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Association between gestational exposure and risk of orofacial clefts: a systematic review and meta-analysis

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Abstract

Background The occurrence of orofacial Clefts (OFCs) is a congenital disease caused by many factors. According to recent studies, air pollution has a strong correlation with the occurrence of OFCs. However, there are still some controversies about the current research results, and there is no relevant research to review the latest results in recent years.

Objective In this paper, the authors conducted a systematic review and meta-analysis to explore the correlation between ambient air pollution and the occurrence of neonatal OFCs deformity.

Methods We searched Pubmed, Web of science, and Embase databases from the establishment of the database to May 2023. We included observational studies on the relationship between prenatal exposure to fine particulate matter 2.5 (PM2.5), fine particulate matter 10 (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), ozone (O3), carbon monoxide (CO) and the risk of cleft lip (CL), cleft palate (CP), cleft lip with or without palate (CL/P). the Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of the literature. Funnel plot and Egger's regression were used to verify the publication bias. Random effect model or fixed effect model was used to estimate the combined relative risk (RR) and 95% confidence interval (95%CI).

Results A total of eleven studies were included in this study, including four cohort studies and seven case-control studies, including 22,453 cases of OFCs. Ten studies had low risk of bias and only one study had high risk of bias. Three studies reported that $PM_{2.5}$ was positively correlated with CL and CP, with a combined RR and 95%CI of 1.287(1.174,1.411) and 1.267 (1.105,1.454). Two studies reported a positive correlation between O_3 and CL, with a combined RR and 95%CI of 1.132(1.047,1.225). Two studies reported a positive correlation between PM_{10} and CL, with a combined RR and 95%CI of 1.108 (1.017,1.206). No association was found between SO_2, CO, NO_2 exposure during pregnancy and the risk of OFCs.

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Conclusion The results of this study showed that there was a significant statistical correlation between exposure to PM_{10}, $PM_{2.5}$, O_3 and the risk of OFCs in the second month of pregnancy. Exposure assessment, research methods and mechanisms need to be further explored.

Keywords Air pollution, Cleft palate, Cleft lip, Gestational exposure, Meta-analysis

Introduction

Birth defects, also known as congenital malformations or congenital diseases, are due to external environmental factors, genetic factors or both leading to structural, functional and metabolic abnormalities in the process of growth and differentiation [1]. OFCs is a common type of birth defect disease. In the global survey report on the prevalence and disease burden of OFCs from 1990 to 2017, about 10.8 million children with OFCs were found, and most of them were distributed in low- and middle-income countries [2].

The incidence of OFCs is very different in countries around the world. From 2006 to 2018, a cross-sectional study of 5.74 million live births in South Korea found that the incidence of OFCs was 19.6/10,000 [3]. From 2007 to 2011, the incidence of CL alone in the United States was 3.1/10,000, the incidence of OFCs was 5.6/10,000, and the incidence of CP alone is 5.9 /10,000 [4]. Compared with other regions, China has a higher incidence of OFCs. From 2015 to 2018, the southern region of China investigated the occurrence of OFCs for four years. It was found that the incidence of OFCs was 7.55/10,000, and the incidence of male children was higher than that of female children. It is considered to be related to the serious pollution of China and the imbalance of economic and medical development [5]. However, the incidence of OFCs in South Africa from 2015 to 2016 was only 3.2/10,000, which may be related to the backward development of the public health system, resulting in a large number of cases not included in the study [6].

Children with OFCs will have many complications due to oral structure problems, such as difficulty in breastfeeding, increased incidence of anemia, and language development disorders [7, 8]. Compared with normal children, children with OFCs are more likely to die from cardiovascular disease [3]. In the Global Burden of Disease (GBI) survey, the disease burden of OFCs from 1990 to 2017 was 652,084 disability-adjusted life years (DALYs). Most of the burden of disease costs occurs in low-and middle-income countries, accounting for about 94.1% of the total cost. This indicates that the occurrence of OFCs will increase the burden of medical resources and social economy [2]. From 2013 to 2018, a survey conducted in South Korea on children with OFCs surgery showed that although the length of hospital stay was slowly decreasing, the number of operations remained basically unchanged, and the cost of hospitalization gradually increased [9]. Relevant studies have shown that air pollution increases the risk of birth defects. In 2005, Beate Ritz et al. used a case-control study to find that with the increase of O_3 exposure dose, the risk of aortic valve defect, pulmonary valve malformation and conotruncal defect increased in a dose-response relationship [10].

A retrospective control study in Ohio, USA, showed that for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the first month of pregnancy, the OR and 95%CI of birth defects were 1.09 (1.01,1.18) [11]. Studies have also shown that air pollutants can increase the risk of diseases such as premature birth and low birth weight [12, 13]. In order to analyze the relationship between air pollutants and the occurrence of OFCs, the author collected the research literature of common air pollutants such as $PM_{2.5}$, PM_{10}, CO and OFCs, and conducted systematic review and meta-analysis to explore the possible correlation between common environmental air pollution and the occurrence of neonatal OFCs.

Materials and methods

Search strategy

According to the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) [14], PubMed, Embase and Web of Science databases were searched with the keywords of "air pollution", "particulate matter", "sulfur dioxide", "nitrogen dioxide", "carbon monoxide", "ozone", "cleft lip", "orofacial Clefts", "cleft palate", "cleft lip with or without cleft palate". See supplementary materials for retrieval criteria. The search time was from the establishment of the database to May 30,2023.

