Relationship between air pollutants and risk of diabetes:a cohort study based meta-analysis

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Abstract

Background : To investigate the effects of air pollutants on the incidence of diabetes, and to provide reliable evidence for the prevention and control of diabetes. Method : Electronic databases of PubMed, Embase, Web of Science, Wanfang Digital Periodicals (WANFANG), WeiPu, China National Knowledge Infrastructure (CNKI), Springer, and Ovid were searched. RevMan5.3 software was used for meta analysis of the literature included in this study, I 2 was used to measure the heterogeneity of the research contents of the included literature, and fixed effect model or random effect model was used for combined analysis of the overall incidence of diabetes and the incidence of diabetes under different air pollutants. Result : A total of 22 articles with high overall quality were included in this study, including 2703882 subjects and 535190 patients with diabetes.Pooled effect of the studies was determined using relative risk(RR). PM 10 （RR =1.00; 95% CI :0.99-1.02, P =0.61), PM 2.5 （RR =1.02 ; 95% C I:1.01-1.04, P =0.01), NO X （RR =1.00; 95% CI :1.00-1.01, P =0.006), NO 2 （RR =1.00; 95% CI :1.00-1.01, P =0.01), O 3 （RR =1.00; 95% CI :0.99-1.01, P =0.99). No correlation was found between PM 10 , NO 2 , O 3 and the risk of type 2 diabetes. The risk of diabetes increased by 1% in people exposed to total air pollutants, increased by 2% in people exposed to PM 2.5 , and increased by 1% in people exposed to NO X . Conclusion : Results of this paper showed that air pollutants are weakly positively correlated with the risk of diabetes. As to the other influencing factors should be further studied.

Background

Diabetes has become one of the serious public health issues in worldwide. In 2017, 451 million people (age 18–99 years) were estimated to be suffering from diabetes, majority of the burden being in low and middle income countries. However, these figures were estimated to upped to 693 million by 2045[1]. The prevalence and incidence rate of diabetes in China is increasing by years[2]. The etiology of diabetes is complex and it is recognized as a chronic non-communicable disease caused by congenital genetic factors and external environmental factors, involving many risk factors. Congenital genetic factors determine the innate susceptibility of each person, environmental factors lead to the incidence of diabetes under the stimulation of environmental factors. In the prevention and control of diabetes, intervention of environmental factors are easier to achieve than genetic factors. Therefore, identifying environmental risk factors and intervening them may reduce the incidence and mortality of diabetes.

Recent studies have shown that exposure to ambient air pollution is an undesirable stimulus and a risk factor for diabetes[3-5]. Air pollution is a ubiquitous exposure that affects a large percentage of the world's population. There are many sources of air pollution, including industrial facilities, cars, ships, and aircraft, as well as home burning devices or forest fires and volcanic eruptions[6]. According to the source of the pollutants, environmental factors (including climatic conditions, time, industrial activity, and traffic density), the size, composition, and concentration of particulate matter vary from one region to another. Gas-state pollutants include nitrogen oxides (NOx), carbon oxides (COx), sulfur oxides (SOx), and ozone (O_3). Aerosol-state pollutants mainly include dust, particulates (PM), etc[7]. Exposure to air pollutants is an important adjustable and reversible environmental risk factor for diabetes. Understanding the

relationship between exposure to air pollution and the development of diabetes is critical to our ability to control air pollution and its impact on diabetes. To our knowledge, several prior studies have performed meta analysis or systematic reviews related to the association between diabetes and air pollutants, but very few of them were based on cohort studies or only reported type 2 diabetes. Therefore we aim to explore the relationship between air pollutants and the risk of diabetes based on cohort studies.

Methods

Literature search strategy

Literature research was conducted with restriction of published year(from January of 2000 to May of 2019) but without restriction of region and publication status. Electronic databases of PubMed, Embase, Web of Science, Wanfang Digital Periodicals (WANFANG), WeiPu, China National Knowledge Infrastructure (CNKI), Springer, and Ovid were searched. Detailed PubMed strategy was listed as follows: ((((diabetes mellitus) OR DM) AND air pollution) AND contaminants). Related articles of the included studies were screened according to the inclusion and exclusion criteria. The title and abstracts of all studies identified by the literature search were evaluated. The full text of any abstract meeting the inclusion criteria was then reviewed. At the same time, more relevant literature is collected by the literature trace method and manual search method.

Inclusion and exclusion criteria

Articles meeting the following criteria were included:subjects included non-diabetic population at baseline;exposure factors included relevant air pollutants;studies outcomes were diabetes (type 1 diabetes, type 2 diabetes, gestational diabetes); cohort studies; the studies provide data information associated with the risk of developing diabetes. The exclusion criteria were as follows: non-cohort studies;the outcome was not suitable for meta analysis; not reporting full information; it was not possible to obtain full text; studies with low reliability and small sample size(less than 1000); repeated articles; reviews.

Data extraction and outcome of interest

The collection of literature data uses a unified data extraction form, the main information extracted from each document: including the first author, publication year, country, study design type, study race, sample size of each group, follow-up time, adjusted confounding factors indicators which are risk ratio(*RR*) and 95% confidence intervals (*CI*), NOS score. Heterogeneity was assessed using the I^2 statistics.

Quality assessment and statistical analysis

Quality assessment was carried out for all retrieved studies. Quality in the systematic review referred to the potential of biases during data analysis. The methodological integrity of the study was carried out

according to the “Newcastle-Ottawa scale”(NOS) for assessing the quality of non-randomized studies in meta-analysis[8].

The *RR* and Hazard Ratio (*HR*) values in the literature are directly regarded as *RR* values. Meta-analysis was performed with Review Manager(version 5.3). Heterogeneity was assessed using the Cochrane handbook and I^2 statistics, P= 0.05 using the χ^2 test for the Q statistic and I^2, 50% for the I^2 statistic were interpreted as low-level heterogeneity. If I^2 <50%, a fixed effect model is used; if $I^2 \geq 50\%$, a random effects model is used for pooled data[9].

The sensitivity of the results was analyzed by comparing the differences between the fixed effect model and the random effect model effect. Through analysis, we explore the effects of research features on outcome variables in the literature and analyze the reasons for their heterogeneity. The funnel plot was used to test the publication bias. If P>0.05, the inverted funnel plot was uniformly symmetrically distributed, indicating no publication bias.

Results

452 articles were retrieved (42 Chinese papers and 410 English papers) in all.The literature screening flow chart is shown in Fig.1. Overall a total of 2703882 individuals were included in these studies.Table 1. indicates the summary of 22 cohort studies contributing data to systematic review. Included basic information: first author, published year, study design, follow-up years, age distribution, number of participants,total number of diabetic patients in the outcome,type of diabetes and quality score. The confounding factors of the included studies were diverse, therefore gender, age, smoking, drinking and comorbidities were adjusted. The NOS scores of included studies were 6-9, indicating high quality literature.

Air pollutants and the risk of diabetes

The air pollutants in the included in studies were SO_2, PM_{10}, $PM_{2.5}$, NO_X, NO_2, O_3. Heterogeneity analysis showed that there was no statistical difference between each included studies (P=0.52, I^2=0%), so fixed effect model was used. The results showed that *RR*=1.01 (95% *CI*: 1.00-1.01), the difference was statistically significant (P<0.05), indicating that air pollutants were associated with the risk of diabetes,the risk of onset increased by 1% in those who exposed to air pollutants. Subgroup analysis was performed according to different regions: (1) North America: the results showed that *RR*=1.01 (95% *CI*: 1.00-1.02), the difference was statistically significant (P<0.05) which indicates that there is a correlation between air pollutants and the risk of diabetes, and the risk of diabetes is increased by 1% in people exposed to air pollutants. (2)Asia:the results showed that *RR*=1.06 (95% *CI*: 1.00-1.13), the difference was statistically significant (P<0.05), this indicates that there is a correlation between air pollutants and the risk of diabetes, and the risk of diabetes is increased by 6% in people exposed to air pollutants. (3)Europe: the results showed *RR*=1.00 (95% *CI*: 1.00-1.01), the difference was statistically significant (P<0.05), details showed in Fig.2.

PM10 and risk of diabetes

A total of 6 articles [11,21-24,27,31] studied PM_{10} as a risk factor,five of them had type2 diabetes as the outcome,another one was gestational diabetes.The cumulative follow-up number was 1,662,778, and the number of people with diabetes was 83,584. Heterogeneity analysis showed that there was no statistical difference between the included studies (P=0.68, I^2=0%), so the data were combined using the fixed effect model, and the meta-analysis of PM_{10} and diabetes risk showed that *RR*=1.00 (95% *CI*: 0.99-1.02), the difference was not statistically significant (P>0.05), indicating that PM_{10} has no correlation with the risk of diabetes, as shown in Fig.3. Removed the literature of gestational diabetes, the meta-analysis of the risk of PM10 and type 2 diabetes showed *RR*=1.01 (95% *CI*: 0.99-1.02), the difference was still not statistically significant (P>0.05), indicating there was no correlation between the risk of developing type 2 diabetes and PM_{10},shown in Fig.4.

