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Title: The influence of outdoor NO₂ exposure on asthma in childhood: a meta-analysis

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Abstract

Background :

It has long been assumed that the development of childhood asthma is related to exposure to environmental chemicals. However, it has thus far not been possible to unequivocally establish this suspected relationship by individual studies. Moreover, studies of children have been scanty and unreliable due to the large diversity of research environments and subject cohorts. The current study was aimed at clarifying this relationship for one factor by means of a meta-analysis of studies investigating the influence of NO₂ exposure on symptomatology of childhood asthma.

Methods :

We searched two electronic databases (MEDLINE and EMBASE) for literature on relationships between environmental chemical exposure and development of childhood asthma using the MeSH terms nitrogen dioxide and asthma. We did this according to the

MOOSE guidelines for meta-analyses of observational studies.

Results :

We retrieved 130 papers of which 12 met the selection criteria. These papers described observational studies from 7 countries. Study subjects were 97,932 ordinary children aged 0-18 years. Random model analysis revealed that the Odds Ratio (OR) for asthma development due to an increment of 10 ppb of NO₂ was 1.135 with a 95% CI of 1.031-1.251 (P=0.01), while the OR for wheezing symptoms was 1.052 with a 95% CI of 1.020-1.085 (P=0.001). It is therefore evident that NO₂ exposure does influence the development of asthma in ordinary children.

Conclusions :

Our meta-analysis indicated that exposure to NO₂ in the air significantly influenced the development of childhood asthma and symptoms of wheezing.

Key words

asthma, asthmatic symptoms ,children, nitrogen dioxide, meta-analysis

Main text

There is worldwide apprehension that chemicals and parental environments may cause deterioration of children's health. Over the last 20 years, the prevalence of childhood

bronchial asthma in Japan has increased two- to three-fold. Automobile emissions and environmental chemicals in the air produced by increased numbers of manufacturing plants have been implicated as partially responsible for this.

Paying attention to potential effects of long-term exposure to air pollutants, we hypothesized that NO₂ in the air should influence the development of asthma in ordinary children inhabiting target regions. NO₂ is an air pollutant produced by oxidization of NO from industrial plants or produced during the combustion process in automobile engines. The amount of discharged NO₂ has increased with industrial development. This gas is also discharged from household heating devices and microwave ovens, as well as from cigarettes.

Since the atmosphere is contaminated by a variety of chemical substances other than NO₂, their influences also needed to be taken into consideration. It is appreciated that different chemical substances in the air affect the human body in different organs as well as to different extents of damage. Specially, it has been suggested that NO₂ and SO₂ exposure is related to childhood asthma development. It may enhance the production of IgE antibody triggered by allergies via a mechanism possibly involving respiratory tract contraction affecting airway resistance. This is thought to trigger

cytokine secretion from intrabronchial cells, causing inflammation of the air ducts.

It was reported that the prevalence of asthma in both boys and girls was proportional to the concentration of atmospheric NO₂ discharged from cars, and was higher than adult asthma.¹ On the other hand, some meta-analyses on the development of asthmatic symptoms in relation to exposure to atmospheric NO₂ or PM₁₀ in children with a history of asthmatic attacks did not support this contention. Thus, Weinmayr et al. reported that PM₁₀ but not NO₂ showed a significant correlation with asthmatic symptoms.² Health damage from environmental chemicals was thus suggested but not consistent in different studies because of heterogeneity of pollutants, study subjects, and survey condition to clarify relationships between the development of asthma and exposure to sustained levels of atmospheric NO₂ at the place of residence of ordinary children. We made a meta-analysis study to bring about highly reliable results for the purpose to clarify relationships between exposure to atmospheric NO₂ and the development of asthma in ordinary children.

Methods

Search strategy

We identified papers that had been uploaded to MEDLINE and EMBASE not later than

September 2010. The former database included papers published from 1976 to August 2010, while the latter contained those published from 1997 to September 2004. Search used the MeSH terms nitrogen dioxide and asthma according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for observational studies. Study subjects were restricted to ages from 0 to 18 years, while the publication language was limited to English.

Inclusion and exclusion criteria

Investigations subjected to meta-analysis included case control, cross-sectional and cohort studies. The inclusion criteria were the following: 1) Exposure to atmospheric NO₂; 2) Subjects aged 0 to 18 years; 3) Odds ratio (OR) and 95% confidence interval (95% CI) described; and 4) Final indexes set at an asthmatic attack or a visit or admission to a medical institution for asthma treatment. 5) Stepwise analysis of NO₂ values enabling assessment of the effects of every 10 ppb increase. The exclusion criteria comprised 1) children at high risk of asthma, 2) wheezing occurring at infant ages (under 3 years)³, and 3) description of the NO₂ concentration at the same time as symptoms appeared. As to the last criterion, the NO₂ concentration expressed as the

mean lag concentration was adopted if the lag model had been employed, otherwise the concentration measured on the day that symptoms appeared was used.

