

Association between Air Pollution and Type 2 Diabetes Mellitus in Developing Countries: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective In recent years, many studies have reported that air pollution is a risk factor for type 2 diabetes mellitus (T2DM). The aim of this systematic review and meta-analysis is to summarize the evidence about the association between exposure to air pollution and T2DM in developing countries.

Methods The databases, including PubMed, EMBASE and Web of Science, were systematically searched for studies published up to 31 March 2022. Studies about the association between air pollution and T2DM prevalence or incidence in developing countries were included. The odds ratio (OR) was used as effect estimate. We synthesized the included studies in the meta-analysis.

Results We included 8 cross-sectional studies and 8 cohort studies, all conducted in developing countries. Meta-analysis of 8 studies on PM_{2.5} (particulate matter $\leq 2.5 \mu\text{m}$ in diameter) showed that T2DM prevalence was significantly associated with PM_{2.5} exposure (OR=1.12; 95% CI: 1.07, 1.17; $P<0.001$). The association between air pollutants and T2DM incidence was not estimated due to the limited relevant studies.

Conclusions The exposure to PM_{2.5} would be positively associated with an increased prevalence of T2DM in developing countries. Some effective measures should be taken to reduce air pollutant exposure in people who are vulnerable to diabetes.

Key words: Air pollutants; PM_{2.5}; type 2 diabetes mellitus

INTRODUCTION

In recent years, with the development of economy, energy consumption and vehicle ownership have increased, which generates a variety of air pollutants including oxides of nitrogen (NO_x), sulphur dioxide (SO₂), carbon monoxide (CO), ozone (O₃), and particulate matter (PM)^[1]. Air pollution then becomes a public health issue of great concern, ranking high among the

risk factors of global disease burden^[2]. Many studies have found that air pollution can increase the morbidities and mortalities of respiratory diseases, cardiovascular diseases, cerebrovascular diseases, and metabolic syndrome and is an important trigger of diabetes mellitus (DM)^[3-7].

In the past decades, the prevalence of DM has increased significantly, varying with age, geographic location, regional economic disparity, and ethnicity. Studies have shown a rapid escalation of type 2 diabetes mellitus (T2DM) in developing countries. The increasing prevalence of DM, mainly due to the continuous rise in the incidence of T2DM, has posed a great threat to the public health^[8-11]. DM is a metabolic dis-

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ease caused by genetic and environmental factors. As the increasing trend of air pollution is similar to that of DM, air pollution might be one of the various potential environmental factors that can increase the risk of DM.

Particulate matter, especially fine particulate pollution in the ambient environment, was a high-risk factor for T2DM^[12]. A large amount of experimental evidence has indicated that the relevant mechanisms may include endothelial dysfunction, visceral inflammation and endoplasmic reticulum stress, concerning insulin transduction, insulin sensitivity, and glucose metabolism^[13, 14]. Long-term exposure to PM_{2.5} (particles with an aerodynamic diameter < 2.5µm) may induce mitochondrial dysfunction of the insulin target tissue by activating signal pathways, possibly leading to abnormal glucose and lipid metabolism^[15, 16]. Alterations in mitochondria and brown adipocytes can eventually promote the occurrence of T2DM^[17-19]. It was reported that 2.6% of the total global deaths was related to T2DM and 13.4% of deaths caused by T2DM was attributable to PM_{2.5} in 2019^[20]. Furthermore, DM is closely related to exposure to air pollution, which may even worsen the outcome of diabetic patients as well^[3, 21-23].

Many studies have explored the relationship between air pollution and T2DM worldwide. Some meta-analyses have been conducted to show the exposure of air pollutants on DM^[24-28]. However, few research has focused on that in developing countries independently so far. In fact, the composition and concentrations of air pollutants are quite different between developed and developing countries, and the prevalence and incidence of T2DM are reported to be much higher in developing countries^[29]. Given the increased risk of T2DM, we explored the possible association between air pollution and T2DM in developing countries.

MATERIALS AND METHODS

Search strategy

We searched databases of electronic documents, including PubMed, EMBASE and Web of Science, with the following terms: "air pollution", "particulate matter", "diabetes mellitus", "T2DM", and "type 2 diabetes". Our search was conducted to identify eligible studies published up to 31 March 2022. After de-duplication, we screened the titles and abstracts for eligibility, and then the related articles were retrieved as full text. This study is based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Me-

ta-Analyses (PRISMA) Statement.