PM2.5 and risk of diabetes

A total of 16 articles [10-20, 23-28, 31] studied PM2.5 as a risk factor. Two of these articles had both type 2 and type 1 diabetes as outcomes,eleven were type 2 diabetes and 3 were gestational diabetes. The cumulative follow-up number was 1198374, and the number of people with diabetes was 459834. Heterogeneity analysis showed that there was no statistical difference between the included studies (P=0.39, I^2=5%), so the data were combined using the fixed effect model.The meta-analysis of PM2.5 and diabetes risk showed *RR*=1.02 (95% *CI*: 1.01-1.04), the difference was statistically significant (P<0.05), indicating that $PM_{2.5}$ was associated with the risk of diabetes, the risk of onset increased by 2%. Subgroup analysis conducted according to the type of diabetes, *RR* = 1.05 (95% *CI*: 1.03-1.08), the difference was statistically significant (P < 0.001), indicating $PM_{2.5}$ and the risk of developing type 2 diabetes is increased by 5% in those who exposed to air pollutants $PM_{2.5}$,shown in Fig.5.

NOx and risk of diabetes

Five articles studied NOx as a risk factor[10-11,13,23,27]. The cumulative follw-up number was 2029159,the number of people with diabetes were 91590. Heterogeneity analysis showed that there was no statistical difference between the included studies (P=0.59, I^2=0%), so the data were combined using the fixed effect model. The meta-analysis of NO_X and diabetes risk showed *RR*=1.01 (95% *CI*: 1.01-1.04), the difference was statistically significant (P < 0.001), indicating that NO_X has a correlation with the risk of diabetes, and the risk of diabetes is increased by 1% in people exposed to air pollutants NO_X,shown in Fig.6.

NO_2 and risk of diabetes

A total of 9 literature [11,13-14,17,19,21-23, 29] including NO_2 as an exposure factor. Two articles had both type 1 and 2 diabetes as outcomes,7 articles had type 2 diabetes as outcomes. The cumulative number of follow-ups was 1876661, and the number of people with diabetes was 89,417. Heterogeneity

analysis showed that there was no statistical difference between the included studies (P=0.69, I^2=0%), so the data were combined using the fixed effect model. The meta-analysis of NO_2 and diabetes risk showed *RR*=1.00 (95% *CI*: 1.00-1.01), the difference was not statistically significant (P>0.05), indicating that NO_2 has no correlation with the risk of diabetes. See Fig.7 for details.

O_3 and risk of diabetes

A total of 3 literature [11,19,27] studied O_3 as a risk factor. The cumulative number of follow-ups were 1,582,148, and the number of people with diabetes were 77,565. Heterogeneity analysis showed that there was no statistical difference between the included studies (P=0.54, I^2=0%), so the data were combined using the fixed effect model. The meta-analysis of the risk of O_3 and diabetes showed that *RR* =1.00 (95% *CI*: 0.99-1.01), the difference was not statistically significant (P>0.05), indicating that there is no correlation between O_3 and the risk of diabetes, shown in Fig.8.

Sensitivity analysis

In the including studies, the most weighted study was removed, and the remaining studies were meta-analyzed. The *RR* value and 95% *CI* of the combined before and after exclusion were not changed much, suggesting that the meta-analysis results are stable and reliable. Shown on Table.2.

Publication bias analysis

As shown in Fig.9-Fig.13, most of the research effect points were concentrated in a narrow area, and the funnel plots were symmetrically distributed, indicating that the included articles had no publication bias.

Discussion

Diabetes is currently one of the most serious public health issues in the world and one of the leading causes of premature death in the global population. In both developed and developing countries, the incidence and prevalence of diabetes is increasing. This phenomenon is related to modern lifestyle characteristics, including obesity and lack of exercise[32]. However, exposure to air pollutants was also considered to be a risk factor in the prevalence of diabetes[33]. The results of this meta-analysis showed that the gaseous pollutants and PM were weakly positively correlated with the risk of diabetes. The results of this study are same with a systematic review published in 2014[34]. This study found that there was no correlation between the risk of diabetes and PM_{10}, NO_2, O_3 respectively. The risk of diabetes increased by 5% in people exposed to air pollutants $PM_{2.5}$, and 1% in those who exposed to NOx. There were sufficient evidences provide that ambient air pollutants play a role in glucose metabolism and type 2 diabetes etiology[35]. Studies have reported that airborne particulate matter $PM_{2.5}$ is rich in persistent semi-steroidal free radicals[36]. A multicountry time-series analysis provides evidence on positive associations between short-term exposure to PM 10 and PM 2.5 and mortality of cardiovascular disease and respiratory disease[37]. Besides,the relaxation of blood vessels and endothelial function decreases

with increasing $PM_{2.5}$[38]. After exposure to $PM_{2.5}$, the levels of tumor necrosis factor (TNF-α), interleukin-6, resistin and leptin were elevated, and the expression of interleukin-10 was decreased, resulting in an increase in adipose tissue macrophages and dysfunction of intravascular cell barriers. The expression of pro-inflammatory and insulin resistance changes[39]. Increased tumor necrosis factor TNF-α and macrophage inflammatory proteins lead to hyperglycemia and deteriorating beta cell function[40].

Air pollution is an influential factor in the pathogenesis of diabetes. However, the mechanism by which air pollutants increase the risk of diabetes is not fully understood. The possible mechanism by which air pollutants increase the risk of diabetes is through:(1)Inducing and/or triggering the body's insulin resistance[41]; (2)They may act directly on the pancreatic tissue of the body, causing impaired beta-cell function in the pancreas to produce insulin, causing the body to not produce enough insulin. They may also act directly on the body's cellular insulin receptor, thereby affecting the receptor's binding to insulin, causing insulin to function normally[42]; (3)Inhaled air pollutants enter the systemic circulation through the alveoli to activate the sympathetic nervous system or through the hypothalamus, or both, thereby activating certain signaling pathways that cause inflammation, oxidative stress, endoplasmic reticulum stress, and mitochondrial function in insulin target tissues,and then the accumulation of body fat tissue, heat production, liver fat deposition, skeletal muscle glucose uptake disorders and other multi-organ sugar metabolism, lipid metabolism abnormalities, thereby promoting the occurrence of diabetes[15]; Environmental factors indirectly increase the risk of diabetes by affecting people's daily behavior. High concentrations of air pollution can affect the air quality of the community, which in turn can reduce the risk of diabetes by reducing opportunities for outdoor recreation, socializing, leisure time and physical activity. At the same time, cognitive stress caused by air pollution may trigger a series of neuroendocrine reactions, leading to hyperglycemia, systemic inflammation, insulin resistance, and ultimately diabetes[42].

There are some limitations in this study: (1) The articles included in this study are all cohort studies, namely observational studies, so there were inevitably mixed biases. In this study, we included articles of different types of diabetes which were type 1, type 2, and gestational diabetes. Diversified research content: research levels, follow-up time, exposure assessment methods, and control of confounding factors were all different. The included subjects in the study were of different ages,gender proportion and ethnicity, which inevitably had a certain bias on the results. (2)The way to obtain the information about the diagnosis of diabetes in the follow-up population was self-reported or doctor's report, and some of them lack of objective evaluation. (3)Since this study only analyzed the relevant influencing factors which analyzed with high frequency in included articles, it is necessary to conduct more comprehensive and detailed research and analysis on the risk of other air pollutants and diabetes in the future.

The published literature on the relationship between air pollution exposure and diabetes is limited and based on the interpretation of different perspectives and backgrounds, while air pollution is a mixture of multiple pollutants, it is impossible to distinguish the effects of each pollutants. Different pollutant mechanisms are different. In summary, air pollutants increase the risk of diabetes. At present, controlling

air pollution should be used as a strategy to prevent and control diabetes. Therefore, people should be aware of the dangers of air pollution and reduce the risk of air pollution by formulating strategies.

Conclusion

Air pollutants are weakly positively correlated with the risk of diabetes. The risk of diabetes increased by 2% in people exposed to air pollutants $PM_{2.5}$, and the risk of diabetes increased by 1% in people exposed to air pollutants NO_X. The results of this meta-analysis did not find a correlation between PM_{10}, NO_2, O_3 and the risk of diabetes.

Abbreviations

DM: Diabetes mellitus.

T2DM: Type 2 diabetes mellitus.

GDM: Gestational diabetes mellitus.

NOx: nitrogen oxides.

COx: carbon oxides.

SOx: sulfur oxides.

O_3: ozone.

PM: particulates.

WANFANG: Wanfang Digital Periodicals.

CNKI: China National Knowledge Infrastructure.

RR: risk ratio.

CI: confidence intervals.

NOS: Newcastle-Ottawa scale.

HR: Hazard ratio.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Availability of data and material

Not applicable

Competing Interests

Not applicable.

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Authors' contributions

Patamu Mohemaiti designed overall article writing, modified data analysis; Qin Xiao Xiao and Aizhatiguli searched included articles, data collecting and analyzing; Aidibai Simayi wrote the manuscript.