Epidemiological studies of childhood asthma or allergic disease are internationally conducted according to the protocol that is used in the International Study of Asthma and Allergies in Childhood (ISAAC). The ISAAC defined asthma symptoms as wheezing, asthmatic attacks, wheezing disturbing sleep, severe wheezing limiting speech, wheezing on exercise, or a night cough in the last 12 months, or ever having had asthma. In the present study, we adopted an asthmatic attack and a wheeze as signs pathognomonic for asthma after we had deliberated on whether these signs validated a diagnosis of asthma or not^{4,5}. We performed a meta-analysis integrating ORs and 95% CIs of the adjusted data described in the individual papers.

Statistical analysis

We calculated ORs and their 95% CIs based on integrated data from relevant papers. We employed both fixed-effect and random-effects models. Publication bias was evaluated using a funnel plot and a Begg test⁶ or an Egger test⁷. Heterogeneity was assessed using Cochrane's Q and I^2 statistics. We performed subgroup analyses to correlate ORs with distinguishing features of individual studies using SAS (SAS Institute Inc., Cary,

North Carolina, USA).

Results

Identification of studies

Of 130 retrieved papers (126 from MEDLINE and 4 from EMBASE) reporting NO₂ in relation to asthma development in children aged 0-18 years, 2 were unavailable. The flow chart depicted in Figure 1 shows how 19 were identified from the above 130 papers based on the selection criteria. After this process, 7 studies were excluded because they did not meet the criteria of outdoor NO₂ or ordinary children as subjects, so that 12 were entered into our meta-analysis.

Study characteristics

Table 1 lists the 12 observational studies subjected to our meta-analysis. They comprised 6 cohort, 1 case control, and 5 cross-sectional studies.⁸⁻¹⁹ Study subjects totaled 97,932 ordinary children aged 0-18 years. These studies were conducted independently in 7 countries: 1 in Japan, 4 in the US, 1 in Canada, 2 in China, 1 in Norway, 2 in France, and 1 in Brazil. The most significant confounding factor was passive smoking, as shown in the following order: 8 for passive smoking, 8 for sex, 6 for a family history of allergy, and 6 for age. Other confounding factors included

parental education level, parental income, breast feeding, and birth weight.

Meta-analysis

Forest plots depicted in both Figures 2 and 3 show ORs and 95% CIs concerning asthma as well as wheezing from each or all of the 12 papers. The OR for an increase of the asthma incidence caused by a 10 ppb elevation of NO₂ was 1.135 with a 95% CI of 1.031-1.251 when a random effects model was used, while it was 1.158 with a 95% CI of 1.108-1.211 when a fixed effects model was applied. A similar OR for wheezing incidence was 1.052 with a 95% CI of 1.020-1.085 irrespective of applied effects models. (Table 2)

Heterogeneity

Heterogeneity was evaluated with Cochrane's Q and I² as shown in Table 2. The P value for Cochrane's Q and the I² (%) was 21.83 and 63.35%, respectively, for asthma, and 7.61 and 0%, respectively, for wheezing. Since there was a somewhat greater variation in the case of asthma, we considered it appropriate to integrate results using the random effects model to achieve an accurate evaluation. We analyzed sensitivity in view of Forest plots given in Figures 2 and 3. Concerning the incidence of asthma, the OR of 0.456 was smaller in the paper of Zhao et al. than in the other papers¹². We therefore

excluded this paper from the scrutinization of the integrated data. As a result, the OR was calculated as 1.143 with a 95% CI of 1.041-1.254, suggesting that this exclusion had not affected the results as a whole. In turn, for the occurrence of wheezing, the OR published by Gauderman et al. was the largest, with a value of 2.589¹⁹. After exclusion of this paper, the OR became 1.051 with a 95% CI of 1.018-1.084 for the remaining papers, suggesting again that this paper exerted no influence on the final result.

Publication bias

Funnel plots shown in Figures 4 and 5 represent publication bias with ORs on the horizontal axis and SEs on the vertical axis. Although the plot distribution created by 9 papers appears somewhat deviated toward the right of center in the case of both asthma and wheezing, this was not statistically significant. Concerning asthma, P values of Begg and Egger tests were 0.83 and 0.62, respectively; for wheezing, these P values were 0.68 and 0.91, respectively (Fixed model). We therefore concluded that there was no publication bias because there was no consistent tendency in any of the 9 papers as to asthma or wheezing no matter how large the papers were. Begg and Egger tests were performed using SAS (version 9; SAS Institute Inc., Cary, North Carolina, USA).