Inclusion and exclusion criteria

The inclusion criteria included: a) cross-sectional, case-control, or cohort studies; b) studies in developing countries; c) language in English; d) studies with clearly-defined air pollutants; e) studies in which DM cases had clear diagnostic criteria; and f) studies that showed quantitative measures of association between exposure to air pollution and DM prevalence or incidence.

The exclusion criteria were: a) studies only on type 1 diabetes mellitus (T1DM) or gestational diabetes mellitus (GDM); b) duplicated articles; c) insufficient data supply; d) animal research; and e) studies only exploring the pathogenesis of DM.

Besides, some studies might not distinguish adult T1DM from T2DM. Cases in these studies were roughly considered as T2DM due to the high proportion of T2DM in diabetic patients^[30]. This method has been applied in several previous meta-analyses^[25, 27]. Since even approximately 85% to 90% of DM cases worldwide are T2DM, it is unlikely to have a substantial effect on the final conclusion^[31].

Data extraction

We extracted the following data from the eligible studies: first author name, year of publication, study design, study period, population demographics, investigated pollutants, and outcomes.

Two researchers developed the search standard together and screened the data independently. If a dispute occurred in the data extraction process, a third researcher would be responsible to determine the inclusion and exclusion.

Quality evaluation

The quality of cross-sectional studies was assessed using the instrument Agency for Research and Health Quality (AHRQ) Methodology Checklist^[32]. The Newcastle-Ottawa Scale (NOS) was applied for the evaluation of case-control or cohort studies^[33]. According to the AHRQ checklist, 11 items would be classified with "yes", "no", or "unclear". Articles were classified as "excellent" (≥ 10 items with "yes"), "good" (7 to 9 "yes"), "weak" (4 to 6 "yes"), and "poor" methodological quality (1 to 3 "yes"). As for NOS, the score ranged from 0 to 9. Studies with ≥ 6 points were considered as high-quality, and those with < 6 points were considered as

low-quality.

Statistical analysis

Effect estimate included odds ratio (OR) or prevalence ratio (PR) for cross-sectional and case-control studies and relative risk (RR) or hazard ratio (HR) for cohort studies. The pooled effect estimate in our study was reported as OR/HR with 95% confidence interval (CI), as previous meta-analyses have considered PR and RR equivalent to OR and HR, respectively^[27]. A *P* value of < 0.05 was considered statistically significant. The between-study heterogeneity was estimated using I^2 statistics. A random-effects model was selected. The calculations were performed with RevMan 5.3 software.

RESULTS

Characteristics of the included studies

A total of 4,493 papers were obtained through literature searching, including 763 from PubMed, 1,921 from EMBASE, and 1809 from Web of Science. After excluding the duplicated articles, we screened title and/or abstract of 3,172 papers, among which 3,137 articles were further excluded. By reading the full text of the remaining 35 papers, 19 were excluded due to the inconformity of literature type, outcomes, and/or study design. Eventually, 16 articles exploring the relationship between air pollutants and DM were enrolled in this study (**Fig 1**), including 8 cross-sectional studies and 8 cohort studies. Each study included one or more air pollutants, and the outcome of each study was the disease prevalence or incidence. These studies were from China, India, Indonesia, Iran, and Mexico. Details of the enrolled studies are presented in **Table 1**. The diagnoses of DM in these studies were based on self-report, diabetic assay index, or intake of any antidiabetic medication. Ten studies precisely indicated T2DM as the outcome, 2 studies did not distinguish between type 1 and type 2 diabetes. Due to the high proportion of T2DM in diabetic patients, cases of DM in these 2 studies was managed as T2DM cases in our study.

Association of PM_{2.5} exposure with prevalence of T2DM

Among these 16 included studies, there are 5 cross-sectional studies and 3 cohort studies that assessed the effect of PM_{2.5} on T2DM prevalence. Of these 8 studies, 5 studies were conducted in China,

and the other studies was carried out in Mexico, India and Indonesia. Totally, 792,206 participants were included in this meta-analysis. A positive relationship of exposure to PM_{2.5} with T2DM prevalence was noted (OR=1.12, 95% CI: 1.07, 1.17, *P*<0.001), with high degree of heterogeneity observed ($I^2 = 76\%$) (**Fig. 2**).