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References

[1]Cho NH, Shaw JE, Karuranqa S, Huang Y, da Rocha Fernandes JD, et al.,2018. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 138: 271–281.

[3]Coogan P F, White L F, Jerrett M, et al.,2012. Air Pollution and Incidence of Hypertension and Diabetes Mellitus in Black Women Living in Los Angeles[J]. Circulation.125(6):767-772.

[4]Renzi M, Cerza F, Gariazzo C, et al.,2017. Air pollution and occurrence of type 2 diabetes in a large cohort study[J]. Environment International.112:68.

[5] Fleisch A F, Kloog I, Luttmann-Gibson H, et al.,2016. Air pollution exposure and gestational diabetes mellitus among pregnant women in Massachusetts: a cohort study[J]. Environmental Health. 15(1):40.

[6]Thiering E, Heinrich J.,2015. Epidemiology of air pollution and diabetes[J]. Trends in Endocrinology & Metabolism. 26(7):384-394.

[7]Wei W , Mandin C , Ramalho O .,2018. Influence of indoor environmental factors on mass transfer parameters and concentrations of semi-volatile organic compounds[J]. Chemosphere.195:223-235.

[8]Wells GA, Shea B, O'Connell D, Peterson J, Welch V,et al.,2017.The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: Accessed April 29, 2017

[9] Shi FH, Li H, Cui M, Zhang ZL, Gu ZC, et al.,2018. Efficacy and safety of once-weekly semaglutide for the treatment of type 2 diabetes: protocol for a systematic review and meta-analysis. Medicine (Baltimore).97:e0420.

[10]Coogan P F, White L F, Jerrett M, et al.,2012. Air Pollution and Incidence of Hypertension and Diabetes Mellitus in Black Women Living in Los Angeles[J]. Circulation.125(6):767-772.

[11]Renzi M, Cerza F, Gariazzo C, et al.,2017. Air pollution and occurrence of type 2 diabetes in a large cohort study[J]. Environment International. 112:68.

[12] Fleisch A F, Kloog I, Luttmann-Gibson H, et al.,2016. Air pollution exposure and gestational diabetes mellitus among pregnant women in Massachusetts: a cohort study[J]. Environmental Health.15(1):40.

[13]Charlotte C, Hind S, Lillian T, et al.,2017. Association of Long-Term Exposure to Transportation Noise and Traffic-Related Air Pollution with the Incidence of Diabetes: A Prospective Cohort Study[J]. Environmental Health Perspectives. 125(8):087025.

[14]Honda T, Pun VC, Manjourides J, Suh H.,2017. Associations between long-term exposure to air pollution, glycosylated hemoglobin and diabetes. *Int J Hyg Environ Health*. 220(7):1124–1132.

[15] Liang F, Yang X, Liu F, et al.,2019.Long-term exposure to ambient fine particulate matter and incidence of diabetes in China: A cohort study. Environ Int.126:568-575.[16]Qiu H , Schooling C M , Sun S , et al.,2018. Long-term exposure to fine particulate matter air pollution and type 2 diabetes mellitus in elderly: A cohort study in Hong Kong[J].Environ Int.113:350-356.

[17]Park S K , Adar S D , O"Neill M S , et al.,2015. Long-Term Exposure to Air Pollution and Type 2 Diabetes Mellitus in a Multiethnic Cohort[J]. American Journal of Epidemiology.181(5):327-336.

[18]Chen H , Burnett R T , Kwong J C , et al.,2013. Risk of Incident Diabetes in Relation to Long-term Exposure to Fine Particulate Matter in Ontario, Canada[J]. Environmental Health Perspectives. 121(7):804-810.

[19] Jerrett M , Brook R , White L F , et al.,2017. Ambient ozone and incident diabetes: A prospective analysis in a large cohort of African American women[J]. Environ Int.102:42-47.

[20] To T, Zhu J, Villeneuve PJ, Simatovic J, et al.,2015. Chronic disease prevalence in women and air pollution — A 30-year longitudinal cohort study[J]. Environ Int.80: 26-32.

[21] Coogan PF, White LF, Yu J, et al.,2016. Long term exposure to NO_2 and diabetes incidence in the Black Women's Health Study[J]. Environ Res. Jul;148: 360-366.[22] Eze IC, Schaffner E, Fischer E, et al.,2014. Long-term air pollution exposure and diabetes in a population-based Swiss cohort[J]. Environ Int.Sep;70:95-105.[23]Hansen AB, Ravnskjær L, Loft S, et al.,2016. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort[J].Environ Int.May;91:243-50.[24] Weinmayr G, Hennig F, Fuks K, et al.,2016. Heinz Nixdorf Recall Investigator Group. Erratum to: Long-term exposure to fine particulate matter and incidence of type 2 diabetes mellitus in a cohort study: effects of total and traffic-specific air pollution[J]. Environ Health. Mar 23;15:45. [25] Coogan PF, White LF, Yu J, et al.,2016. $PM_{2.5}$ and Diabetes and Hypertension Incidence in the Black Women's Health Study[J]. Epidemiology. Mar;27(2):202-10.

[26]Benjamin B , Yan X , Tingting L , et al.,2018. The 2016 global and national burden of diabetes mellitus attributable to PM air pollution[J]. The Lancet Planetary Health.2(7):e301-e312.

[27] Robledo CA, Mendola P, Yeung E, et al.,2015. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus [J]. Environ Res. Feb;137:316-22. [28] Fleisch AF, Gold DR, Rifas-Shiman SL, et al.,2014.Air pollution exposure and abnormal glucose tolerance during pregnancy: the project Viva cohort[J]. Environ Health Perspect. Apr;122(4): 378-83.[29] Andersen ZJ, Raaschou-Nielsen O, Ketzel M, et al.,2012. Diabetes incidence and long-term exposure to air pollution: a cohort study[J].Diabetes Care. Jan;35(1):92-8. [30] Malmqvist E, Jakobsson K, Tinnerberg H,et al.,2013.Gestational diabetes and preeclampsia in association with air pollution at levels below current air quality guidelines[J].Environ Health Perspect. Apr; 121(4): 488-93.

[31]Puett R C , Hart J E , Schwartz J , et al.,2010. Are Particulate Matter Exposures Associated with Risk of Type 2 Diabetes[J] Environmental Health Perspectives. 119(3):384-389.

[32]Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS,et al.,2001. The continuing epidemics of obesity and diabetes in the United States[J]. JAMA.286:1195–200.

[33]Zúñiga J, Tarajia M, Herrera V, Urriola W, Gómez B,et al.,2016. Assessment of the Possible Association of Air Pollutants PM_{10}, O_3, NO_2 With an Increase in Cardiovascular, Respiratory, and Diabetes Mortality in Panama City: A 2003 to 2013 Data Analysis. *Medicine (Baltimore)*.95(2):e2464.

[34]Janghorbani M , Momeni F , Mansourian M.,2014. Systematic review and meta analysis of air pollution exposure and risk of diabetes[J]. European Journal of Epidemiology. 29(4):231-242.

[35]Alderete TL, Chen Z, Toledo-Corral CM, et al.,2018. Ambient and Traffic-Related Air Pollution Exposures as Novel Risk Factors for Metabolic Dysfunction and Type 2 Diabetes. *Curr Epidemiol Rep.*;5(2):79–91.

[36]Squadrito GL, Cueto R, Dellinger B, Pryor WA.,2001. Quinoid redox cycling as a mechanism for sustained free radical generation by inhaled airborne particulate matter[J]. Free Radic Biol Med.31(9):1132–8.

[37]Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y,et al.,2019.
Ambient Particulate Air Pollution and Daily Mortality in 652 Cities.N Engl J Med.Aug 22;381(8):705-715.

[38]Schneider A, Neas L, Herbst MC, et al.,2008. Endothelial dysfunction: associations with exposure to ambient fine particles in diabetic individuals[J]. Environ Health Perspect.116:1666–1674.

[39]O'Neill MS, Veves A, Sarnat JA, et al.,2007. Air pollution and inflammation in type 2 diabetes: a mechanism for susceptibility. *Occup Environ Med*.64(6):373–379.

[40]Robertson RP, Harmon J, Tran PO, Poitout V.et al.,2004. Beta-cell glucose toxicity, lipo-toxicity, and chronic oxidative stress in type 2 diabetes[J].Diabetes.53(Suppl 1):S119–24.

[41]Honda T, Pun VC, Manjourides J, Suh H.,2017. Associations between long-term exposure to air pollution, glycosylated hemoglobin and diabetes. *Int J Hyg Environ Health*.220(7):1124–1132.

[42]Dzhambov, Angel M .,et al.2018 Ambient air pollution and diabetes in China[J]. The Lancet Planetary Health.2(2):e52-e5.

Tables

Table 1.Summary of 22 cohort studies contributing data to systematic review.