Discussion

We undertook a meta-analysis in an attempt to clarify whether or not atmospheric NO₂ exposure was related to the development of asthma in ordinary children. Although some earlier work had failed to identify any clear correlations between the prevalence of asthma or bronchitis and atmospheric NO₂ levels in ordinary elementary school children, here we were able to demonstrate that atmospheric NO₂ did exert a significant influence on the occurrence of asthma symptomatology in ordinary children²⁰. We believe that this meta-analysis does provide more reliable evidence.

In the process of the current meta-analysis, we put a high priority on the selection criteria so that appropriate data could be retrieved from the database of the past papers without any biases entered by investigators' specialties, knowledge, and/or experiences.

We assessed publication bias taking it into account that generally large scale studies tended to be published irrespective of the magnitude of ORs and that small scale studies tended to result in larger ORs. The Funnel plot analysis revealed that the retrieved data showed a tendency, although not significant, to have some publication bias which was characteristic of observational studies. It was thus verified that the studies reviewed in the current meta-analysis represented the whole papers ever published without any publication bias. We therefore think that the papers we meta-analyzed were not biased

and were of high quality.

Homogeneity of the retrieved papers was verified because the results concerning either asthma or wheeze did not differ between in fixed-effect and random-effects models that we employed for data integration for the meta-analysis. Although the latter model is assumed likely to produce prudent results because of its capability to integrate inhomogeneous study data through taking into account inter-study variances, it was shown from ORs and 95% CIs that NO₂ influenced the development of childhood asthma.

In our opinion, changed lifestyle/eating habits are among confounding factors for increasing the incidence of childhood asthma. Living environment has been improved by carpeting rooms, air conditioning, humidifying devices, and airtight housing, which provides house dust mites and fungi with an ideal habitat. Indoor pollution by chemical substances such as formaldehyde can not be ignored in houses that are built with a lot of new construction as well as adhesive materials.

The mainstream of the Japanese diet has changed from Japanese to Western food that is predominated by eggs, milk products, and meat, leading to an enormous intake of protein. There is also apprehension that rising use of antiseptic as well as coloring

agents as an additive to food is partially responsible for the increasing incidence of asthma.

This study has several limitations. First, the literature of observational studies on childhood asthma is inevitably scanty since a large scale investigation of relationship between an air pollutant and children's health hazard has scarcely been done. We consider it ascribable to observational study-specific difficulty finding appropriate study regions, standardizing study conditions, and recruiting a lot of participants as well as investigators. In addition, such an investigation is very time consuming and costs too much money because children, who are in the growing phase and are differentially affected by environment at different ages, have to be observed in detail over a long period. Second, it is required but very difficult to standardize region-by-region measurement methods for air pollutants across the world in view of air pollutant concentrations changing according to climate and environment factors. Many countries adopted an appropriate measurement method as an official method. However, various easy measurement methods are often used instead of the official one in actual research survey, that is not aimed to monitor the compliance of regulatory standards, due to problems with the official one including sampling difficulty, complicated and expensive

procedures, time-consuming analyses, and predetermined measurement times.

It is suggested at the present time that urban regions tends to show high levels of NO₂, SO₂, CO, SPM, NO, OX, and HC which are highly correlated with each other and share the same discharge sources such as soot and smoke, fine particles, and automobiles.

The contribution of each pollutant in determining the outcome and the effects of this mixture may vary.

We selected studies which calculated ORs for asthma or wheeze development due to NO₂, PM₁₀, or SO₂ exposure from all the retrieved ones to examine correlations between asthma or wheeze and the air pollutants based on ORs acquired at increments of 10 ppb of the pollutant concentrations. Six papers reported the influence of NO₂ and PM₁₀ exposure on asthma development in terms of ORs, while 9 papers were available reporting in the same way concerning NO₂ and SO₂. Similarly, there were 5 and 4 papers concerning wheeze respectively.

Asthma or wheeze development tended to be correlated as a whole with NO₂ and PM₁₀ or with NO₂ and SO₂ in terms of ORs although some papers failed to show such correlations. In the survey by Andersen ZJ et al., ORs of NO₂ or PM₁₀ had no clear relationship with wheeze development, which might be explained by our assumption

that they diagnosed wheeze seen in children under 3 years of age as asthma to acquire ORs²¹. Pénard-Morand C et al. reported that there was no correlation between ORs for NO₂ or SO₂ and asthma or wheeze development. Characteristically in regions where these investigators surveyed, ORs for SO₂ were higher than those for NO₂ and the SO₂ concentration in the air tended to be relatively high¹³: They estimated 3-year concentrations of air pollutants and found that the mean concentration of SO₂ was as high as 9.6 µg/m³. In our country, environmental standards for the air pollutant of SO₂ set the mean daily value of hourly concentrations at 40 ppb or smaller with hourly concentrations of 100 ppb or smaller, whereas those for NO₂ were set at the counterpart value ranging from 40 to 60 ppb. Their higher ORs for SO₂ compared to NO₂ might be ascribed to the fact that effects of individual air pollutants on the human body vary depending on their concentrations.

