM_{2.5}$, rather than PM_{10}, is associated with an increased risk of T2D. The use of air purifiers and anti-smog masks may potentially help reduce the risk of T2D. Further research is needed to elucidate the specific effects and underlying mechanisms of $PM_{2.5}$ and PM_{10} on T2D.

Key Words:
Particulate matter, Type 2 diabetes, Mendelian randomization, Single nucleotide polymorphism, Inverse variance weighted.

Abbreviations

Confidence interval (CI); Inverse variance weighted (IVW); Mendelian randomization (MR); odds ratio (OR); Particulate matter (PM); Pleiotropy Residual Sum and Outlier (PRESSO); Single nucleotide polymorphism (SNP); Type 2 diabetes (T2D).

Introduction

Particulate matter (PM) is a key indicator used to measure various natural and human activities that cause air pollution, which can remain suspended for long periods and travel long distances in the atmosphere[1]. Exposure to high concentrations of PM, especially fine PM, can lead to the accumulation of free radicals and peroxidation in the body, an imbalance of calcium regulation between cells, and inflammatory reactions, which can result in various diseases[2,3]. Currently, $PM_{2.5}$ and PM_{10} are the major types of PM that researchers pay attention to[1], and they have become a significant global public health issue[3]. According to the Global Burden of Disease Study[4] in 2015, 4.2 million deaths were attributed to $PM_{2.5}$, accounting for 7.6% of the total global deaths. Previous studies[5] have shown that exposure to PM is associated with an increased risk of respiratory system diseases, cardiovascular diseases, and cancer, and reducing exposure to PM can reduce the risk of these diseases. Therefore, exploring the effects of PM on different diseases can help researchers better understand the diseases and develop relevant prevention and treatment strategies.

Type 2 diabetes (T2D) is a chronic metabolic disease characterized by dysfunction of pancreatic beta cells and peripheral insulin resistance[6]. It was reported that approximately 462 million people worldwide had T2D in 2017, and its incidence is still on the rise[7]. The main feature of T2D is the continuous increase of blood glucose levels[8].

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As T2D progresses, patients often develop microvascular and macrovascular complications, which are the main causes of death in T2D patients[8]. Smoking, obesity, unhealthy diet, and other factors are risk factors for T2D, and paying attention to these risk factors is of great significance for the prevention and treatment of T2D[9]. Previous studies[10,11] have shown that PM may be associated with an increased risk of T2D and is a potential risk factor. Exploring the effects of $PM_{2.5}$ and PM_{10} on T2D susceptibility will help guide clinical prevention and treatment strategies.

Mendelian randomization (MR) is a method that uses genetic variations to analyze the causal effects of exposure on outcomes, which has the advantages of being less susceptible to confounding factors and reverse causality[12]. This study used MR to evaluate the effects of $PM_{2.5}$ and PM_{10} on the risk of T2D in Europeans, aiming to reveal their causal relationship in the European population.

Materials and Methods

Study Design

Mendelian randomization (MR) is based on three fundamental assumptions: association, independence, and exclusivity[13,14]. The association assumption (Assumption 1) states that single nucleotide polymorphisms (SNPs) are closely related to exposure. The independence assumption (Assumption 2) states that SNPs are independent of confounding factors. The exclusivity assumption (Assumption 3) states that SNPs only act on outcomes through exposure and not through other pathways. The MR design is shown in Figure 1.

Data Sources

The UK Biobank (www.ukbiobank.ac.uk) provided the datasets for $PM_{2.5}$ and PM_{10}, and FinnGen (www.finngen.fi/fi) provided the datasets for type 2 diabetes. Due to these datasets being sourced from public databases, no additional ethical approval was necessary for this study.