First author	Published year	Follow-up years	Age	Number of participants	Number of diabetic outcomes	Type of diabetes	NOS score
Coogan, P. F[10]	2012	10	21-69	4204	183	T2DM	7
Renzi M[11]	2018	6	35+	1319193	65,995	T2DM	8
Fleisch A F[12]	2016	5	20+	159373	5381	GDM	8
Charlotte C[13]	2017	4	45-84	380738	12941	DM	8
Honda T[14]	2017	---	57+	4121	916	DM	6
Liang F[15]	2019	4	35-74	88397	6439	T2DM	7
Qiu H[16]	2018	9.8	65+	61447	806	T2DM	8
Park S K[17]	2015	9	45-84	5839	622	T2DM	7
Chen H[18]	2013	8	54.9	62012	6310	T2DM	9
Jerrett M[19]	2017	10	21-69	43003	227	T2DM	8
To T[20]	2015	30	40-59	29549	6447	T2DM	9
Coogan PF[21]	2016	17	21-69	43003	4387	T2DM	7
Eze IC[22]	2014	10	29-73	6392	315	T2DM	8
Hansen AB[23]	2016	15	44+	24174	1137	T2DM	8
Weinmayr G[24]	2015	5	45-75	3607	331	T2DM	6
Coogan PF[25]	2016	17	21-69	33771	4387	T2DM	8
Benjamin B[26]	2018	8.5	---	1729108	397966	T2DM	7
Robledo CA[27]	2015	7	24-28	219952	11334	GDM	8
Fleisch AF[28]	2014	12	31.8	2093	118	GDM	7
Andersen ZJ[29]	2012	9.7	50-65	51818	2877	T2DM	8
Malmqvist E[30]	2013	6	25+	81110	1599	GDM	8
Puett RC[31]	2011	23	40-75	15048	688	T2DM	8
			30-55	74412	3784	T2DM	

Table 2.Sensitivity analysis.

	Before sensitivity analysis	Removed article	After sensitivity analysis
PM_{10} and diabetes	1.00 [0.99, 1.02]	Renzi M 2018[2]	1.01 [0.98, 1.03]
$PM_{2.5}$ and diabetes	1.02 [1.01, 1.04]	Charlotte C 2017[4]	1.03 [1.01, 1.05]
NO_X and diabetes	1.01 [1.00, 1.01]	Renzi M 2018[2]	1.02 [1.00, 1.03]
NO_2 and diabetes	1.01 [1.00, 1.01]	Renzi M 2018[2]	1.01 [0.99, 1.02]

Figures

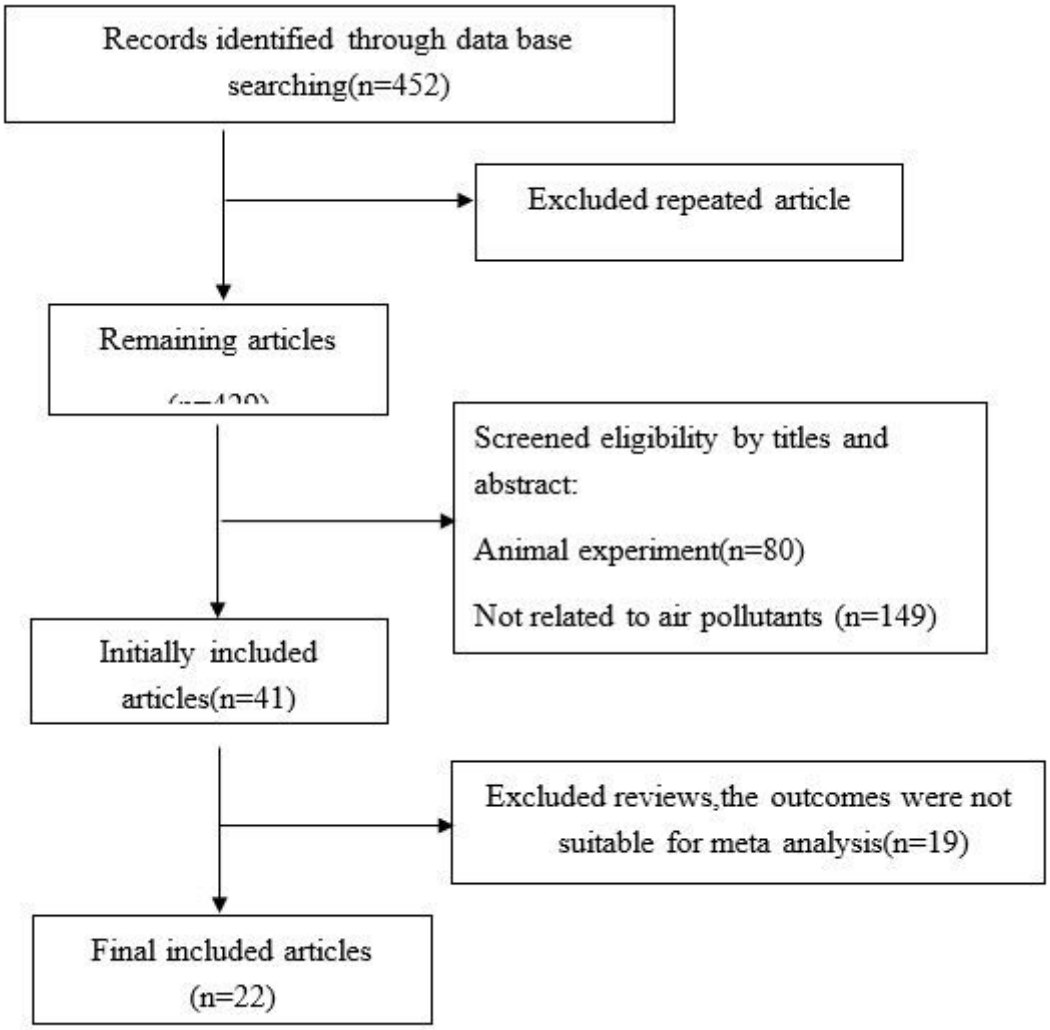

Figure 1

Flow diagram of studies identified, included, and excluded.

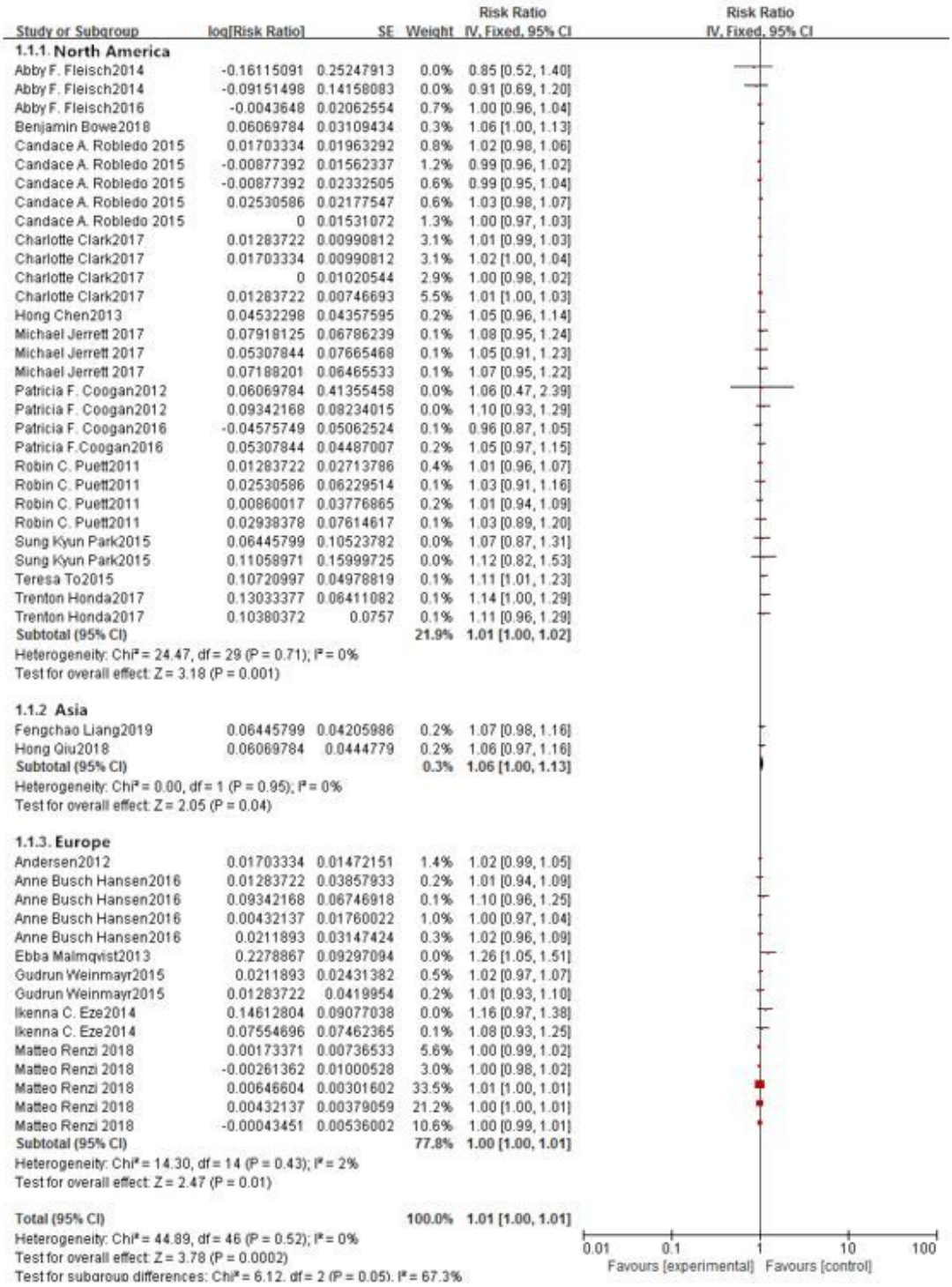

Figure 2

Forest plots of air pollutants and diabetes risk.