In an attempt to search for relationship between PM₁₀ or SO₂ concentrations (µg/m³) and ORs for NO₂, we selected relevant papers from all the retrieved ones and tenaciously examined them only to find no clear relationship.

There are two reasons for it. One reason is that relationships between individual air pollutants and ORs for NO₂ can greatly change depending on subjects exposed to the

gas, measurement methods for the pollutant concentration, and measurement times. The other is that the air pollutant, even if its concentration is the same, is expected to exert different influences in different climate or natural features of surveyed regions. It is extremely hard to identify papers in which a survey was conducted under the perfectly same conditions because it was observational studies that we performed the meta-analysis. We were therefore short of data size.

Since it was suggested that an NO₂-other air pollutant complex influenced the development of childhood asthma, it is reasonable to consider that there are correlations between each of air pollutants. However, we could not verify it because of the present situation: shortage of retrieved papers, too much a variety of surveyed pollutants as well as survey methodology, and small collection size of data to provide evidence. This problem needs to be solved in future.

Earlier studies have not been unanimous in determining whether children's sex or age differently affected such correlations. We retrieved 4 papers that reported gender difference in the influence of exposure to air pollutants^{15, 17, 18, 24}. Two of them reported odds ratios for asthma as well as wheeze development separately in male and female subjects while one of them reported similarly only for asthma. We integrated these three

papers to examine gender difference and found the following: OR : 1.091, 95%CI : 1.011 to 1.177 for asthma in males; OR : 1.008, 95% CI : 0.995 to 1.020 for wheeze in males; OR : 1.011, 95% CI : 1.001 to 1.021 for asthma in females; OR : 0.995, 95% CI : 0.981 to 1.009 for wheeze in females.

These results seem to suggest that there is gender difference in asthma or wheeze development. We, however, think that their data was too small to draw definite conclusion, so that this issue must be addressed in future. The remaining one paper reported OR of 0.69 with 95% CI of 0.48 to 1.00 for asthma, showing no clear gender difference. According to other papers than ones we retrieved, gender difference in the frequency of asthmatic attacks or in severity differed among ages in one paper²⁵, there was no definite gender difference in a second paper²⁶, and male children were more likely to develop only wheeze in a third paper¹⁷. From the above, we think that relationship between asthma and gender remains to be established at the present time although they are a very important. Our current study could not conclude about gender difference because of shortage of papers that shed light on it.

It seems that air pollution effects differ among children of different ages, as well as between adults and children. This may be because children in the growth period have a

smaller number of pulmonary alveoli than adults and because the polluted air can more easily penetrate their bronchi which are additionally endowed with inferior defensive capacity. Another possible reason is that children are more active and exercise more in the open air, resulting in breathing relatively larger amounts of the air into and out of the lungs every day²⁷. Three of the retrieved papers pointed out a difference in the degree of NO₂ exposure between adults and children. Ordinary children were more sensitive to outdoor NO₂ exposure than adults²⁸. Moreover, younger children aged 3-12 years were compared to adolescent or nearly adult subjects aged 13-21 years regarding the frequency of asthma-related visits to medical institutions following outdoor NO₂ exposure. It was found that the younger group sought medical care more often, whereas the other group did not show an obvious increase in consultations²⁹. It was also reported that children with a history of asthma presented with respiratory symptoms including asthmatic attacks in response to indoor NO₂ exposure, although adults did not³⁰.

Thus, children of different ages most likely do differ in asthma development stimulated by environmental chemical exposure but the number of studies is too small to draw definitive conclusions on this point. Future prospective studies are required to draw more attention to and clarify this issue. Here, we undertook a meta-analysis of

observational studies based on certain inclusion and exclusion criteria. One hundred thirty papers were retrieved, including those mentioned below. The current study explored ordinary children whereas childhood asthma patients were studied in terms of air pollutant exposure and presentation with asthma symptoms in 5 other papers. Of these, 3 described ORs and 95% CIs which showed a tendency to be statistically significant in each paper³¹⁻³³. However, since endpoints of asthma symptoms differed among studies, a definitive conclusion could not be reached.

The 130 retrieved papers included 3 which reported on a combination of two or more air pollutants using the multi-pollutant model³⁴⁻³⁶. None of these 3 papers met the selection criteria for our meta-analysis, and were accordingly omitted. Since environmental chemicals such as SO₂, PM, and O₃ as well as atmospheric NO₂ interact strongly with each other, it was considered inappropriate to study multiple influences of these environmental chemicals treated as coincidental variables.