Genetic Instrumental Variables

To satisfy Assumption 1, we searched the datasets for SNPs closely associated with exposure ($p < 5\times10^{-6}$). We then searched for independent SNPs ($R^2 < 0.001$ and kb = 10,000). Furthermore, we identified SNPs strongly correlated with the exposure ($F > 10$), where $F = [R^2/(1-R^2)]\times[(N-K-1)/K]$, with R representing the cumulative explained variance, N representing the sample size of the genome-wide association study, and K representing the number of paired samples. To satisfy Assumption 2, we searched for the meanings of the SNPs in PhenoScanner (Cambridge, UK), excluding any SNPs potentially associated with

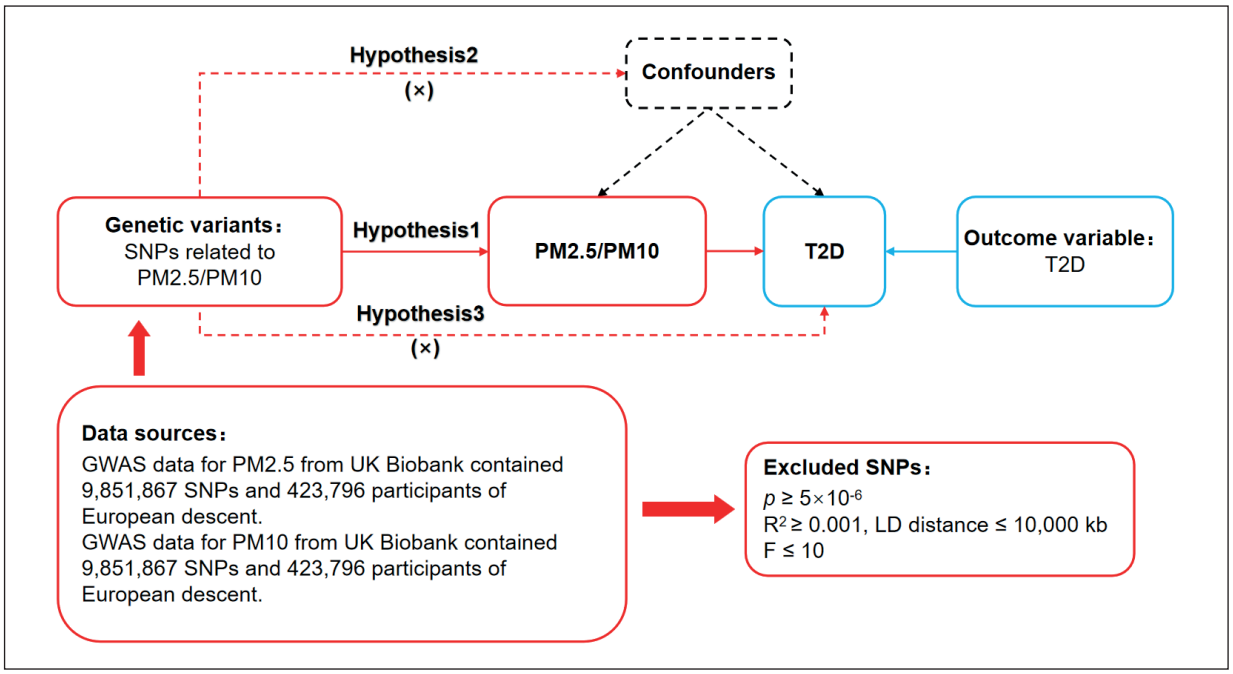

Figure 1. MR design for PM on T2D. MR, Mendelian randomization; PM, particulate matter; T2D, type 2 diabetes.

Table I. Details of the GWAS studies included in the Mendelian randomization.

Year	Trait	GWAS ID	Population	Sample size	Web source
2018	$PM_{2.5}$	ukb-b-10817	European	423,796	www.ukbiobank.ac.uk
2018	PM_{10}	ukb-b-18469	European	423,796	www.ukbiobank.ac.uk
2023	T2D	finngen_R10_T2D	European	400,197	www.finngen.fi/fi

PM, particulate matter; T2D, type 2 diabetes.

outcomes. We also excluded unmatched SNPs when adjusting the allele direction of exposure and outcome. Finally, we used the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) to eliminate SNPs with significant bias ($p < 1$).

Data Analysis

This study adhered to the STROBE-MR guidelines[15]. MR analysis was performed using the "TwoSampleMR (0.5.7)" software in R 4.3.1. The primary evaluation tool was inverse variance weighting (IVW), which allows unbiased causal analysis without multiple effects. Additionally, we employed the weighted median and MR-Egger methods as secondary evaluation tools. The weighted median method is less sensitive to error values and outliers, while MR-Egger enables effective causal analysis in the presence of multiple effects. $p < 0.05$ is defined as a statistical significance of MR analysis. We assessed horizontal pleiotropy using the MR-Egger intercept, with $p \geq 0.05$ indicating no significant horizontal pleiotropy, satisfying Assumption 3. Heterogeneity was evaluated using Cochran's Q test, with $p \geq 0.05$ indicating no significant heterogeneity. We conducted a leave-one-out sensitivity analysis to assess the robustness of the MR results, demonstrating robustness when the combined effect sizes consistently favored the same direction.