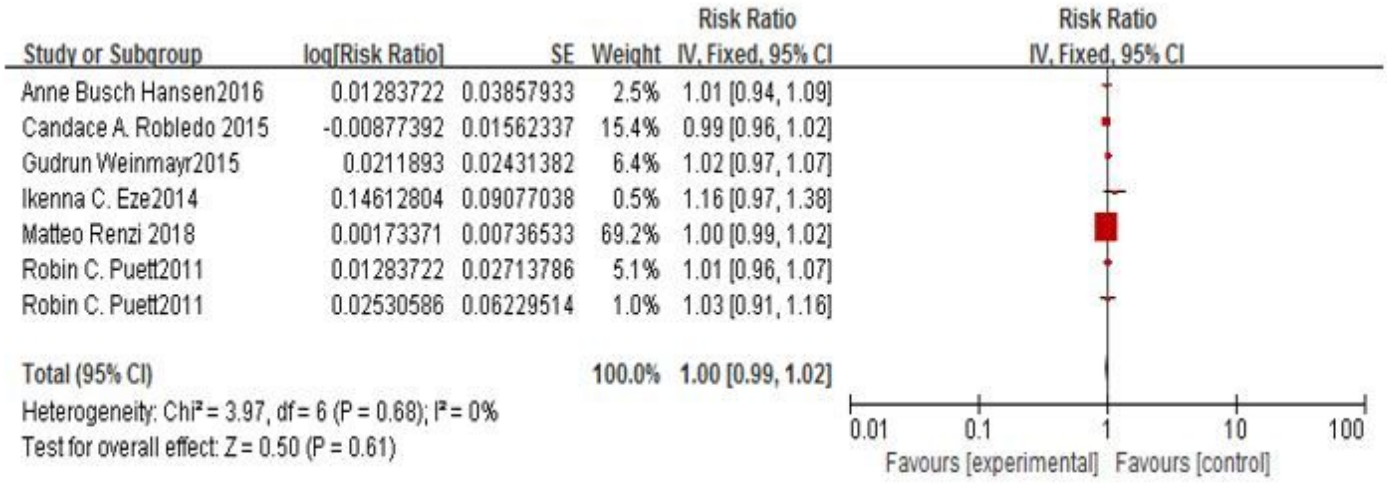

Figure 3

Forest plots of PM10 and risk of diabetes.

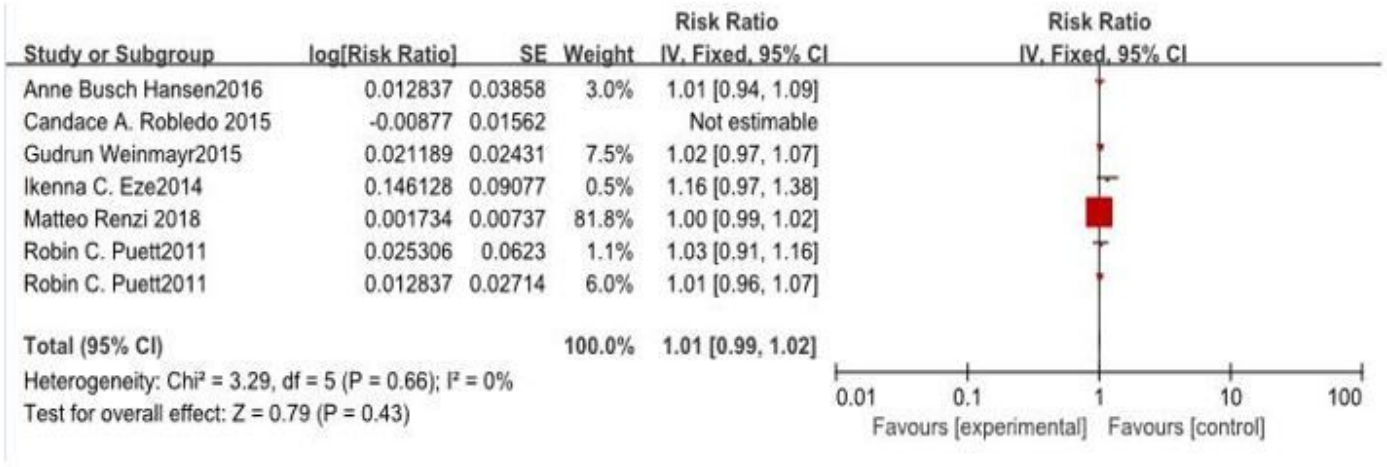

Figure 4

Forest plots of the relationship between PM10 and risk of type 2 diabetes.

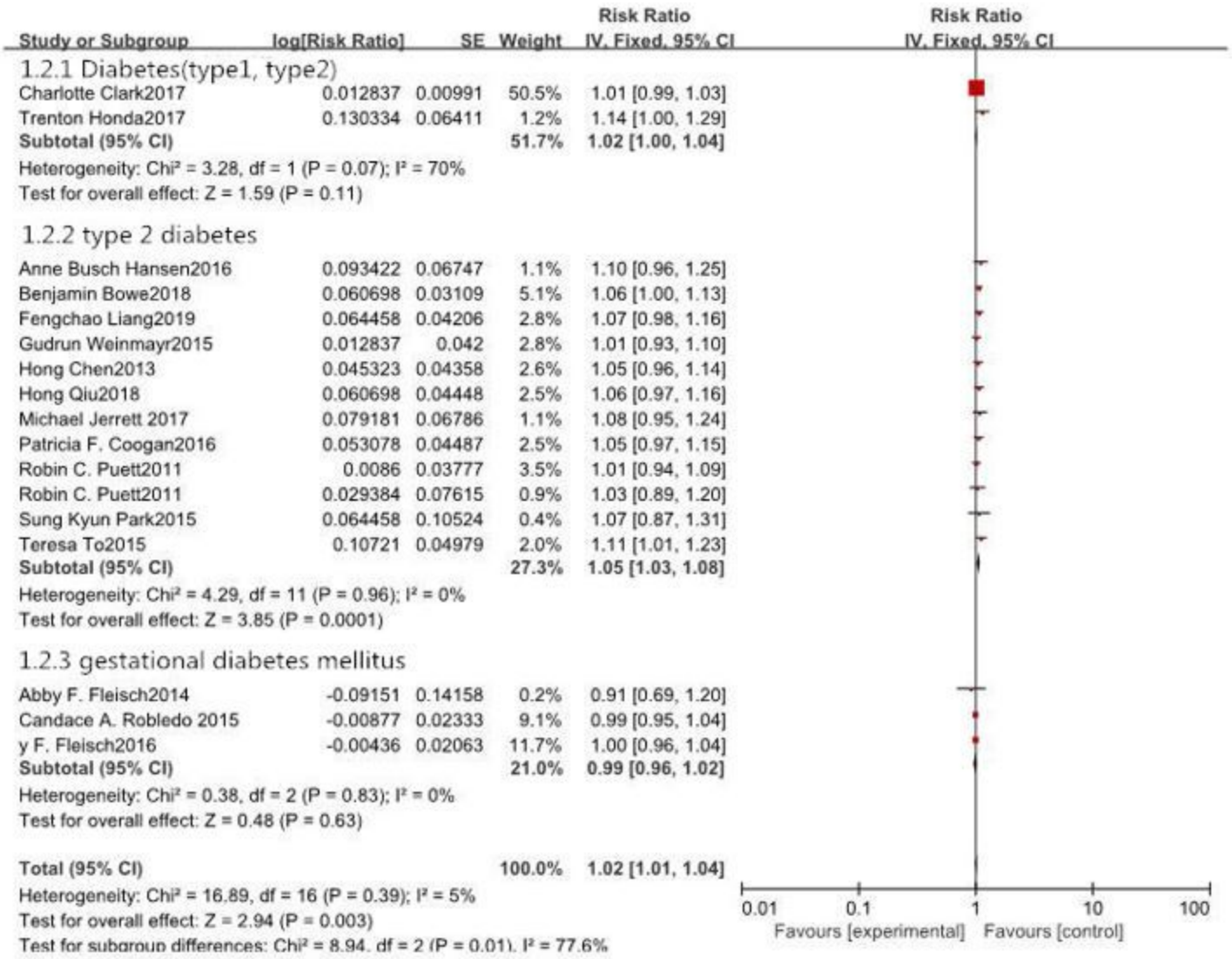

Figure 5

Forest plot of PM2.5 and risk of diabetes.