Nested case control, cross-sectional and cohort studies were included in the selected papers for the current meta-analysis. The incidence of asthma or wheezing did not depend on whether subjects were diagnosed by physicians or not (Table 3). This is explained in part by the existence of the ISAAC and European Community Respiratory

Health Survey (ECRHS) questionnaires which are internationally approved for a surveys of the prevalence of allergic disease or asthma. The papers included in our meta-analysis contained 5 cross-sectional studies^{10, 12-15}, 4 of which¹²⁻¹⁵ employed ISAAC or ECRHS. One cohort study also used ISAAC⁹. Regarding papers that were omitted from our meta-analysis, four also used ISAAC questionnaires³⁷⁻⁴⁰. ISAAC and ECRHS questionnaires are commonly used for a surveys in many different countries. They are so reliable that asthma is readily diagnosed without the requirement for a physician's opinion, because patients and their parents or guardians can provide accurate information on symptoms via questionnaires or the telephone.

There are no certain criteria helpful for a meta-analysis of observational studies, as in the current meta-analysis for evaluating the quality of individual studies. "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) was developed partly for this reason, beginning in 2004. However, the STROBE declaration was issued not in an attempt to standardize reporting nor for regimenting reports of observational studies of fixed design. In our view, appropriate criteria cannot be proposed for the reason that it is impossible to perform a study under the same conditions everywhere because of the intrinsic nature of observational studies.

One of the issues still requiring clarification relates to the contribution indoor NO₂ discharged from microwave ovens or heating devices. Several studies showed that indoor NO₂ caused childhood asthma.^{12, 15, 18, 31-33, 41-44} Seven of the papers in our meta-analysis studied indoor NO₂ as an exposure source and asthma development in ordinary children. Six of them described ORs and 95% CIs. Indoor NO₂ is derived from tobacco smoking¹², classrooms¹⁵, bedrooms⁴³, gas stoves or microwaves³⁸, living rooms¹⁸, and from kitchens⁴⁴. Correlations between exposure to indoor NO₂ and asthma development tended to be statistically significant in many of the individual retrieved papers. However, the number of available papers was small and exposure sources as well as assay conditions were very heterogeneous, so no definitive conclusions could be reached. In order to obtain reliable results on the influence of indoor NO₂, it would be necessary to undertake large scale investigations of environmental chemicals discharged from household or school electronic devices and to limit the sources of and subjects studied. Our meta-analysis confirmed that atmospheric NO₂ is implicated in the development of asthma in ordinary children. It is hoped that large scale prospective studies will substantiate our results in future, and contribute to the healthy growth of children.

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Table1-a

Characteristics of studies on the relation between outdoor NO₂ exposure and asthma in the general population (0-18year children)

Reference	Country	Region	Year of study	No.of cases	Age	Season	Outcomes studied	Adjustment factor	Study design
Clark et al .2010	Canada	British Columbia	1999-2000	37401	3-4	others	①Increased risk of asthma diagnosis	parity,breast-feeding, income quintile, maternal education status,birth weight,and gestational length.	Nested case control
Akinbami et al.2010	USA	US census Region (Northeast. South. Midwest. West)	2001-2004	34073	3-17	others	①Current asthma ②Asthma attack	†,‡,¶, race, ethnicity, single parent household, parental education, poverty status, region of residence	Cross sectional
Oftedal et al.2009	Norway	Oslo	2001-2002	2871	9-10	others	①Current wheeze ②Current severe wheeze ③Current dry cough	‡,§, race, maternal smoking in education, paternal education,maternal marital status at the children 's birth, indicator for cohort population, keeping furry pets now, dampness problems now	Cohort
Annesi et al.2007	French	Bordeaux. Clermont-Ferrand. Creteil. Marseille. Strasbourg. Reims	1999-2000	5338	10.4+/- 0.7	others	①(pastyear) asthma ②(lifetime) asthma	†,‡,§,¶	Cohort
Sole et al.2007	Brazil	Sao Paulo South/Sao Paulo West/Santo Andte/Curitiba/Por to Alegre	Not given	3181	13-14	others	①Current Wheeze ②Severe Asthma ③Nighttime Asthma	(-)	Cross sectional
Millstein et.al.2004	USA	California	1994-1995	2034	9-10	(others)	①Wheeze ②Chest tightness	†,‡,¶, race,allergies, Hispanic, home heating system and fuel ,home water damage,pet cat carpet in home,education of signer, doctor-diagnosed asthma	Cohort