Association of other air pollutants with risk of T2DM

According to the enrolled studies on air pollutants other than PM_{2.5}, as shown in **Table 1**, we could find that other air pollutants, including PM₁, PM₁₀, NO₂, SO₂ and O₃, also remain great concerns on the burden of T2DM. Among the 16 included studies, there was one study that discussed the effect of air pollution exposure on both DM prevalence and incidence. Eventually, 10 studies involved the result concerning DM prevalence, and 7 studies involved the result including DM incidence. However, owing to the different kinds of air pollutants in each study, the number of studies that discussed the influence of each air pollutant on the risk of DM was limited. Thus, the meta-analysis of the

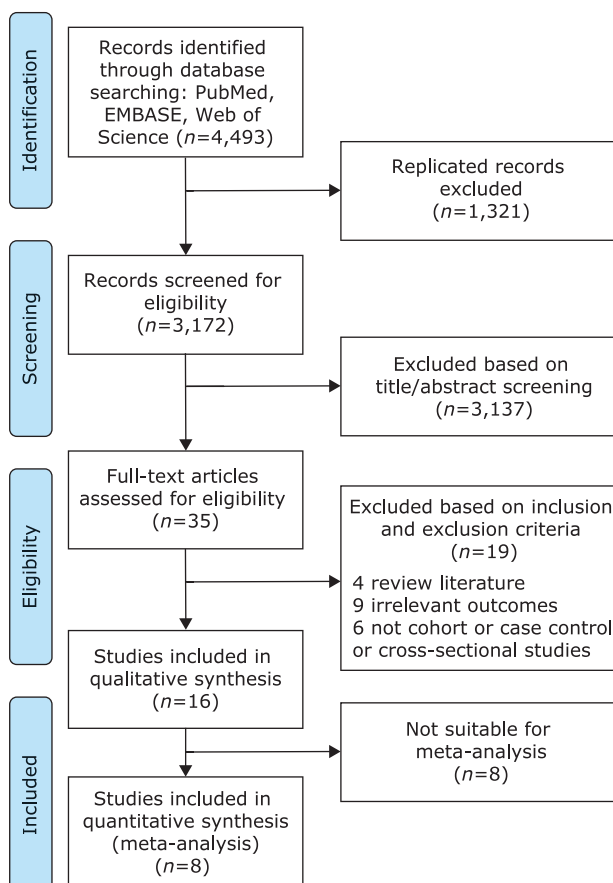


Figure 1. Flowchart for study selection

Table 1. Characteristics of the included studies

Author and year	Study design	Location	Participants	Study period	Pollutants	Average exposure	Effect estimate (95% CI)	Outcomes	Definition of diabetes
Bo Y, et al (2021) ^[34]	Cohort	Taiwan, China	146,789	2001 - 2014	PM _{2.5}	27 µg/m ³	1.28 (1.19, 1.39)	T2DM incidence	Self-report of physician-diagnosed T2DM
Chilian-Herrera OL, et al (2021) ^[35]	Cohort	Municipalities of the State of Mexico and Mexico City	2,297	2006 - 2012	PM _{2.5}	24.8 µg/m ³	3.09 (1.17, 8.15)	DM prevalence	Self-report information of "having received a medical diagnosis of diabetes or high blood sugar"
Hassanvand MS, et al (2017) ^[36]	Cross-sectional	5 large cities in Iran	2,916	2006 - 2011	PM ₁₀	120.15 µg/m ³ (study group), 83.95 µg/m ³ (control group)	1.32 (1.03, 1.69)	T2DM prevalence	Defined as a positive response to either of the following two questions: 1) "Have you ever been told by a doctor or other health worker that you have diabetes?"; 2) "Are you currently taking oral medication or insulin for diabetes prescribed by a doctor or other healthcare professional?"