Study selection

Studies were selected according to the following criteria: [1] The study included exposure to PM_{10}, $PM_{2.5}$, SO_2 and other common air pollutants during pregnancy; [2] The types of included studies were cohort studies and case-control studies, while reviews, case reports, and conference proceedings were not included [3]. The study data included OR, RR and 95%CI [4]. All the literature is in English. Two authors independently searched the literature and resolved the differences through discussion.

Data extraction and quality assessment

Two authors extracted the following information from the retrieved literature: first author, study design method, publication year, study location, study duration, sample size, exposure time, exposure method, related covariates,

OR, RR and 95%CI. The Newcastle-Ottawa quality assessment scale (NOS) was used by two authors to independently evaluate the quality of the literature, with a total score of 9 points. There were three main evaluation criteria: selection of subjects, comparability between groups, and measurement of exposure factors [15]. If at least two of the three evaluations meet the evaluation criteria, the study will be considered to have a low risk of bias [16, 17].

Statistical analysis

First, we used the funnel plot and Egger's test to verify the publication bias, and $P<0.1$ indicated that there was publication bias. Secondly, when extracting the RR value, we chose the RR value in the single pollutant model, because not all studies have adjusted other pollutants as covariates, and there is a certain collinearity between multiple pollutants [18]. Heterogeneity was assessed by chi-square test and inconsistency coefficient I^2. When $P>0.1$ and $I^2 \leq 40$, the fixed effect model was used to evaluate the RR value. Otherwise, we use the random effects model [19]. Finally, we selected the literature with low quality in the group with high heterogeneity ($I^2>40$) and no publication bias for sensitivity analysis.

In addition, the literature we included has the problem of different exposure time. Excluding the potential impact of exposure time, we chose the most critical period of facial partialization and development. The 5–10 weeks of gestation and the second month of gestation mentioned in the most literature are the most critical period for the differentiation and development of OFCs. We use these periods as an exposure period [20, 21]. All analyses were performed using STATA 16.0. Bilateral test was used, and $P<0.05$ indicated that the difference was statistically significant.

Results

Literature selection

By searching the database, we retrieved 353 articles, deleted 95 duplicate articles, read the titles and abstracts of the remaining 258 articles, and deleted 194 articles according to the criteria set above. The remaining 64 articles were further evaluated. After full-text reading, 53 articles that did not meet the requirements were excluded, including 22 articles on animal experiments, 28 articles on reviews, conferences, and case reports, and 3 articles on lack of data evaluation. Finally, 11 articles were included in the study [10, 22–31](Fig. 1).

Study characteristics

In this paper, 11 articles were included, including a total of 22,453 children. All research data were from the birth defect registration system and hospital monitoring system, including all children with live births, stillbirths or
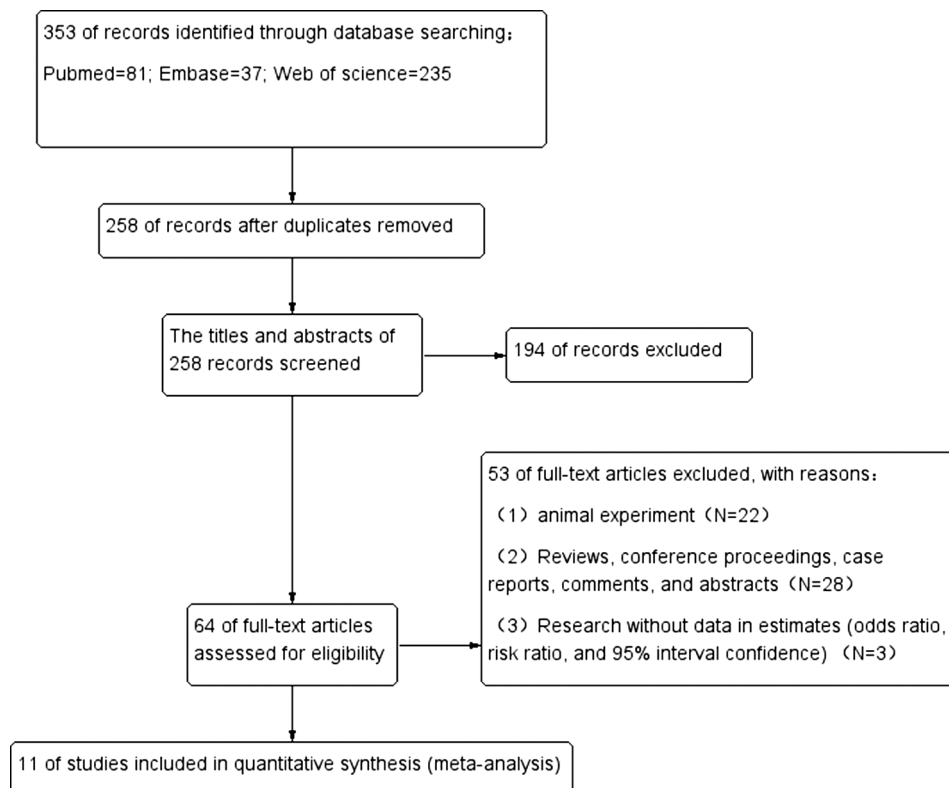

Fig. 1 Flow chart of the study selection process

selective termination of pregnancy. Of the 11 studies, 7 were case-control designs and 4 were cohort studies. 5 studies were from the United States, 4 from China, and 2 from other regions and countries. The study time ranged from 1997 to 2018. The time window of air pollutant exposure was mainly concentrated in the first 3 months of pregnancy, and the risk of OFCs was mainly concentrated in the first 2 months of pregnancy (Table 1).