† passive smoking , ‡ sex , § family history of allergy , ¶ age

Table1-b

Reference	Country	Region	Year of study	No.of cases	Age	Season	Outcomes studied	Adjustment factor	Study design
Pénard-Morand et.al.2005	French	Bordeaux/ Clermont- Ferrand/ Cr eteil/ Marseille / Strasbourg /Reims	1999-2000	4901	9-11	others	①Past year asthma ②Life time asthma	† ,‡ ,§ ,¶, parental education, highest correlated air pollutant	Cross sectional
Gauderman et.al .2003	USA	Southern California	1996-1999	208	9-10/ 12-13	others	Recent wheeze	‡ , race, Hispanic ethnicity, cohort, community	Cohort
Peters JM et al. 1999	USA	Southern California	1986-1994	3676	9-16	others	①Current asthma ②wheeze	† ,§ ,race,height,BMI,Hay fever,insurance,Plants,Waterdamage, Mildew,Roaches,Carpet, Vitamins, Active smoker, Pets,Gas stove, Air conditioning, More outdoors	Cohort
Zhang et al. 2008	China	Taiyuan/ Shanxi province	Not given	1993	11-15	others	①wheeze or whistling in the chest ②cumulative asthma	† ,‡ ,§ ,¶, recent home paintintg, new floor and new furniture in the preceding 12 months	Cross sectional
Mi et.al.2006	China	Shanghai	2000	1414	13 -14	others	①Current asthma ②Asthma attacks	† ,‡ ,¶	Cross sectional
Shima et.al.2000	Japan	Chiba	1991-1993	842	9-10	others	①Incidence of asthma ②Incidence of wheeze	† ,§ , Respiratory disease under 2 years of age, Breastfeeding in fancy, Use of unvented heater in winter, using the logistic regression model, History of allergic disease, Outdoor NO2 concentration 10ppb increase, history of allergic disease	Cohort

† passive smoking , ‡ sex , § family history of allergy , ¶ age

Table 2.

Association of NO₂ with episode of asthma and wheeze,
for a 10 ppb increase of pollutant.

Symptom	asthma	wheeze
n	9	9
Fixed Effect model	OR:1.158(95% CI:1.108-1.211)	OR:1.052(95% CI:1.020-1.085)
Random Effect model	OR:1.135(95% CI:1.031-1.251)	OR:1.052(95% CI:1.020-1.085)
Cochrane's Q [†] (P-Value)	21.83	7.61
I ² (%) [†]	63.35	0
Egger / Begg [‡] bias test (P-Value)	0.62 / 0.83	0.91 / 0.68

[†] Heterogeneity between studies was tested by Cochrane's Q with I² test.

[‡] Egger and Begg test reflect a publication bias.

Table 3.

Asthmatic symptoms and Doctor's diagnosis.

Odds ratios(ORs) and 95% confidence intervals(95% CIs) were calculated in relation to an increase in 10ppb NO₂

Diagnosis	model	asthma	wheeze
YES	Fixed Effect model	OR:1.129 (95% CI :1.064-1.197)	OR:1.047 (95% CI :0.960-1.142)
	Random Effect model	OR:1.110 (95% CI :0.979-1.258)	OR:1.059 (95% CI :0.915-1.225)
NO	Fixed Effect model	OR:1.200 (95% CI :1.121-1.286)	OR:1.053 (95% CI :1.018 -1.089)
	Random Effect model	OR: 1.193 (95% CI :0.846-1.685)	OR:1.053 (95% CI :1.018 -1.089)