Results

GWAS Data for Exposure

The UK Biobank provided the $PM_{2.5}$ datasets (ukb-b-10817) and the PM_{10} datasets (ukb-b-18469) containing GWAS data from 423,796 Europeans. After a step-by-step screening process, we identified 58 SNPs for $PM_{2.5}$ and 30 SNPs for PM_{10} that met the basic assumptions (**Supplementary Tables I-II**). We excluded SNPs with mismatched directions and significant bias, leaving us with the SNPs listed in **Supplementary Tables III-IV**.

GWAS Data for Outcome

We obtained the T2D datasets (finngen_R10_T2D) from FinnGen, which included GWAS data for 400,197 Europeans. The sources of the exposure and outcome datasets are presented in Table I.

Two-Sample MR Analysis Results

We used MR to evaluate the causal effects between exposure ($PM_{2.5}$ and PM_{10}) and outcome (T2D), as displayed in Figure 2 (forest plot) and Figure 3 (scatter plot). The MR-Egger intercept analysis is provided in **Supplementary Table V**, and Cochran's Q test results are presented in **Supplementary Table VI** and Figure 4. Figure 5 shows the results of the leave-one-out sensitivity analysis.

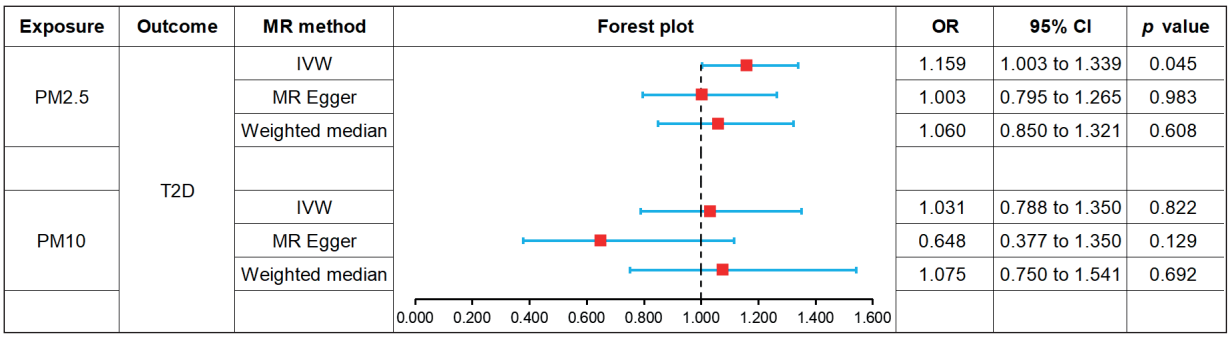

Figure 2. Forest plot of MR analysis for PM on T2D. MR, Mendelian randomization; PM, particulate matter; T2D, type 2 diabetes.