Quality assessment

The NOs was used to evaluate the quality of the included articles. The scores were between 6 and 8 points, and the average score of the NOs was 7 points. The specific scores are shown in Table 2. For PM10, groups with highest heterogeneity was "PM10-CP", I^2 was 79.0%. For PM2.5, groups with highest heterogeneity was "PM2.5-CL/P", I^2 were 86.9%. For O_3, groups with highest heterogeneity was "O_3-CP", I^2 were 83.7%. No publication bias was found in the results of all groups. The heterogeneity test and publication bias of each group were detailed in Table 3.

Data synthesis

Overview of meta-analyses

For PM_{10}, $PM_{2.5}$, SO_2, O_3 and other air pollutants, we studied the relationship between these pollutants and OFCs. In the preliminary analysis, PM_{10} was positively correlated with CL/P, with RR and 95%CI of 1.108(1.017,1.206). $PM_{2.5}$ was positively correlated with CL and CP, with RR and 95%CI were 1.287(1.174,1.411) and 1.267 (1.105,1.454). O_3 was positively correlated with CL, RR and 95%CI were 1.132(1.047,1.225). There was no significant correlation between residual air pollutants and CL, CP, CL/P (Table 3).

Association between PM10 and OFCs

Seven studies reported the association between PM_{10} exposure during pregnancy and the risk of OFCs. Four of the seven studies reported the association between PM_{10} exposure during pregnancy and the risk of CL. Six of the seven studies reported the association between PM_{10} exposure during pregnancy and the risk of CP. Four of the seven studies reported the association between PM_{10} exposure during pregnancy and the risk of CL/P.

Among the four studies reporting the association between PM_{10} and the risk of CL/P, Zhao J et al. observed a significant positive correlation between PM_{10} exposure during pregnancy and the risk of CL/P (RR=1.11, 95%CI= (1.00,1.23)) [24]. The pooled RR=1.108, 95%CI= (1.017,1.206), heterogeneity was low (I^2=44.3%), (Table 3), Egger's test did not detect publication bias (*P*=0.652). In the study of the association between PM_{10} and the risk of CL/P, no significant association between PM_{10} and the risk of CL/P was found.

Association between PM2.5 and OFCs

Five studies reported the correlation between $PM_{2.5}$ exposure during pregnancy and the risk of OFCs. Two of the five articles studied the relationship between $PM_{2.5}$ exposure during pregnancy and the incidence of CL. Five studies studied the relationship between $PM_{2.5}$ exposure during pregnancy and CP, CL/P.

In the literature on the association between $PM_{2.5}$ exposure during pregnancy and the risk of CL, Zhao J et al. observed a significant positive correlation between $PM_{2.5}$ exposure during pregnancy and the risk of CL, with RR=1.29, 95%CI= (1.171,1.421), and the combined RR=1.287, 95%CI= (1.174,1.411) [24]. Similarly, in the literature on the association between exposure to $PM_{2.5}$ during pregnancy and the risk of CP, Zhao et al., Zhu et al., Zhou et al. observed a significant positive correlation between $PM_{2.5}$ and the risk of CP [24, 27, 28]. The combined results of 5 studies showed that for every 1 μg/m³ increase in $PM_{2.5}$ exposure in the second month of pregnancy, the risk increased by 26.7%, 95%CI= (1.105,1.454) and the heterogeneity was high(I^2=72.4%), Egger 's test did not detect publication bias (*P*=0.704) (Table 3). Due to the poor quality of Zhu Y et al. 's research literature, we excluded it. The final study combined RR=1.226, 95%CI= (1.088,1.381), I^2=63.5%, Egger's test (*P*=0.720), heterogeneity decreased, and no publication bias was detected. In the association study between $PM_{2.5}$ and the risk of CL/P, no significant association was found between $PM_{2.5}$ and the occurrence of CL/P.

Association between SO2 and OFCs

Eight studies reported the correlation between exposure to SO_2 during pregnancy and the risk of OFCs. Four of the eight articles studied the relationship between exposure to SO_2 during pregnancy and the incidence of CL. Six of the eight articles studied the relationship between SO_2 and CP, CL/P.

In the literature on the association between SO_2 exposure during pregnancy and the risk of CL/P, Jiang W et al. observed a significant positive correlation between SO_2 exposure during pregnancy and the risk of CL/P, with RR=1.350, 95%CI=(1.140,1.610), and the remaining correlation was found in the remaining five articles [23]. The combined RR=1.111, 95%CI= (0.956,1.291) was not statistically significant. In the study of the association between SO_2 and the risk of CL/P, no significant association was found between SO_2 and the occurrence of CL/P (Table 3).

Association between O3 and OFCs

Eight studies reported the correlation between exposure to O_3 during pregnancy and the risk of OFCs. Three of the eight articles studied the relationship between exposure to O_3 during pregnancy and the incidence of CL.