Jabbari F, et al (2020) ^[37]	Cohort	Municipal district 13 of Tehran, Iran	2,428	2009 - 2011	PM ₁₀	82.6 µg/m ³	1.50 (1, 2.32)	T2DM incidence	Defined as the concentration of FBG ≥ 126 mg/dL, non-FBG ≥ 200 mg/dL, and regular use of glucose-lowering medication
Jacob AM, et al (2019) ^[38]	Cross-sectional	Chennai, Tamil Nadu, India	410	2017 - 2018	PM _{2.5}	74.22 µg/m ³ (study group) 27.22 µg/m ³ (control group)	2.19 (1.40, 2.43)	T2DM prevalence	Meeting either of the following two criteria: 1) RCBG ≥ 140 mg/dl (7.8 mmol/l); 2) RCBG >200 mg/ dl (11.1 mmol/l) and reporting any one of the classic symptoms or weight loss
Liu C, et al (2016) ^[39]	Cross-sectional	150 counties or districts from 28 provinces, China	11,847	2011 - 2012	PM _{2.5}	72.6 µg/m ³	1.14 (1.08, 1.20)	T2DM prevalence	Self-reported diabetes, and/or FBG ≥ 7 mmol/L, and/or HbA1c ≥ 6.5%, and/or insulin use according to ADA's recommendation
Liu F, et al (2019) ^[40]	Cohort	Rural areas of Henan province, China	39,259	2015 - 2017	PM ₁ PM _{2.5} NO ₂	57.4 µg/m ³ 73.4 µg/m ³ 39.9 µg/m ³	1.040 (1.026, 1.054) 1.068 (1.052, 1.084) 1.050 (1.039, 1.061)	T2DM prevalence	Previously diagnosed with T2DM and currently using antidiabetic medicines and/or FBG ≥ 7.0 mmol/L
Li CY, et al (2019) ^[41]	Cohort	Taiwan, China	505,151	2001 - 2012	PM _{2.5}	27.28 µg/m ³	1.08 (1.06, 1.10)	T2DM incidence	Based on ICD-9
Li YL, et al (2021) ^[42]	Cohort	Taiwan, China	6,426,802	2005 - 2010	O ₃ SO ₂	26.21 ppb 4.77 ppb	1.058 (1.053, 1.064) 1.011 (1.007, 1.015)	T2DM incidence	Based on ICD-9
Qiu H, et al (2018) ^[43]	Cohort	Hong Kong, China	61,447	1998 - 2001	PM _{2.5}	35.8 µg/m ³	1.06 (1.01, 1.11) 1.15 (1.05, 1.25)	T2DM prevalence T2DM incidence	Based on ICD-9
Shan A, et al (2020) ^[44]	Cohort	Four cities in northern China	38,529	1998 - 2009	PM ₁₀ SO ₂ NO ₂	143.36 µg/m ³ 66.71 µg/m ³ 40.74 µg/m ³	1.831 (1.778, 1.886) 1.287 (1.256, 1.318) 1.472 (1.419, 1.528)	T2DM incidence	Self-reported physician diagnosis (from at least a class three hospital), intake of antidiabetic drugs or injection of insulin simultaneously