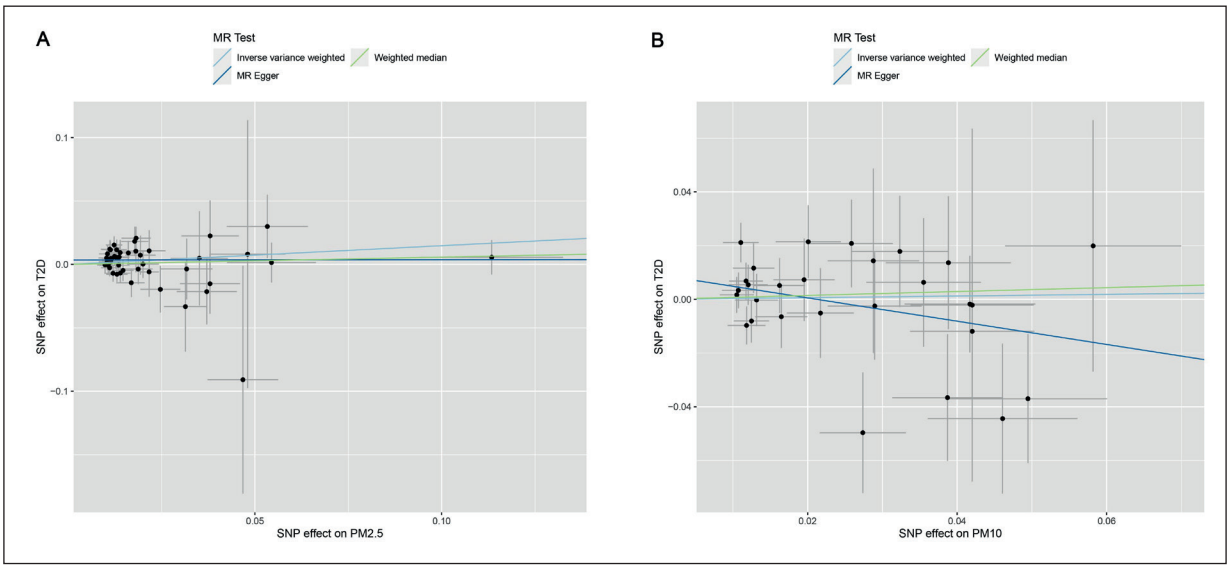

Figure 3. Scatter plot of MR analysis for PM on T2D. **A**, $PM_{2.5}$ on T2D; (**B**) PM_{10} on T2D. MR, Mendelian randomization; PM, particulate matter; T2D, type 2 diabetes.

Effect of $PM_{2.5}$ on T2D

IVW showed that $PM_{2.5}$ was associated with an increased risk of T2D (OR: 1.159, 95% CI: 1.003 to 1.339, $p = 0.045$), while MR-Egger (OR: 1.003, 95% CI: 0.795 to 1.265, $p = 0.983$) and weighted median (OR: 1.060, 95% CI: 0.850 to 1.321, $p = 0.608$) did not observe this effect. The MR-Egger intercept indicated no significant horizontal pleiotropy ($p = 0.125$), and Cochran's Q test revealed no significant heterogeneity ($p = 0.828$). The leave-one-out sensitivity analysis demonstrated the robustness of the results.

Effect of PM_{10} on T2D

IVW (OR: 1.031, 95% CI: 0.788 to 1.350, $p = 0.822$), MR-Egger (OR: 0.648, 95% CI: 0.377 to 1.350, $p = 0.129$), and weighted median (OR: 1.075, 95% CI: 0.750 to 1.541, $p = 0.692$) all showed no association between PM_{10} and the risk of T2D. The MR-Egger intercept indicated no significant horizontal pleiotropy ($p = 0.068$), and Cochran's Q test revealed no significant heterogeneity ($p = 0.184$). The leave-one-out sensitivity analysis demonstrated the robustness of the results.