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Table 1 Characteristics of the studies in the review

author(year)	Exposure period	Pollutant(s)	Study design	Exposure assessment	Statistical method	Adjustment variables	Data source	Period	Total Number	Case number	Location
Gilboa SM et al.(2005)	Weeks 3–8 of pregnancy	PM10、O3、CO、SO2、NO2	Case-control	Air pollutants data from the nearest monitoring station	Logistic regression models	Alcohol consumption or smoking during pregnancy, maternal gravidity, maternal age, maternal education, maternal illness, maternal race/ethnicity, parity, plurality, prenatal care, season of conception and so on.	The Texas Birth Defects Registry provided data on birth defect diagnoses for 7,381 livebirths and fetal deaths of infants	1997–2000	607500	293	USA
Hwang BF et al.(2008)	First trimester	PM10、O3、CO、SO2、NOx	Case-control	The inverse distance weighting method	Logistic regression models	Sex of infant, maternal age, plurality, gestational age and season of conception.	The Taiwanese Birth Registry from 2001 through 2003	2001–2003	721289	653	Taiwan
Hansen CA et al.(2009)	Weeks 3–8 of pregnancy	PM10、O3、CO、SO2、NO2	Case-control	Air pollutants data from the nearest monitoring station	Conditional logistic regression	neonate gender	The Queensland Health Perinatal Data Collection Unit	1997–2004	150308	none	Australia
Marshall EG et al.(2010)	Weeks 3–8 of pregnancy	PM2.5、PM10、O3、CO、SO2、NO2	Case-control	Air pollutants data from the nearest monitoring station	Logistic regression models	mother's age, race, ethnicity, smoking and drinking alcohol during pregnancy, and season of conception	The New Jersey Department of Health and Senior Services (NJDHSS) Special Child Health Services registry.	1998–2003	690000	717	USA
Zhu Y et al.(2015)	Weeks 3–8 of pregnancy and the 3 months pre-pregnancy	PM2.5、PM10、O3、CO、SO2、Nox	Cohort	The inverse distance weighting method	Logistic regression models	site/region, maternal age, race, marital status, insurance, pregnancy body mass index, nulliparity, smoking and/or alcohol consumption during pregnancy and so on.	The Consortium on Safe Labor included 12 clinical centers	2002–2008	188102	159	USA

Table 1 (continued)

author(year)	Exposure period	Pollutant(s)	Study design	Statistical method	Adjustment variables	Data source	Period	Total Number	Case number	Location
Tanner JP et al. (2015)	Weeks 3–8 of pregnancy	PM2.5、benzene	Cohort	Multi-variable Poisson regression	Maternal race/ethnicity, Maternal age, Maternal education, Maternal marital status, Parity	The Florida Birth Defects Registry	2000–2009	2123874	923	USA
Zhou Y et al. (2017)	Weeks 5–10 of pregnancy	PM2.5、O3	Case-control	Conditional logistic regression	infant sex, maternal race and ethnicity, maternal education, smoking status during pregnancy, mother's age, and parity.	The National Birth Defects Prevention Network (NBDPN) and the Centers for Disease Control and Prevention (CDC).	2001–2007	4697523	7035	USA
Zhao J et al. (2018)	First trimester	PM2.5、PM10、O3、CO、SO2	Cohort	Multivariate logistic regression models	maternal ages, education levels, infant sexes, parities, the season of conception, the air temperature, the humidity, and the air pressure.	The Wuhan Maternal and Child Health Management Information System	2011–2013	108167	133	China
Wang L et al. (2019)	First trimester	SO2、NO2、PM10	Cohort	Poisson generalized additive model	long-time trend, seasonality, temperature and relative humidity	The Xi'an Birth Defects Monitoring System	2010–2015	755551	8865	China
Jiang W et al. (2021)	First trimester	CO、NO2、SO2、O3、PM2.5、PM10	Case-control	Multivariate logistic regression models	maternal age、maternal educational level、gravidity、infant sex, plurality, temperature and relative humidity.	The hospital based birth defect monitoring (HBBDM) system of Hunan Province and the electronic medical records (EMR)	2015–2018	none	589	China

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Table 1 (continued)

author(year)	Exposure period	Pollutant(s)	Study design	Statistical method	Adjustment variables	Exposure assessment	Data source	Period	Total Number	Case number	Location
Liu FH et al.(2021)	First trimester and the 3 months pre-pregnancy	SO_2	Case-control	Univariate logistic regression	maternal age, education, season of conception and the mean levels of PM10, as well as NO2 during the same period.	The mean concentration of all air monitoring stations in the city	14 city institutions of maternal and child health.	2010–2015	1365000	3086	China

Seven of the eight articles studied the relationship with CP, CL/P.

In the literature on the association between exposure to O_3 during pregnancy and the risk of CL, Zhao J et al. and Hwang BF et al. observed a significant positive correlation between exposure to O_3 during pregnancy and the risk of CL, with RR of 1.120 and 1.220, 95%CI of (1.020,1.220) and (1.030,1.460), respectively. The combined RR of the three studies was 1.132, 95%CI= (1.047,1.225), and the heterogeneity was moderate(I^2=67.9%), Egger 's test (*P*=0.793) did not detect publication bias (Table 3) [24, 29]. In the literature on the association between exposure to O_3 during pregnancy and the risk of CP, two articles reported a significant positive association, five articles reported an insignificant association, and the combined effect estimate was close to one, but not statistically significant. In the study of the association between O_3 and the risk of CL/P, no significant association between O_3 and the risk of CL/P was found (Table 3).