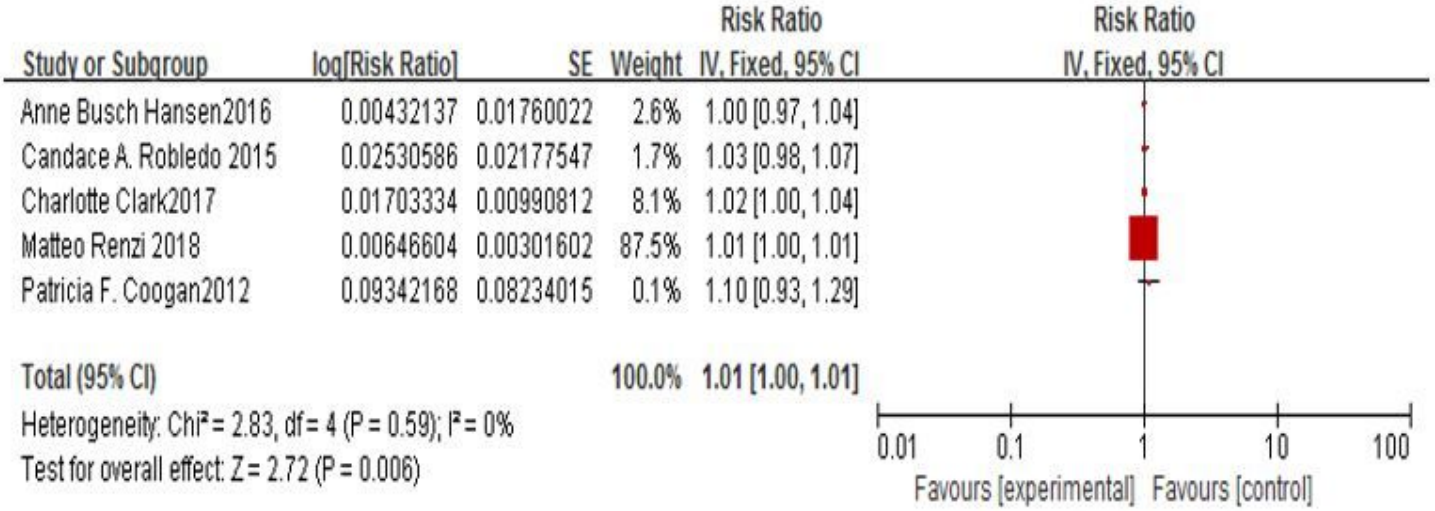

Figure 6

Forest plot of NOx and risk of diabetes.

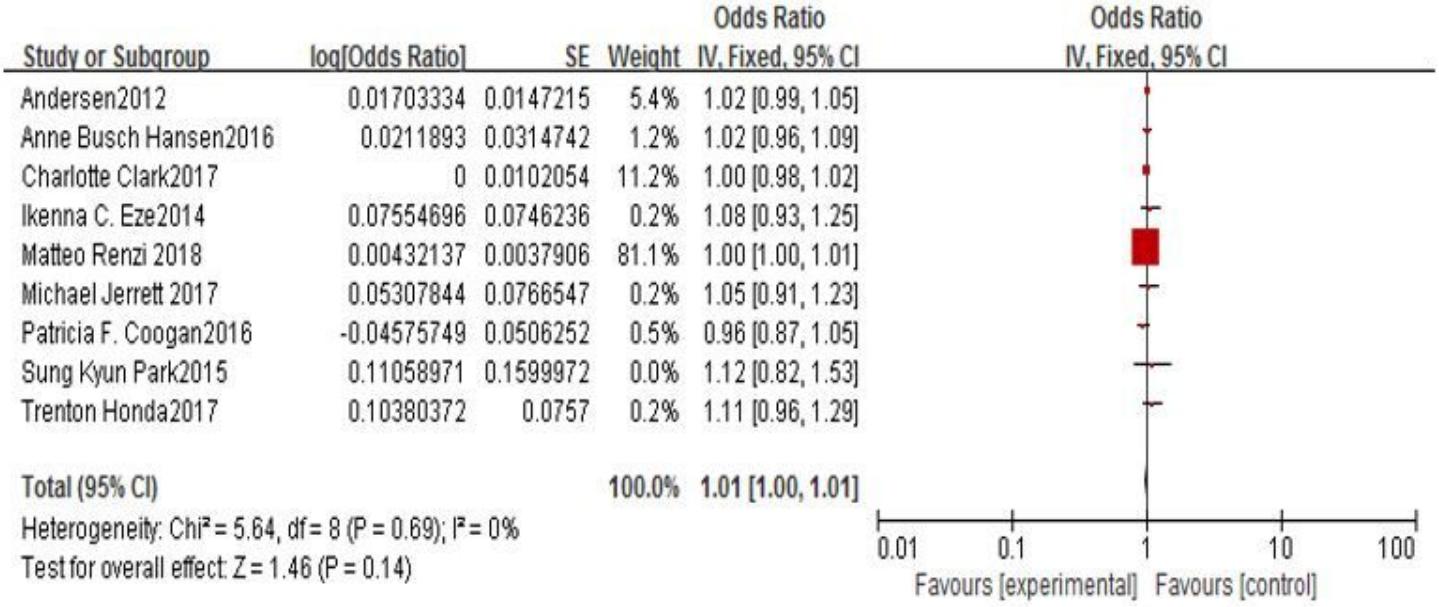

Figure 7

Forest plot of NO2 and risk of diabetes.

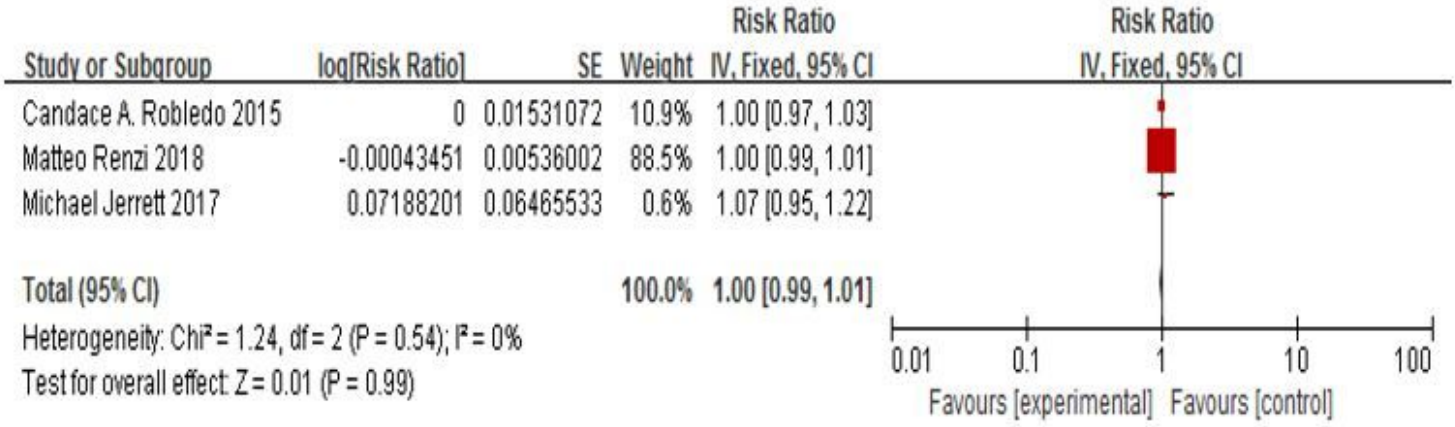

Figure 8

Forest plots of O3 and risk of diabetes.