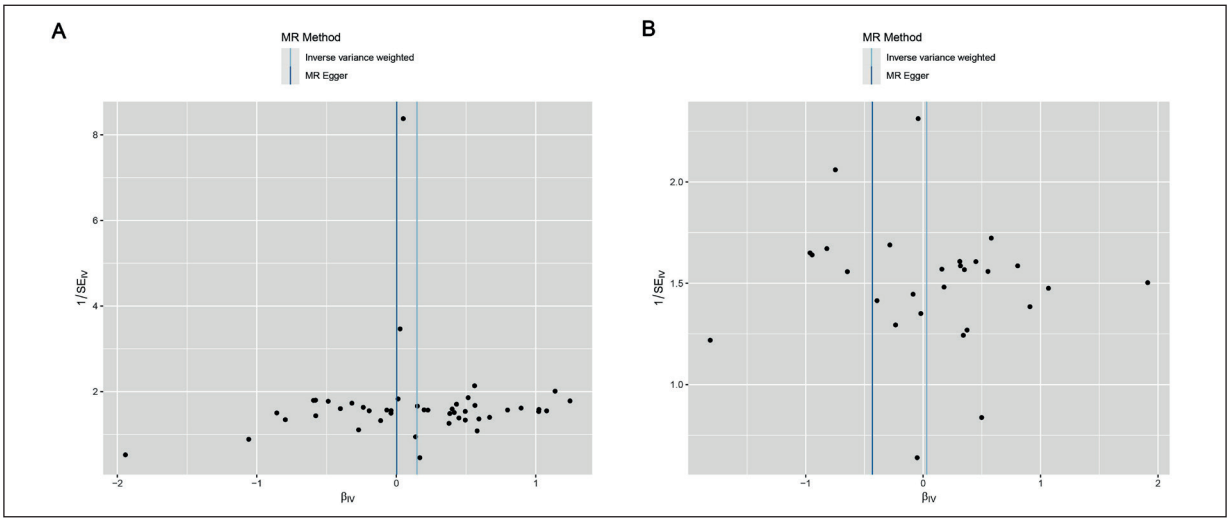

Figure 4. Funnel plot of MR analysis for PM on T2D. **A**, $PM_{2.5}$ on T2D; (**B**) PM_{10} on T2D. MR, Mendelian randomization; PM, particulate matter; T2D, type 2 diabetes.

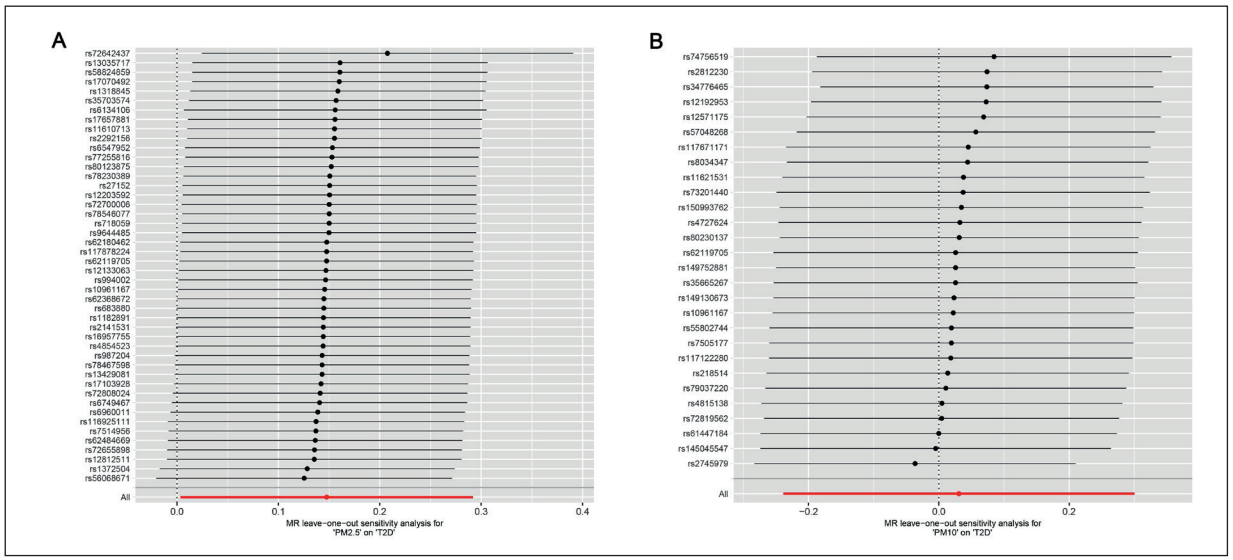

Figure 5. Leave-one-out sensitive analysis for PM on T2D. **A**, $PM_{2.5}$ on T2D; (**B**) PM_{10} on T2D. PM, particulate matter; T2D, type 2 diabetes.

Discussion

T2D is a significant threat to human health[16]. Attention and control of related risk factors are essential in the prevention and treatment of T2D[17]. Environmental particulate matter has been reported to be associated with an increased risk of T2D and may be a potential risk factor for T2D[18,19]. However, there is still controversy over whether environmental particulate matter independently increases the risk of T2D. This study will use gene-based prediction and MR analysis to examine the relationship between environmental particulate matter and the risk of T2D. In this MR analysis, we found that $PM_{2.5}$ is associated with an increased risk of T2D, while PM_{10} is not. These results show high credibility as there is no heterogeneity or level of multiple effects.