Association between CO and OFCs

Seven studies reported the association between exposure to CO during pregnancy and the risk of OFCs, three of the seven articles studied the relationship between exposure to CO during pregnancy and the risk of CL, and six articles studied the relationship between exposure to CO during pregnancy and the risk of CP, CL/P.

In the literature on the association between CO exposure during pregnancy and the risk of CL, Zhao J et al. observed a significant positive correlation between CO exposure during pregnancy and the risk of CL, with RR=1.240, 95%CI= (1.110,1.40) [24]. The combined RR=1.057, 95%CI= (0.865,1.291) was not statistically significant. In the literature on the association between CO exposure during pregnancy and the risk of CP, Zhu Y et al. observed that there was a significant positive correlation between CO exposure during pregnancy and the risk of CP. For every 1 μg/m^3 increase in CO exposure in the second month of pregnancy, the risk increased by 174%, 95%CI= (1.620,4.620), and no significant correlation was found in the remaining articles [27]. The combined RR=1.048, 95%CI= (0.714,1.539) was not statistically significant. No significant association was found between CO and the risk of CL/P (Table 3).

Association between NO2 and OFCs

Seven studies reported the correlation between NO_2 exposure during pregnancy and the risk of OFCs. Two of the seven articles studied the relationship between NO_2 exposure during pregnancy and the incidence of CL. Six and five studies studied the relationship with CP, CL/P, respectively.

In the literature on the association between NO_2 exposure during pregnancy and the risk of CP, three articles

Table 2 NOs score of studies included in the systematic review and meta-analysis

Study	Selection	Comparability	Outcome/Expose	Total score
Wang L et al.	3	2	2	7
Jiang W et al.	4	1	2	7
Zhao J et al.	4	2	2	8
Marshall EG et al.	4	1	2	7
Hansen CA et al.	4	1	2	7
Zhu Y et al.	3	1	2	6
Zhou Y et al.	4	2	2	8
Hwang BF et al.	4	1	2	7
Liu FH et al.	4	2	2	8
Gilboa SM et al.	3	2	2	7
Tanner JP et al.	4	1	2	7

Table 3 Summary of meta-analysis of studies on air pollutant exposures and OFCs

Air pollutants and OFCs	Studies Included	Summary RR and (95% CI)	I2 (%)	Egger's test P-value
PM10				
CL	22、23、24、27	1.021、(0.978, 1.066)	68.00%	0.252
CP	10、22、23、24、25、29	1.029、(0.947, 1.117)	79.00%	0.446
CL/P	22、24、25、29	1.108、(1.017, 1.206)	44.30%	0.652
PM2.5				
CL	22、30	1.287、(1.174, 1.411)	0.00%	0.826
CP	22、23、25、26、30	1.267、(1.105, 1.454)	72.40%	0.704
CP(sensitivity analysis)	22、23、26、30	1.226、(1.088, 1.381)	63.50%	0.72
CL/P	22、23、25、26、30	1.136、(0.979, 1.317)	86.90%	0.362
SO2				
CL	22、23、24、27	1.070、(0.840, 1.364)	83.70%	0.424
CP	21、22、23、24、25、29	0.887、(0.743, 1.058)	60.30%	0.344
CL/P	21、22、24、25、28、29	1.111、(0.956, 1.291)	81.50%	0.205
O3				
CL	22、24、27	1.132、(1.047, 1.225)	67.90%	0.793
CP	21、22、23、24、25、26、29	1.026、(0.885, 1.190)	82.20%	0.638
CL/P	21、22、23、24、25、26、29	0.993、(0.961, 1.025)	51.60%	0.774
CO				
CL	22、24、27	1.057、(0.865, 1.291)	96.80%	0.824
CP	21、22、23、24、25、29	1.048、(0.714, 1.539)	93.10%	0.737
CL/P	21、22、23、24、25、29	1.175、(0.936, 1.475)	92.90%	0.461
NO2				
CL	24、27	0.976、(0.831, 1.147)	66.60%	0.884
CP	20、21、23、24、25、29	1.201、(0.828, 1.742)	93.20%	0.949
CL/P	21、23、24、25、29	1.187、(0.938, 1.503)	85.30%	0.16

reported a significant positive association, and the other reported an insignificant association. The combined RR=1.201, 95%CI= (0.828,1.742) was not statistically significant. Jiang W et al. observed a significant positive correlation between NO$_2$ exposure during pregnancy and the risk of CL/P, with RR=1.48, 95%CI=(1.250,1.750) [23]. The combined effect estimates were close to one, not statistically significant. No significant association was found between NO$_2$ and the risk of CL.

Discussion

Our results showed that there was a significant positive correlation between exposure to PM$_{2.5}$, PM$_{10}$, O$_3$ in the second month of pregnancy and the risk of CL/P. Among them, PM$_{10}$ was associated with an increased risk of CL/P. This is consistent with the results of Rao A et al. 's previous meta-analysis that O$_3$ increases the risk of OFCs [32].