Continued Table 1. Characteristics of the included studies

Author and year	Study design	Location	Participants	Study period	Pollutants	Average exposure	Effect estimate (95% CI)	Outcomes	Definition of diabetes
Suryadhi MAH, et al (2020) ^[45]	Cross-sectional	487 regencies/municipalities in all 33 provinces in Indonesia	647,947	2007 - 2013	PM _{2.5}	8.3µg/m ³	1.09 (1.05, 1.14)	DM prevalence	Using the following question "Have you ever been diagnosed with diabetes mellitus by a doctor?"
Wang M, et al (2020) ^[46]	Cross-sectional	Jinchang city, Gansu province, China	19,884	2011 - 2013	PM ₁₀	109.43µg/m ³	1.17 (1.08, 1.26)	DM incidence	Defined according to the diagnostic criteria recommended by ADA as FBG ≥ 7.0 mmol/L and/or self-report clinical diagnosed of diabetes and/or self-report used of anti-diabetes drugs
Yang BY, et al (2018) ^[47]	Cross-sectional	Liaoning province, China	15,477	2009	PM ₁ PM _{2.5} PM ₁₀ SO ₂ NO ₂ O ₃	66.0µg/m ³ 82.0µg/m ³ 123.1µg/m ³ 54.4µg/m ³ 35.3µg/m ³ 49.4µg/m ³	1.13 (1.04, 1.22) 1.14 (1.03, 1.25) 1.20 (1.12, 1.28) 1.12 (1.04, 1.21) 1.22 (1.12, 1.33) 1.14 (1.05, 1.25)	DM prevalence	Defined according to ADA's recommendations, as FBG ≥ 7.0 mmol/L or 2 h glucose ≥ 11.1mmol/L, or intake of any antidiabetic medication (both insulin and oral antidiabetic drugs), or both
Yang Y, et al (2018) ^[48]	Cross-sectional	8 provinces across China	11,504	2007 - 2010	PM _{2.5}	46.97µg/m ³	1.27 (1.12, 1.43)	DM prevalence	Self-reported information using the following three criteria: 1) diagnosed with diabetes mellitus by a health care professional; 2) taking insulin or other medical treatments to reduce blood glucose levels during the last 12 months before the survey; 3) consuming a special diet and physical exercise regimen related to diabetes as recommended by medical professionals
Zhang Q, et al (2021) ^[49]	Cross-sectional	150 counties or districts from 28 provinces, China	13,013	2011 - 2012	NO ₂	24µg/m ³	1.13 (1.01, 1.26)	DM prevalence	Primary definition of diabetes meeting at least one of the following criteria: FBG >126 mg/dl, a non-FBG >200 mg/dl, HbA1c > 6.5%, or using antidiabetic medications; self-reported diabetes defined as answering "Yes" to the question "Have you been diagnosed with diabetes or high blood sugar?"

SD: standard deviation; CI: confidence interval; DM: diabetes mellitus; T2DM: type 2 diabetes mellitus; ICD-9: International Classification of Disease, Ninth Revision; FBG: fasting blood glucose; RCBG: random capillary blood glucose; HbA1c: glycosylated hemoglobin, %; ADA: American Diabetes Association; PM₁: particulate matter with an aerodynamic diameter less than or equal to 1 mm; PM_{2.5}: particulate matter with an aerodynamic diameter less than or equal to 2.5 mm; PM₁₀: particulate matter with an aerodynamic diameter less than or equal to 10 mm; SO₂: sulfur dioxide; NO₂: nitrogen dioxide; O₃: ozone.

The data analyses of the 8 cross-sectional studies were actually based on case control studies. It was due to application of analysis methods of case control studies that the OR and 95% CI could be obtained.

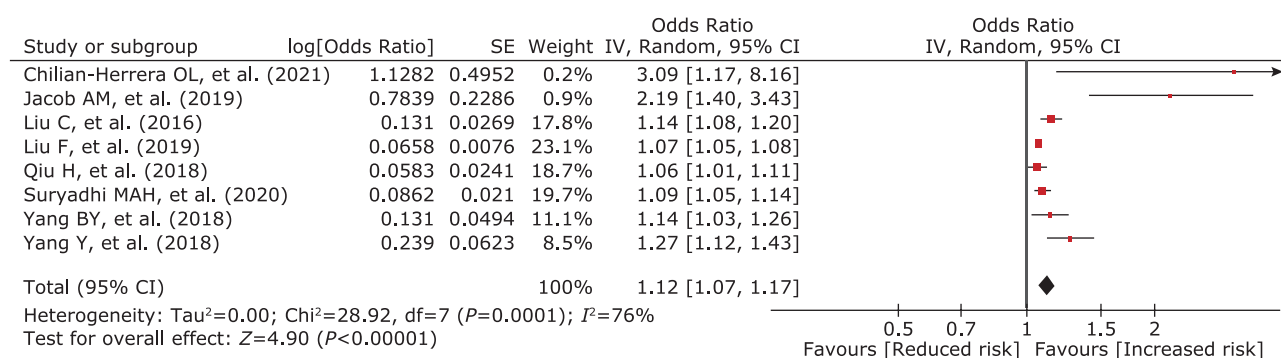


Figure 2. Forest plot of the association between PM_{2.5} and T2DM prevalence

effect of air pollutants other than PM_{2.5} on the incidence or prevalence of DM was not applicable.