Published studies[20-24] support that $PM_{2.5}$ is a risk factor for diabetes. A study[20] involving 66,885 Japanese individuals showed that a 1 μg/m^3 increase in $PM_{2.5}$ concentration increased the risk of diabetes by 2.9% (HR: 1.029, 95% CI: 1.004-1.055). A study[21] of African American women showed that exposure to $PM_{2.5}$ at 2.9 μg/m^3 was positively correlated with the risk of diabetes after adjusting for age, questionnaire period, and urban area factors (HR: 1.13, 95% CI: 1.04-1.24). A study[22] of 4,121 elderly Americans showed that a mean one-year moving average of 3.9 μg/m^3 $PM_{2.5}$ was positively correlated with an increased incidence of diabetes (OR: 1.35, 95% CI: 1.19-1.53). A retrospective study[23] in Taiwan showed that a 10 μg/m^3 increase in $PM_{2.5}$ concentration increased the risk of diabetes by 11% (95% CI: 8.0%-13.0%). A study[24] using large-scale epidemiological survey data from southwestern China showed that $PM_{2.5}$ (OR: 1.08, 95% CI: 1.01-1.15) and its effective components black carbon (OR: 1.07, 95% CI: 1.01-1.15), ammonium (OR: 1.07, 95% CI: 1.00-1.14), nitrate (OR: 1.08, 95% CI: 1.01-1.16), organic matter (OR: 1.09, 95% CI: 1.02-1.16), and soil particles (OR: 1.09, 95% CI: 1.02-1.17) are all associated with an increased risk of diabetes. These studies[20-24] indicate that $PM_{2.5}$ is associated with a higher risk of diabetes, although they do not distinguish between types of diabetes.

Additionally, some studies[25-29] have reported the specific effects of $PM_{2.5}$ on blood glucose levels and the risk of T2D. A study conducted in India[25] showed that a difference of 10 μg/m^3 in the monthly average exposure to $PM_{2.5}$ increased FPG by 0.40 mg/dL (95% CI: 0.22-0.58) and HbA1c by 0.021% (95% CI: 0.009-0.032). A retrospective cohort study[26] involving 21,325 Thai military personnel demonstrated that the incidence rate of T2D in groups exposed to 14.64-19.17 μg/m^3, 19.18-21.64 μg/m^3, 21.65-24.37 μg/m^3, and 24.38-25.16 μg/m^3 of $PM_{2.5}$ was 21.87/1,000 person-years, 25.47/1,000 person-years, 23.07/1,000 person-years, and 18.13/1,000 person-years, respectively. A study[27] utilizing longitudinal data from the China Health and Retirement Longitudinal Study conducted between 2011 and 2018 revealed that a 10 μg/m^3 increase in $PM_{2.5}$

concentration significantly increased the risk of T2D by 26% (HR: 1.26, 95% CI: 1.22-1.31). A cross-sectional study[10] conducted in 33 communities in Liaoning Province, China, indicated that $PM_{2.5}$ exposure increased the risk of T2D by 14% (OR: 1.14, 95% CI: 1.03-1.25). A study[28] involving 147,908 Taiwanese individuals showed that participants exposed to $PM_{2.5}$ levels of 21.7-24.1 μg/m^3, 24.1-28.0 μg/m^3, and ≥ 28.0 μg/m^3 had a 28% (HR: 1.28, 95% CI: 1.18-1.39), 27% (HR: 1.27, 95% CI: 1.17-1.38), and 16% (HR: 1.16, 95% CI: 1.07-1.26) increased risk of T2D compared to those exposed to $PM_{2.5}$ < 21.7 μg/m^3. A meta-analysis[11] incorporating 11 cohort studies demonstrated that long-term exposure to $PM_{2.5}$ was associated with an additional 25% risk of T2D (RR: 1.25, 95% CI: 1.10-1.43). The Global Burden of Disease Study[29] in 2019 revealed that approximately 13.4% of T2D deaths and 13.6% of T2D disability-adjusted life years were attributed to environmental $PM_{2.5}$. This evidence suggests that $PM_{2.5}$ is associated with increased blood glucose levels and T2D incidence, which means it is a potential risk factor for T2D.