In 2016, the results of the global death factor survey showed that air pollutants were the sixth leading cause of death, and 7.5% of global deaths were attributed to ambient air pollution. The countries with higher deaths included China and India [33]. PM can be emitted

directly from sources such as construction sites, roads, fields, chimneys, or formed by complex reactions of chemicals such as sulfur dioxide and nitrogen oxides. PM consists of hundreds of different chemicals [34]. Relevant studies have found that particulate pollutants can freely pass through the placenta and accumulate on the side of the fetus by comparing the levels of particulate pollutants on both sides of the placenta under different exposure levels of particulate pollutants [35]. PM may exert its adverse effects by directly acting as a pro-oxidant or free radical generator for lipids and proteins, promoting oxidative stress and inducing inflammatory responses [36, 37].

Ozone (O_3) is a photochemical environmental pollutant affected by climate. It is easy to form when the temperature fluctuates greatly [38]. Studies have shown that high concentrations of ozone pollution can lead to adverse health effects and increase the morbidity and mortality of respiratory and cardiovascular systems [39–42]. This is consistent with our results that there is a significant positive correlation between exposure to $PM_{2.5}$, PM_{10}, O_3 and the risk of OFCs during the critical period of pregnancy.

There are many reasons for the occurrence of OFCs, including genetics, environment and their combined effects. The combination of genetics and environment is called "epigenetics" [43]. Related studies have shown that low-income families, pesticide exposure history, smoking during pregnancy, gestational diabetes, and heavy metal exposure history such as Pb(lead), Cd (cadmium), and Sr(strontium) are all high-risk risks of OFCs. The reasonable supplement of vitamin, potassium and calcium during pregnancy is a protective factor to reduce the occurrence of OFCs [44–47]. However, due to the limitation of the number of studies included in this paper and the difference in the quality of the literature, Hansen CA et al. only adjusted the gestational age as a covariate, and lacked corrections for other covariates, which would lead to deviations in the analysis results [26].

Whether the address change during pregnancy will affect the accuracy of the results, many scientists have studied it. Two cohort studies in the United States have shown that the address registered at birth can well replace the residential address during pregnancy. The exposure concentration of air pollutants will not be significantly different due to the difference between the registration address at birth and the residence address during pregnancy [48, 49]. But a cohort study in China 's Gansu province found that people who moved were less likely to have adverse birth outcomes than those who did not [50]. Most pregnant women have no movement during pregnancy, and a few pregnant women have short-distance movement during pregnancy. Using the registration address at birth, there may be registration

errors. However, there is no significant difference in the exposure concentration of air pollutants during pregnancy, so the address registered at the birth of the fetus can be a good substitute for the residential address during pregnancy [51].

Our study has several advantages. First, we conducted a systematic review and meta-analysis. Compared with individual studies, the evidence level of systematic reviews and meta-analysis is relatively high. Second, we divided OFCs into CL, CP, CL/P and analyzed them with air pollutants respectively. Finally, among the 11 articles we included, 10 studies were low risk of bias and only 1 study was high risk of bias. After adjusting for them, we found that the heterogeneity was lower than before.

There are some limitations in our research. First of all, we study the high heterogeneity between some literatures, which is related to the limited number of literatures, different geographical locations, different exposure methods, and large research time span. Secondly, there may be differences in the diagnosis of diseases in different studies. There are no trained nurses to inquire about prenatal exposure factors, and professional doctors use relevant scales to classify and evaluate diseases [52, 53]. Third, in the included literature, there is not enough information for dose response assessment, and we have not been able to assess whether there is a linear relationship between pollutant exposure concentration and the occurrence of OFCs. Fourthly, different studies have different exposure assessment methods. Marshall EG et al., Hansen CA et al. and Liu FH et al. used air quality monitoring stations to monitor the exposure assigned by individuals within a specified radius around, which may lead to measurement errors in exposure concentration, which may cause errors in risk assessment and result deviations [25, 26, 30]. Finally, we used the pregnancy address as the exposure point all studies in this meta-analysis, without considering the possibility of mobility during pregnancy.

Conclusion
In conclusion, the results of this study show that there is a positive correlation between $PM_{2.5}$, PM_{10}, O_3 and OFCs, and there is no statistical significance between residual air pollutants and OFCs. However, this association may be affected by the study area and research-related exposure methods, which are important factors causing heterogeneity, and further large-scale cohort studies are needed to verify this association. It is recommended that future public health work should minimize exposure of pregnant women to related air pollutants.