Quality evaluation

Of the 8 cross-sectional studies, 7 studies were assessed as high-quality with the scores between 6 and 10, 1 study as low quality with the score of 5; the 8 cohort studies were scored between 6 and 10 in NOS, indicating high-quality (**Table 2**). To be noted, the 8

cross-sectional studies were evaluated in assessment tool of case control studies, since the data analyses in these studies were based on the method of case control studies. Therefore, NOS of case control studies was applied to evaluate these studies.

Publication bias

In the meta-analysis for PM_{2.5} with T2DM prevalence, we evaluated the publication bias. The funnel plot of

Table 2. Assessment of the quality of the enrolled studies on air pollutant and diabetes mellitus

Study and year	Selection				Comparability	Exposure			Score
	1	2	3	4	1	1	2	3	
Cross-sectional studies									
Hassanvand MS, et al. (2017)	*	*	*	*	*		*		6
Jacob AM, et al. (2019)	*		*	*	*		*		5
Liu C, et al. (2016)	*	*	*	*	**		*	*	8
Suryadhi MAH, et al. (2020)	*	*	*	*	**		*	*	7
Wang M, et al. (2020)	*	*	*	*	**	*	*		8
Yang BY, et al. (2018)	*	*	*	*	**	*	*	*	9
Yang Y, et al. (2018)	*	*	*	*	**		*		7
Zhang Q, et al. (2021)	*	*	*	*	**	*	*		8
Cohort Studies									
Bo Y, et al. (2021)		*	*	*	**	**	*	*	9
Chilian-Herrera OL, et al. (2021)		*	*	*	**	*		*	7
Jabbari F, et al. (2020)	*	*	*	*	**	*		*	8
Liu F, et al. (2019)	*	*	*	*	**	*		*	8
Li CY, et al. (2019)		*	*	*	**	*	*	*	8
Li YL, et al. (2021)		*	*	*	**	*	*	*	8
Qiu H, et al. (2018)	*	*	*	*	**	**	*	*	10
Shan A, et al. (2020)		*	*	*	**	*	*	*	8

The included cross-sectional studies were evaluated in assessment tool of case control studies, since the data analyses of the included cross-sectional studies were actually based on case control studies. *The corresponding item is applicable to the study.

PM_{2.5} exposure with T2DM prevalence was asymmetric (**Fig. 3**). However, the number of the included studies was too limited to evaluate the publication bias by Egger's test^[50]. Sensitivity analysis was performed through single removal of studies, which indicated no significant change in the result of positive association between exposure to PM_{2.5} and prevalence of T2DM (**Fig. S1**).

DISCUSSION

In this meta-analysis of 8 cross-sectional studies and 8 cohort studies, we found that exposure to PM_{2.5} could be positively associated with T2DM prevalence in developing countries. The influence of other pollutants including PM₁, PM₁₀, NO₂, SO₂, and O₃ was not assessed in this meta-analysis because of the lack of evidence. Notably, some potential biases and confounders might exist. For example, the subjects might have different age ranges or living environments, and some studies only included women or elderly people.

The increased risk of T2DM is related to many factors including genetic factors, obesity, and social factors. Air pollution, a product of economic development, is believed to be one of the risk factors^[13]. In recent years, quite a few studies have investigated the impact of air pollution exposure on DM and its mechanism. Mouse models with simulated air pollution exposure have indicated that air pollution could induce inflammatory reaction, lipid metabolism disorder, abnormal glucose metabolism, and insulin resistance, which increased the risk of DM or aggravated its development^[18, 51, 52]. However, since the physiological structure differs between experimental animals and human beings, the results of animal experiments can not be

directly applied in patients. Population-based studies on the relationship between air pollution and T2DM have been carried out recently, and several related meta-analyses have already been published. Increased inflammation was found in patients with T2DM, and there was a significant correlation between inflammation and glycemic control^[53]. A 30-year global analysis in 204 countries and regions has shown the patterns and trends of T2DM associated with PM_{2.5} from 1990 to 2019^[54]. Due to inequalities in air pollution control and health care resources, T2DM burden related to PM_{2.5} is different between developed and developing countries. In developing countries, the high PM_{2.5} exposure and immature social infrastructure may result in a heavier burden on T2DM compared with that in developed countries^[55, 56]. Some published meta-analyses have shown positive association between air pollution exposure and T2DM^[24-28]. The major sources of air pollutants are vehicular exhaust and construction activities in developed countries and continuous burning activities in developing countries^[1, 57]. The quantity of ground testing of PM_{2.5} also varies between developed and developing countries^[29]. Thus, the results of this meta-analysis can provide a new idea for controlling T2DM in developing countries.