It is worth noting that several studies[30-32] have reported a positive correlation between $PM_{2.5}$ exposure concentration and the risk of T2D. A cross-sectional study in India[30] showed that individuals living in high-exposure areas had a higher prevalence of T2D compared to those living in low-exposure areas (34.8% *vs*. 19.6%). A cohort study[31] in Taiwan revealed that the risk of developing diabetes increased by 14%, 40%, and 42% for individuals exposed to $PM_{2.5}$ levels of 29.5-33.3 μg/m^3, 33.4-41.2 μg/m^3, and > 41.2 μg/m^3, respectively, compared to those exposed to $PM_{2.5}$ < 29.5 μg/m^3. A study[32] involving 124,204 Chinese individuals indicated that in the group with $PM_{2.5}$ > 50 μg/m^3, each 1 μg/m^3 increase in cumulative $PM_{2.5}$ exposure level resulted in a 17.7% increase in diabetes risk (HR: 1.177, 95% CI: 1.172-1.181). Laorattapong et al[26] also noted that compared to $PM_{2.5}$ changes in the range of -5.86 ~ -0.65, $PM_{2.5}$ changes in the range of -0.64 ~ -0.30, 0.31 ~ 1.02, and 1.03 ~ 6.06 increased the risk of T2D by 36% (95% CI: 1.11-1.65), 97% (95% CI: 1.61-2.42), and 267% (95% CI: 2.99-4.51), respectively. This evidence indicates that not only $PM_{2.5}$ exposure is associated with an increased risk of T2D, but the level of $PM_{2.5}$ exposure also contributes to additional T2D risk.

Interestingly, our MR analysis reveals that there is no association between PM_{10} and T2D risk, which differs from the reported results of existing clinical studies[10,19]. A cross-sectional study[10] in China showed a 20% increased T2D risk with PM_{10} exposure (OR: 1.20, 95% CI: 1.12-1.28). Another study[19] in Iran demonstrated a higher prevalence of T2D in the group with PM_{10} > 100 μg/m^3 compared to the group with PM_{10} concentration < 100 μg/m^3 (OR: 1.32, 95% CI: 1.03-1.69). These studies[10,19] suggest that PM_{10} may be a potential risk factor for T2D. We speculate that the differences between the MR analysis and clinical studies might be related to ethnicity, as our MR analysis focused on Europeans, while the two existing clinical studies focused on Chinese and Iranians[10,19], respectively. Considering the limited existing research and clinical evidence, the role of PM_{10} in T2D cannot be conclusively determined. Future epidemiological and genomic studies are needed to explore the causal relationship between PM_{10} and T2D.

It is undeniable that this MR analysis has some limitations. First, this MR analysis primarily reveals the impact of $PM_{2.5}$ and PM_{10} on T2D risk in Europeans, which may not be applicable to other ethnicities. Second, although this MR analysis shows no association between PM_{10} and T2D risk, there is still a lack of sufficient clinical evidence supporting this finding. Third, there may be unidentified pathways or confounding factors between exposure factors and outcome measures, which could increase the bias risk of the MR results. Given the aforementioned limitations, we look forward to future multicenter and large-scale stratified trials to further investigate the role of $PM_{2.5}$ and PM_{10} in T2D. Additionally, continued efforts in human genomic research are needed to provide more comprehensive data for MR analysis across different ethnicities.

Conclusions

This MR analysis suggests that $PM_{2.5}$, rather than PM_{10}, is associated with an increased risk of T2D. The use of air purifiers and anti-smog masks may potentially help reduce the risk of T2D. Further research is needed to elucidate the specific effects and underlying mechanisms of $PM_{2.5}$ and PM_{10} on T2D.

Data Availability

The original data presented in this study are included in the manuscript and supplementary material. For more information, contact the corresponding author.

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Ethics Approval
Due to the fact that the data for this study is sourced from publicly available databases, ethical approval is not applicable.

Informed Consent
Due to the fact that the data for this study is sourced from publicly available databases, informed consent is not applicable.

Conflict of Interest
The authors declared that there are no conflicts of interest in this study.

Authors' Contributions
Design: Can Hu, Zhenjie Liu. Conduct/data collection: Manli Zhou, Gang Hu. Analysis: Manli Zhou, Gang Hu. Writing manuscript: Can Hu, Manli Zhou, Gang Hu, Zhenjie Liu. All the authors have read and approved the final manuscript.

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