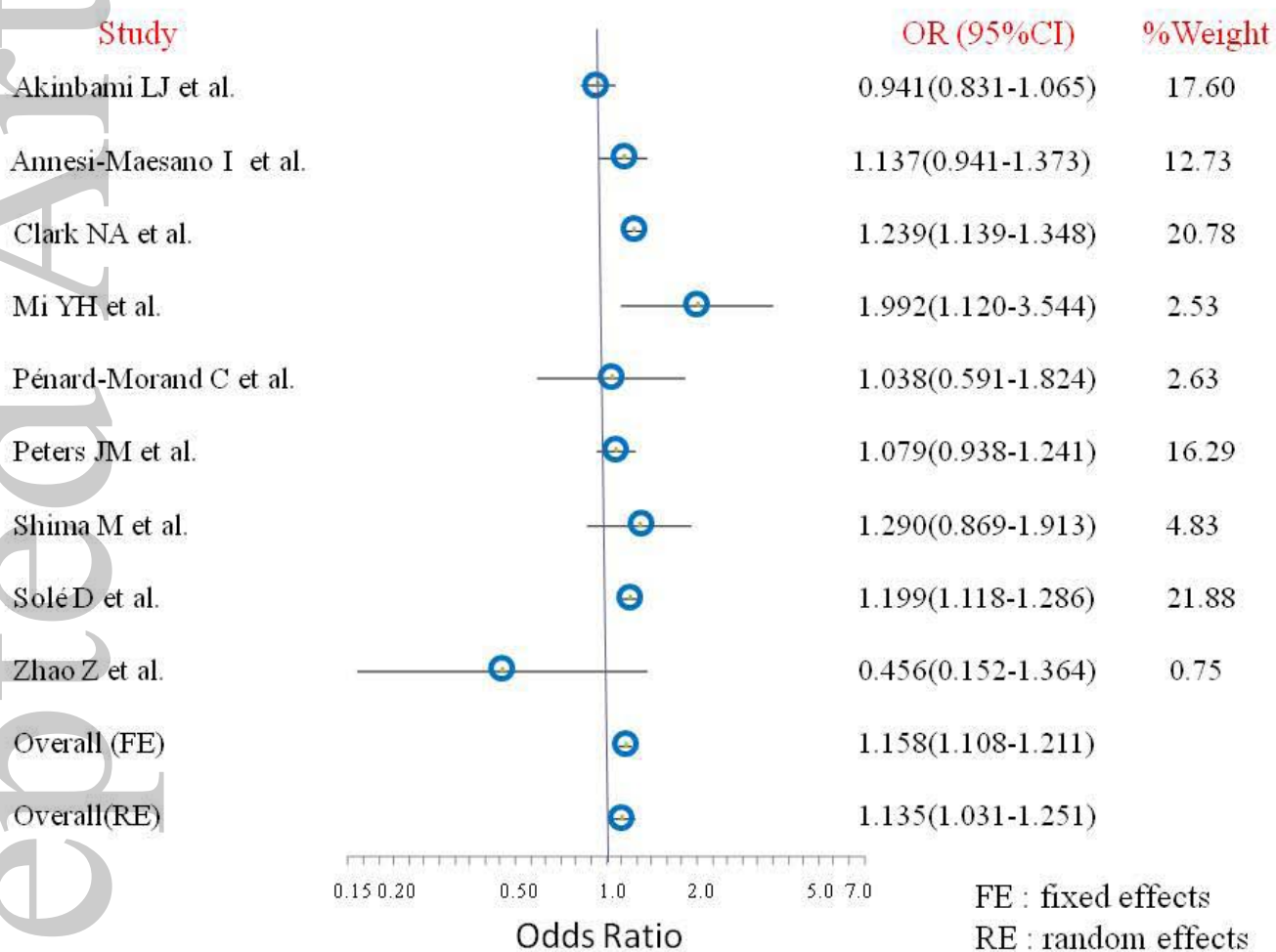


Figure 2 .jpg

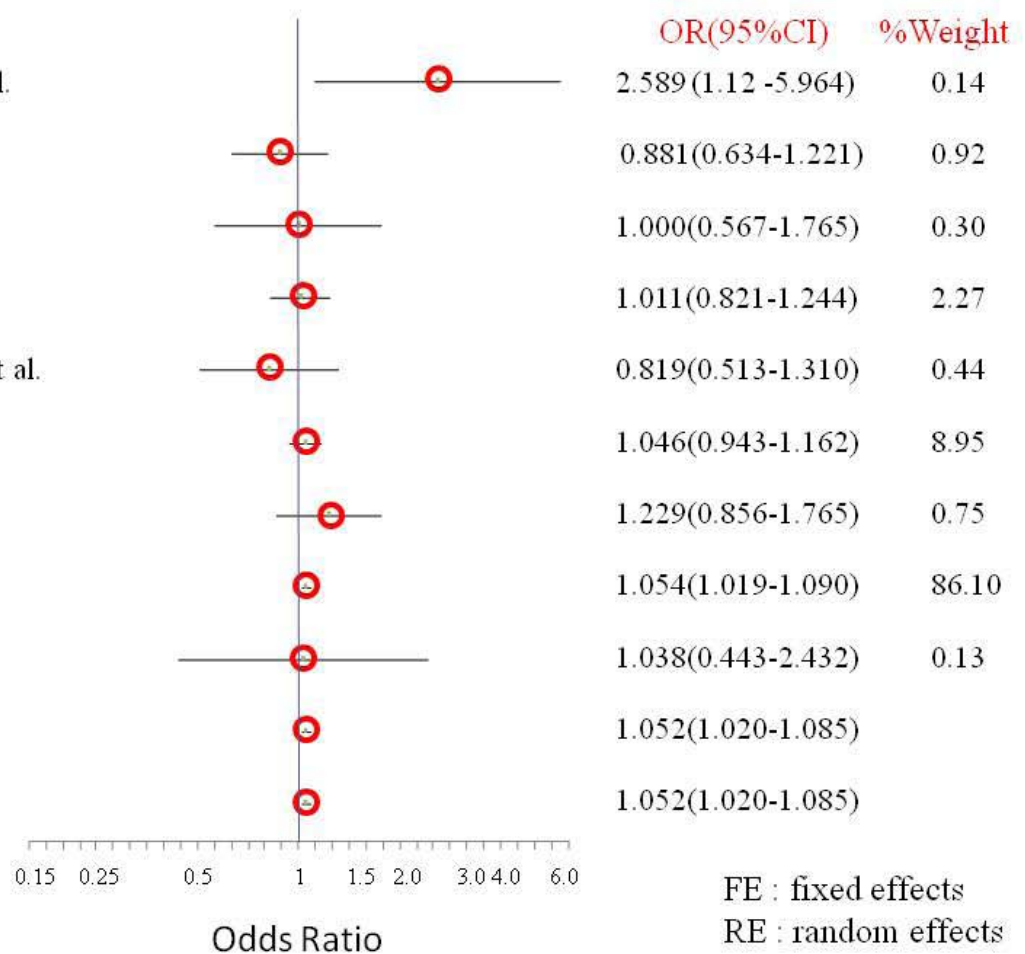