While an increasing number of studies on the impact of air pollution on T2DM have been published, only a small proportion of them were conducted in developing countries, possibly due to the lack of public awareness on this issue. Air pollution is monitored only for a short period of time at a small number of monitoring sites, which limits research on air pollution in developing countries in the perspectives of epidemiology and environmental health.

Our current meta-analysis has several limitations. First, despite the application of multiple search strategies, the association between air pollutants and T2DM incidence was not estimated due to the limited relevant studies. Similarly, the impact of some other pollutants, except PM_{2.5}, on T2DM prevalence was also not assessed. Second, the heterogeneity was high and it would damage the creditability of our analysis. The high heterogeneity might come from a few aspects including the different study design and the rough approximation of the type of DM. Finally, some studies have not accounted for the combined effects of different pollutants and thus the potential interaction among multi-pollutants cannot be examined. Therefore, more studies about the air pollution and T2DM are required.

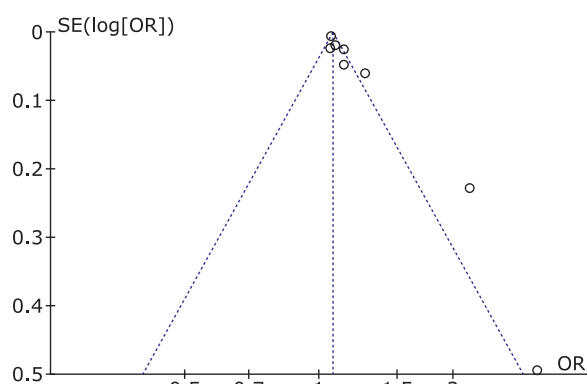


Figure 3. Funnel plot of the association between PM_{2.5} and T2DM prevalence

In conclusion, as shown in our meta-analysis, the increase in T2DM prevalence is associated with PM_{2.5} exposure in developing countries. As air pollution is still a tough issue in developing countries, more efforts should be made to prevent T2DM. In addition, the risk of T2DM may be lowered with the gradual control of air pollution. Of course, further research on the impact of air pollution on T2DM is warranted in developing countries.

Supplementary material

Available at <http://cmsj.cams.cn/EN/10.24920/004065>.

Figure S1. Forest plot of sensitivity analysis of PM_{2.5} and T2DM prevalence

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

Chen ZH and Li NS conceived and designed the study. All authors performed data collection and analysis. Chen ZH and Zhao Z drafted the manuscript, and all authors revised the manuscript and approved the final version. Deng CW and Li NS made critical revisions.

Data availability

The data that support the finding of this study are available from the corresponding author upon reasonable request.

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发展中国家空气污染与 2 型糖尿病的系统评价和 Meta 分析

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摘要

目的 研究指出空气污染是 2 型糖尿病的危险因素。本文采用 Meta 分析方法评价发展中国家空气污染与 2 型糖尿病之间的联系。

方法 使用计算机检索 PubMed、EMBASE 和 Web of Science 数据库内截至 2022 年 03 月 31 日发表的发展中国家空气污染与 2 型糖尿病患病率或发病率之间关系的研究论文。使用比值比 (OR) 来评估疗效，对纳入的研究进行 Meta 分析。

结果 共纳入在发展中国家进行的 8 项横断面研究和 8 项队列研究。对 8 项 PM_{2.5} 相关的研究进行的 Meta 分析显示，暴露于 PM_{2.5} 使 2 型糖尿病患病率增加，相关性为 1.12 (95% CI 1.07, 1.17) ($P<0.001$)。由于纳入文献数量有限，未能定量评价空气污染与 2 型糖尿病发病率之间的相关性。

结论 在发展中国家，暴露于 PM_{2.5} 会导致 2 型糖尿病患病率增加。糖尿病易感人群应该注意减少空气污染暴露。

关键词：空气污染；PM_{2.5}；2 型糖尿病

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