Supplementary Information

Supplementary Material 1

Data availability
Any data in this study can be obtained from the corresponding author upon reasonable request. The final manuscript was read and approved by all authors.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Lewanda AF. Birth Defects. In: Benson JB, editor. Encyclopedia of Infant and Early Childhood Development (Second Edition). Oxford: Elsevier; 2020. p. 165 – 76.
2. Massenburg BB, Hopper RA, Crowe CS, Morrison SD, Alonso N, Calis M, et al. Global Burden of Orofacial Clefts and the World Surgical workforce. Plast Reconstr Surg. 2021;148(4):568e–80e.
3. Ryu JY, Park TH, Cho BC, Choi KY. The prevalence, risk of premature births, mortality and causes of death of cleft lip with or without palate in South Korea: a nationwide population-based cohort study. Int J Epidemiol. 2022;51(3):974–83.
4. Mai CT, Cassell CH, Meyer RE, Isenburg J, Canfield MA, Rickard R, et al. Birth defects data from population-based birth defects surveillance programs in the United States, 2007 to 2011: highlighting orofacial clefts. Birth Defects Res a Clin Mol Teratol. 2014;100(11):895–904.
5. Zhu Y, Miao H, Zeng Q, Li B, Wang D, Yu X, et al. Prevalence of cleft lip and/ or cleft palate in Guangdong province, China, 2015–2018: a spatio-temporal descriptive analysis. BMJ Open. 2021;11(8):e046430.
6. Hlongwa P, Dandajena TC, Rispel LC. Comparative analysis of healthcare provision to individuals with cleft lip and/or palate at specialised academic centres in South Africa. S Afr Med J. 2019;109(6):426–30.
7. Miranda-Filho AEF, Gomes HS, Silva RBV, Marques NP, Martelli Júnior H, Marques NCT. Do Orofacial Clefts impair breastfeeding and increase the prevalence of Anemia? Cleft Palate Craniofac J. 2023;60(1):63–8.
8. de Araújo LL, Alonso N, Fukushiro AP. Treatment of cleft lip and palate in the Amazon Region in Brazil: Speech results and Sociodemographic aspects. Cleft Palate Craniofac J. 2022;59(5):595–602.
9. Mo YW, Lee DL. Data analysis of recent cleft lip and palate Surgery in Korea using the National Health Insurance Service (NHIS) database. J Plast Reconstr Aesthetic Surg. 2021;74(2):387–95.
10. Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D, et al. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000. Am J Epidemiol. 2005;162(3):238–52.
11. Ren S, Haynes E, Hall E, Hossain M, Chen A, Muglia L, et al. Periconception exposure to Air Pollution and Risk of congenital malformations. J Pediatr. 2018;193:76–84. e6.
12. Lu C, Zhang W, Zheng X. Combined effects of ambient air pollution and home environmental factors on low birth weight. Chemosphere. 2019;240:124836.
13. Lu C, Cao L, Norback D, Li Y, Chen J, Deng Q. Combined effects of traffic air pollution and home environmental factors on preterm birth in China. Ecotoxicol Environ Saf. 2019;184:109639.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
15. Wells G, editor. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies in Meta-Analyses. Symposium on Systematic Reviews: Beyond the Basics; 2014.
16. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of Cardiovascular Disease, renal Disease, and death: systematic review and meta-analysis. BMJ. 2016;354:i4482.
17. Gong TT, Wu QJ, Lin B, Ruan SK, Takimoto M. Observational studies on the Association between Post-diagnostic Metformin Use and Survival in Ovarian Cancer: a systematic review and Meta-analysis. Front Oncol. 2019;9:458.
18. Huang Z, Qiu Y, Qi J, Ma X, Cheng Q, Wu J. Association between air pollutants and birth defects in Xiamen, China. Front Pead. 2023; 11–2023.
19. Mantel NJ, Haenszel WH. Statistical aspects of the analysis of data from retrospective studies of Disease. J Natl Cancer Inst. 1959;22(4):719–48.
20. Tolarova´ M, Cervenka J. Classification and birth prevalence of Orofacial Clefts. Am J Med Genet A. 1998;13(2):126–37.
21. Sperber GH. Craniofacial Embryogenesis: normal developmental mechanisms. 2002 ed. John Wiley & Sons, Inc.; 2003. pp. 31–59.
22. Wang L, Xiang X, Mi B, Song H, Dong M, Zhang S, et al. Association between early prenatal exposure to ambient air pollution and birth defects: evidence from newborns in Xi'an, China. J Public Health. 2019;41(3):494–501.
23. Jiang W, Xie W, Ni B, Zhou H, Liu Z, Li X. First trimester exposure to ambient gaseous air pollutants and risk of orofacial clefts: a case-control study in Changsha, China. BMC Oral Health. 2021;21(1).
24. Zhao J, Zhang B, Yang S, Mei H, Qian Z, Liang S, et al. Maternal exposure to ambient air pollutant and risk of oral clefts in Wuhan, China. Environ Pollut. 2018;238:624–30.
25. Marshall EG, Harris G, Wartenberg D. Oral cleft defects and maternal exposure to ambient air pollutants in New Jersey. Birth Defects Res a Clin Mol Teratol. 2010;88(4):205–15.
26. Hansen CA, Barnett AG, Jalaludin BB, Morgan GG. Ambient air pollution and birth defects in brisbane, Australia. PLoS ONE [Electronic Resource]. 2009;4(4):e5408.
27. Zhu Y, Zhang C, Liu D, Grantz KL, Wallace M, Mendola P. Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. Environ Res. 2015;140:714–20.
28. Zhou Y, Gilboa SM, Herdt ML, Lupo PJ, Flanders WD, Liu Y, et al. Maternal exposure to ozone and PM(2.5) and the prevalence of orofacial clefts in four U.S. states. Environ Res. 2017;153:35–40.
29. Hwang BF, Jaakkola JJ. Ozone and other air pollutants and the risk of oral clefts. Environ Health Perspect. 2008;116(10):1411–5.
30. Liu FH, Xing Z, Gong TT, Zhang JY, Huang YH, Li J, et al. Maternal exposure to sulfur dioxide and the risk of oral clefts in Liaoning Province, China: a population-based case-control study. Environ Sci Pollut Res Int. 2021;28(29):39101–9.
31. Tanner JP, Salemi JL, Stuart AL, Yu H, Jordan MM, DuClos C, et al. Associations between exposure to ambient benzene and PM(2.5) during pregnancy and the risk of selected birth defects in offspring. Environ Res. 2015;142:345–53.
32. Rao A, Ahmed MK, Taub PJ, Mamoun JS. The correlation between maternal exposure to Air Pollution and the risk of Orofacial Clefts in infants: a systematic review and Meta-analysis. J Oral Maxillofacial Res. 2016;7(1):e2.

33. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of Disease Study 2017. Lancet. 2018;392(10159):1923–94.

34. Particulate matter (PM) basics [Internet]. United States Environmental Protection Agency. 2018 [cited 26 March 2019](Available from: https://www.epa.gov/pm-pollution/particulate-matter-pmbasics.).

35. Bove H, Bongaerts E, Slenders E, Bijnens EM, Saenen ND, Gyselaers W, et al. Ambient black carbon particles reach the fetal side of human placenta. Nat Commun. 2019;10(1):3866.

36. Kampa M, Castanas E. Human health effects of air pollution. Environ Pollut. 2008;151(2):362–7.

37. Huang Y, Guo Z, Liu H, Zhang S, Tong Y. Heterojunction Architecture of N-Doped WO3 nanobundles with Ce2S3 nanodots hybridized on a Carbon Textile enables a highly efficient flexible photocatalyst. Adv Funct Mater. 2019;29(45).

38. Shi CCJLWSTLX. Temperature-modified Acute effects of ozone on human mortality - Beijing Municipality, Tianjin Municipality, Hebei Province, and surrounding areas, China, 2013–2018. China CDC Wkly. 2021;3(45):964–8.

39. Bm A, Rm A, Pa B, Ra A. Ozone pollution, oxidative stress, synaptic plasticity, and neurodegeneration. 2021.

40. C YWAB, B OW AXC, D QW EMG. A HC, Health impacts of long-term ozone exposure in China over 2013–2017. Environ Int. 2020;144.

41. Chen Y, Li Q, Karimian H, Chen X, Li X. Spatio-temporal distribution characteristics and influencing factors of COVID-19 in China. Sci Rep. 2021;11(1):3717.

42. Mullins, Jamie T. Ambient air pollution and human performance: contemporaneous and acclimatization effects of ozone exposure on athletic performance. Health Econ. 2018.

43. Garland MA-O, Sun B, Zhang S, Reynolds KA-O, Ji Y, Zhou CA-O. Role of epigenetics and miRNAs in o rofacial clefts. Birth Defects Research. 2020(2472 – 1727).

44. Silvestre CMR, Silva Amc Fau - Ferreira, da Silva RCG et al. Ferreira da Silva Rcg Fau - Bittencourt WS, Bittencourt Ws Fau - Borba AM, Borba Am Fau - Fernandes V, Fernandes V Fau - da Silva CAL,. Environmental Factors at the Periconceptional Period and the Occurrence of Cleft Lip and Palate in a Midwest Brazil Population: A Case-Control Study. J Occup Environ Med. 2022 Nov(1536–5948 (Electronic)).

45. Oginawati K, Susetyo SH, Cahyani ZN, Fahimah N. Investigation of exposure to heavy metals (hg, Pb, Cd, Co, and cr) as the cause of congenital anomaly cases (orofacial cleft) in infants. Environ Sci Pollut Res. 2022;29(54):82169–85.

46. Yin S, Wei J, Wang C, Jin L, Wang L, Li Z, et al. Alkali and alkaline earth elements in maternal serum and occurrence of orofacial clefts in offspring. Reprod Toxicol. 2022;110:97–104.

47. Vu GH, Warden C, Zimmerman CE, Kalmar CL, Humphries LS, Mcdonald-Mcginn DM, et al. Poverty and risk of cleft lip and palate: an analysis of United States Birth Data. Plast Reconstr Surg. 2022;149(1):169–82.

48. Pereira G, Bracken MB, Bell ML. Particulate air pollution, fetal growth and gestational length: the influence of residential mobility in pregnancy. Environ Res. 2016;147:269–74.

49. Chen L, Bell EM, Caton AR, Druschel CM, Lin S. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. Environ Res. 2010;110(2):162–8.

50. Tang Z, Zhang H, Bai H, Chen Y, Zhao N, Zhou M, et al. Residential mobility during pregnancy in Urban Gansu, China. Health Place. 2018;53:258–63.

51. Bell ML, Belanger K. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. J Expo Sci Environ Epidemiol. 2012;22(5):429–38.

52. Khokha MK, Mitchell LE, Wallingford JB. An opportunity to address the genetic causes of birth defects. Pediatr Res. 2017;81(2):282–5.

53. Matas JL, Agana DFG, Germanos GJ, Hansen MA, Modak S, Tanner JP, et al. Exploring classification of birth defects severity in national hospital discharge databases compared to an active surveillance program. Birth Defects Research. 2019;111(18):1343–55.

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