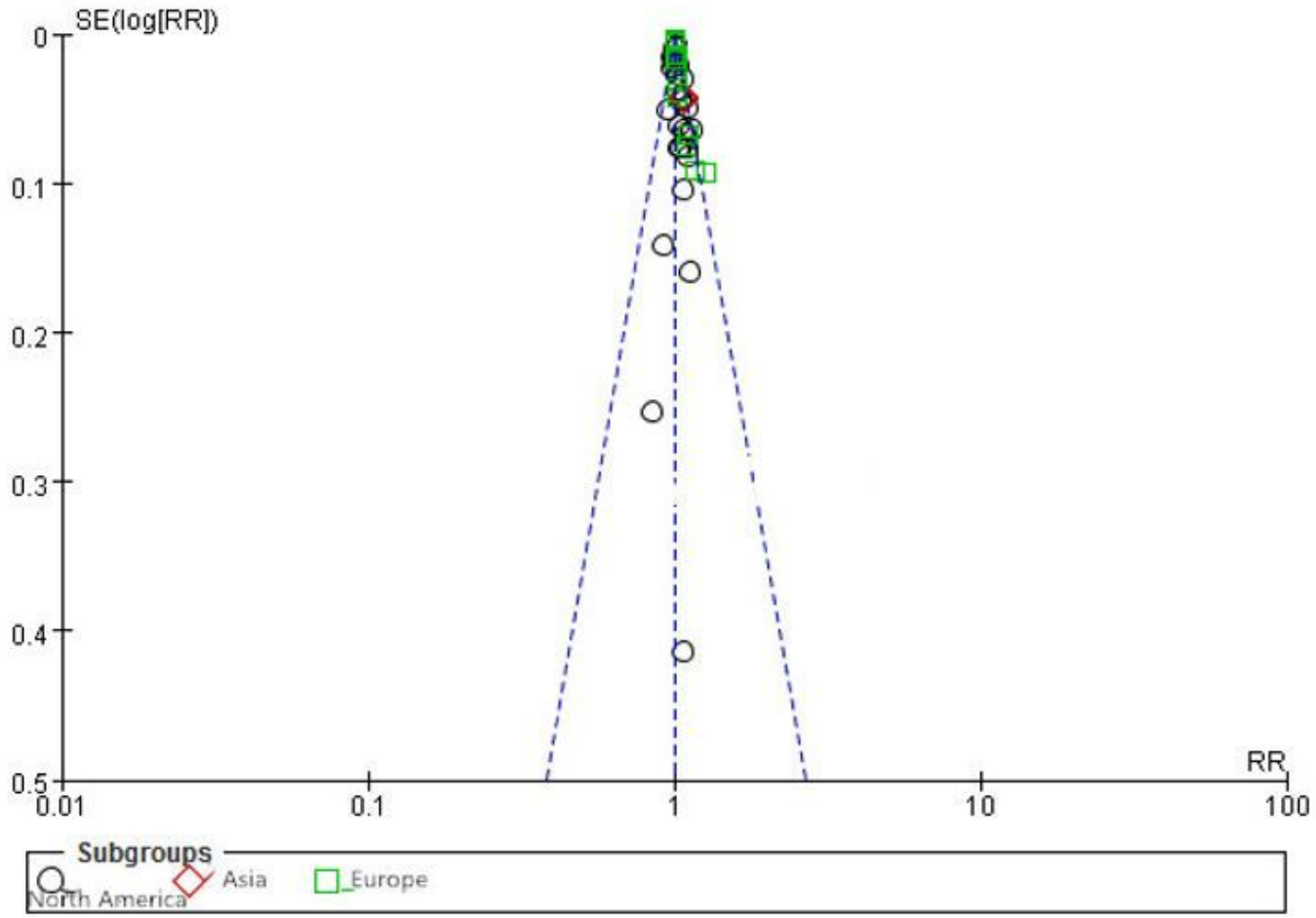

Figure 9

Funnel plots of air pollutants.

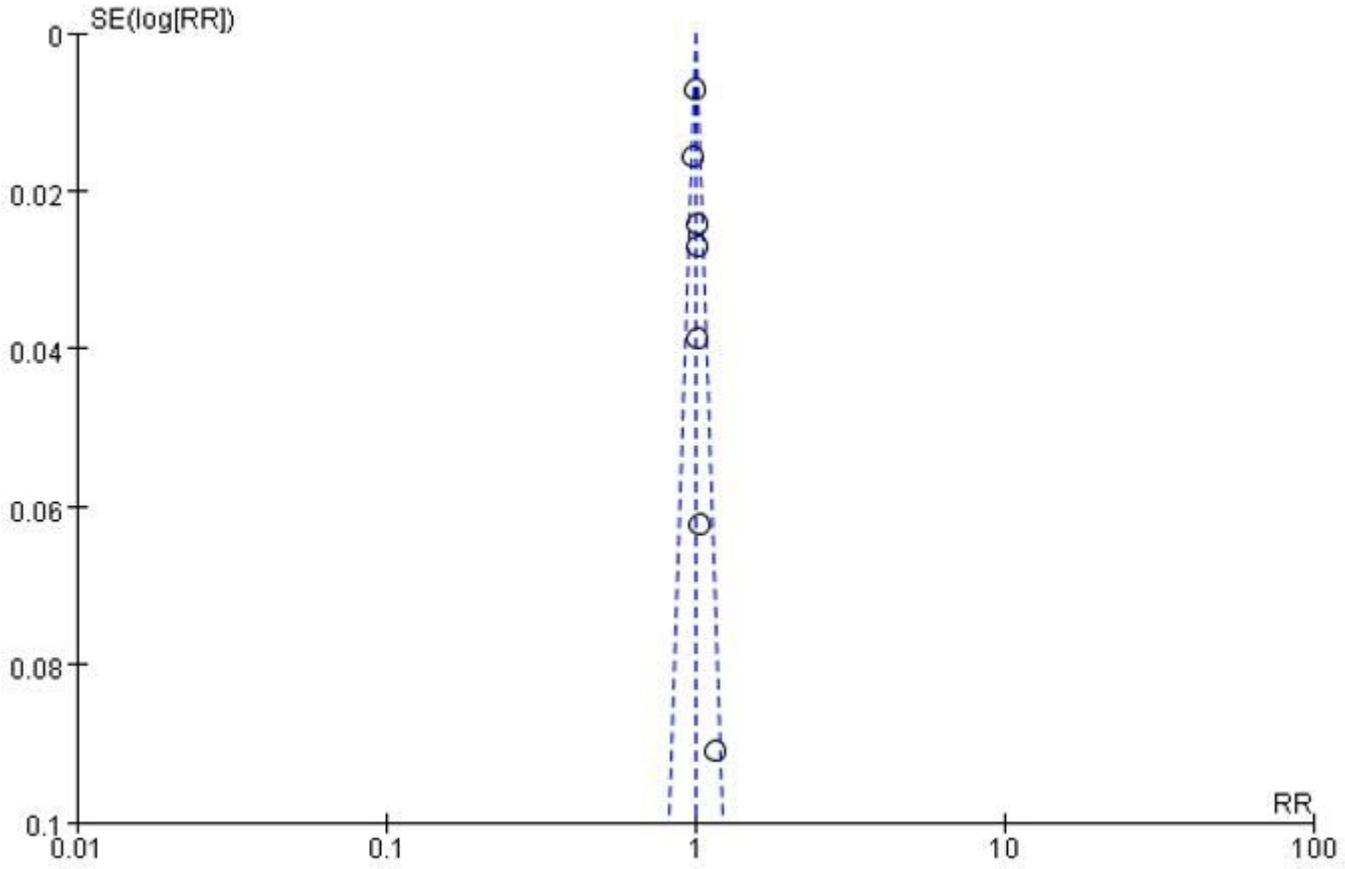

Figure 10

Funnel plots of PM10

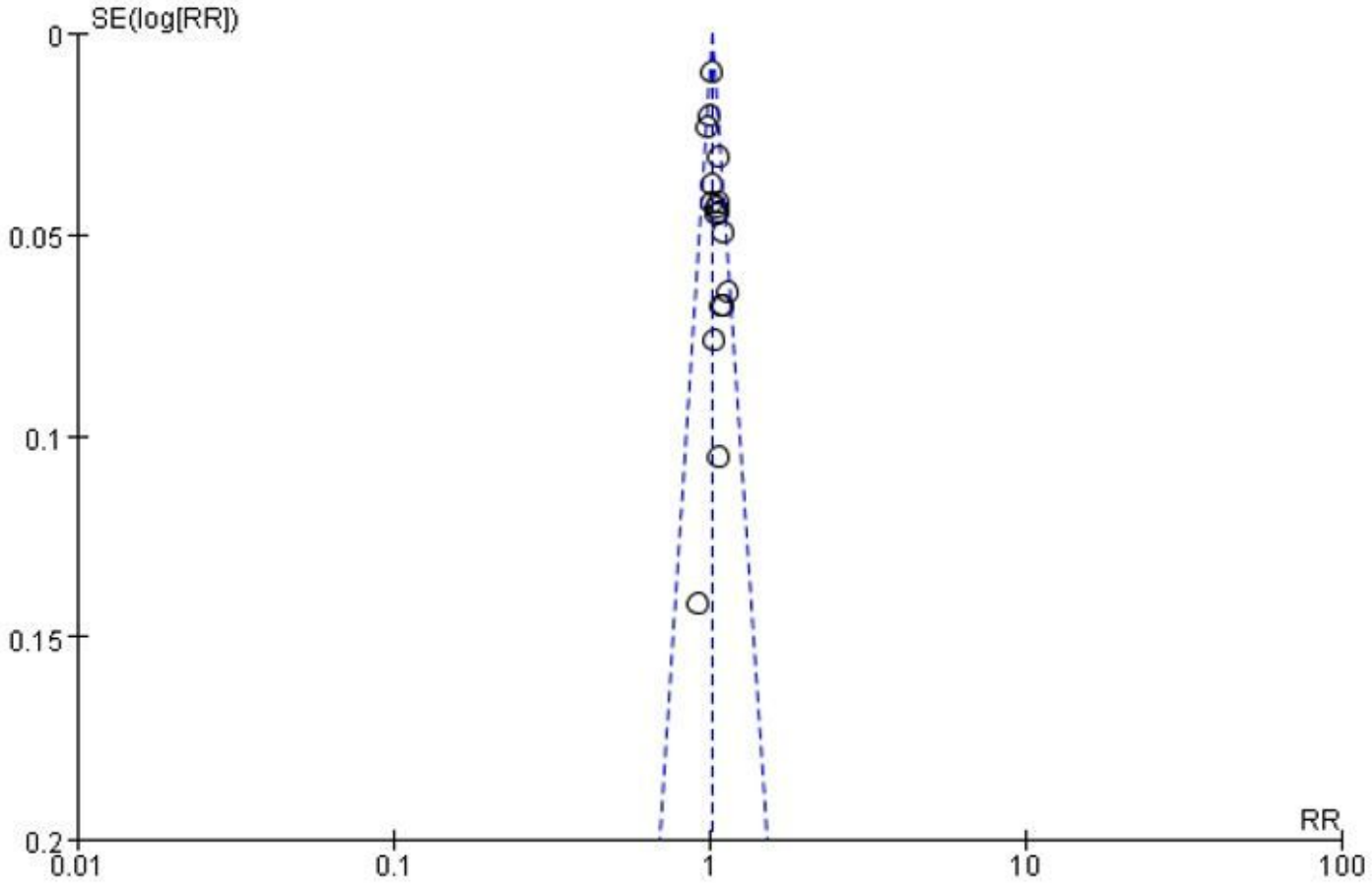

Figure 11

Funnel plots of PM2.5

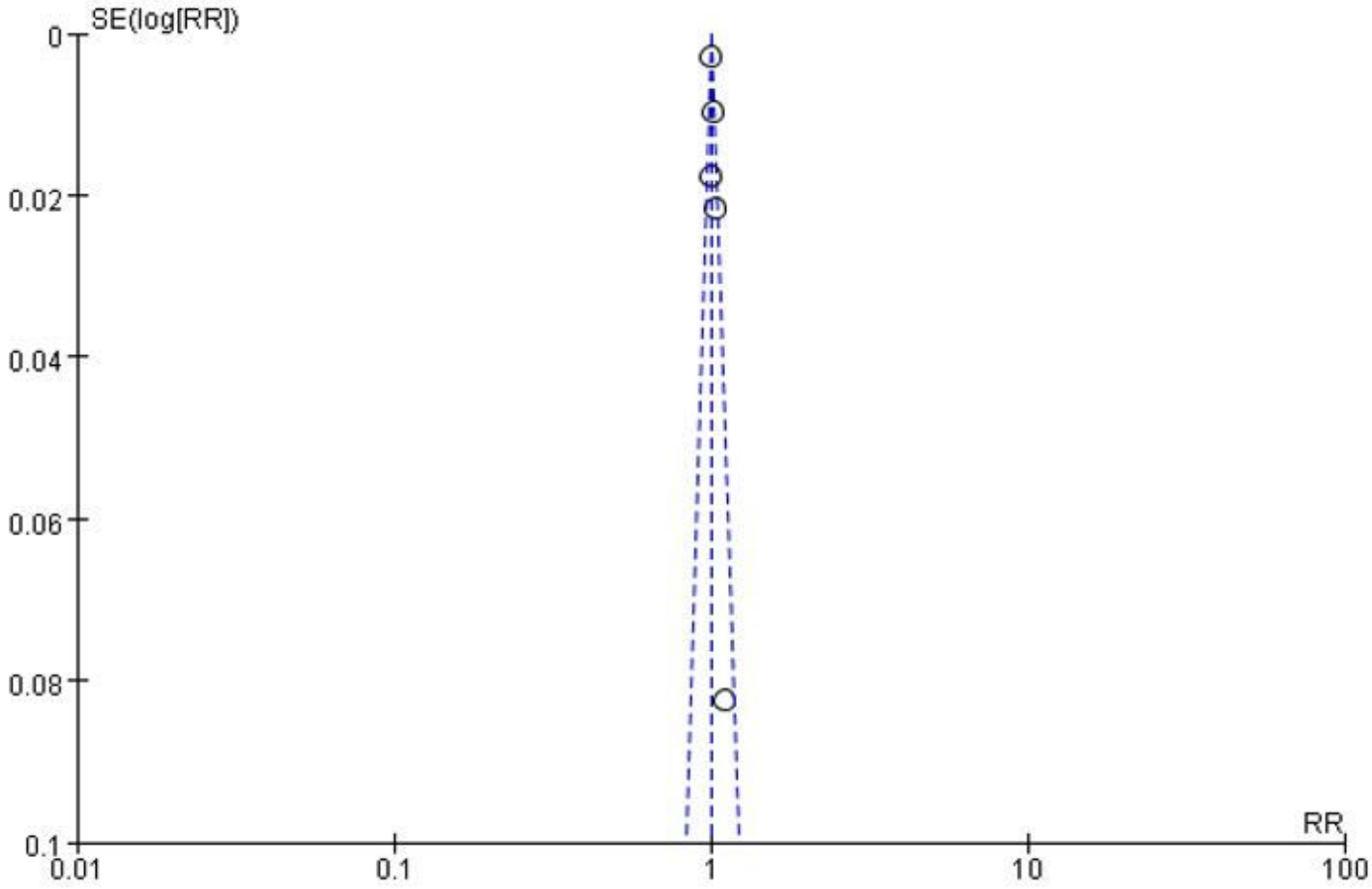

Figure 12

Funnel plots of NOx

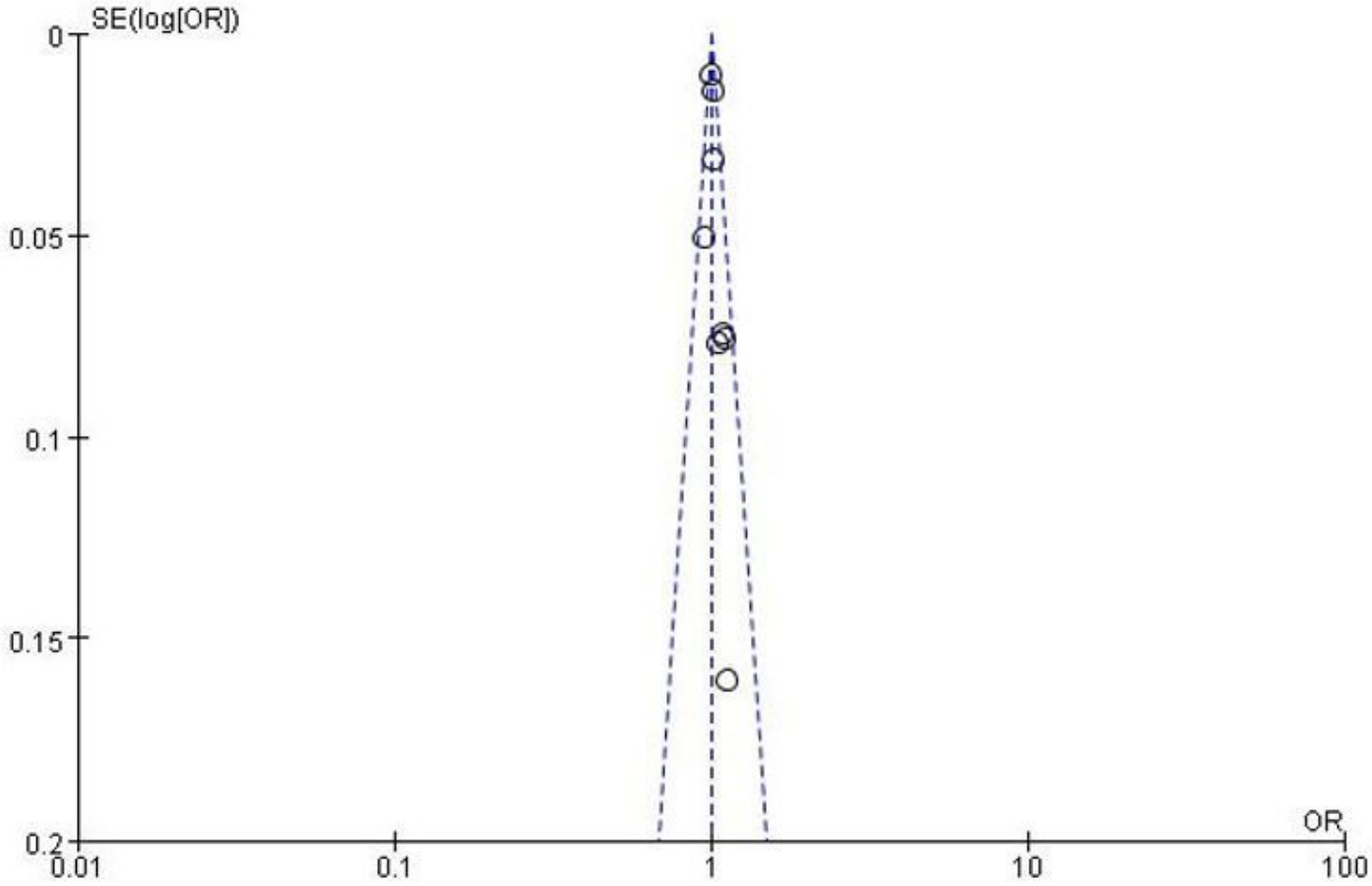

Figure 13

Funnel plots of NO2.