Figure 3 .jpg

Standard error

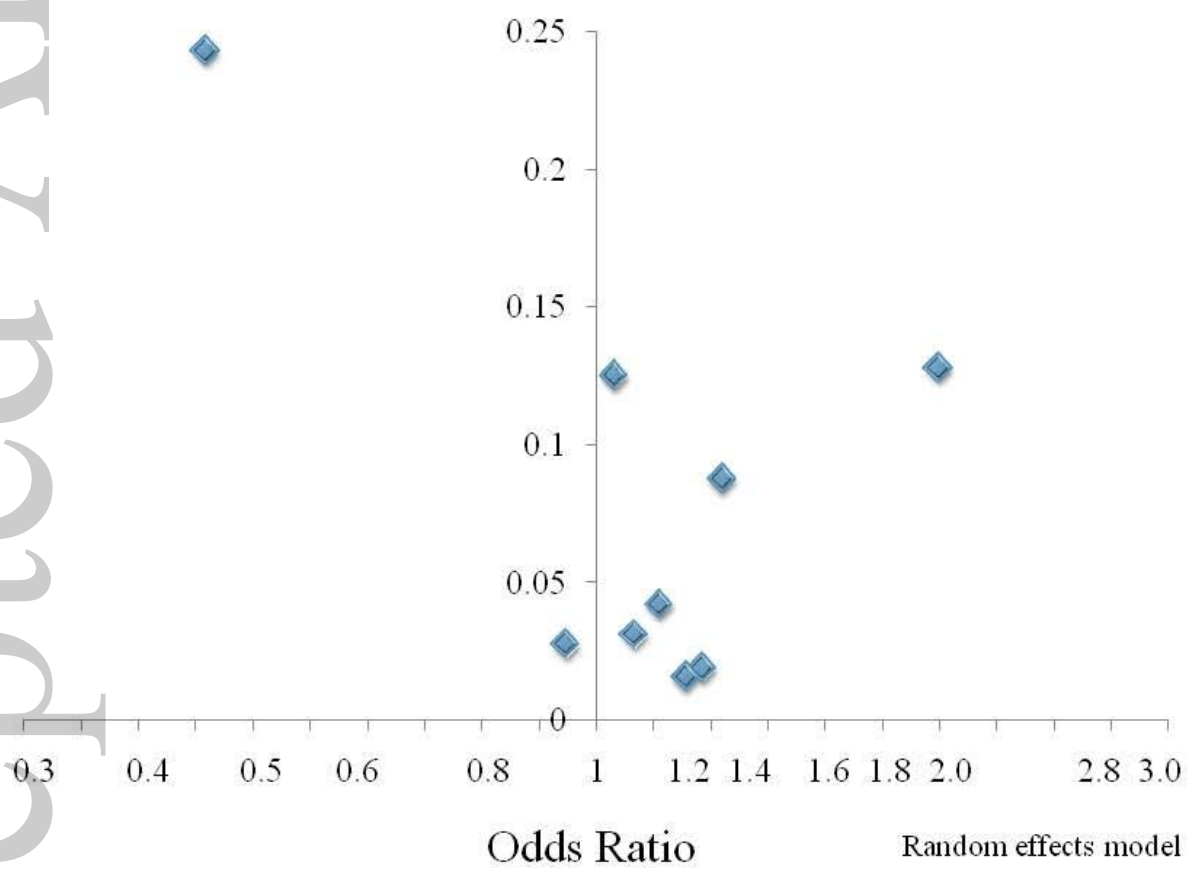


Figure 4 .jpg

Standard error

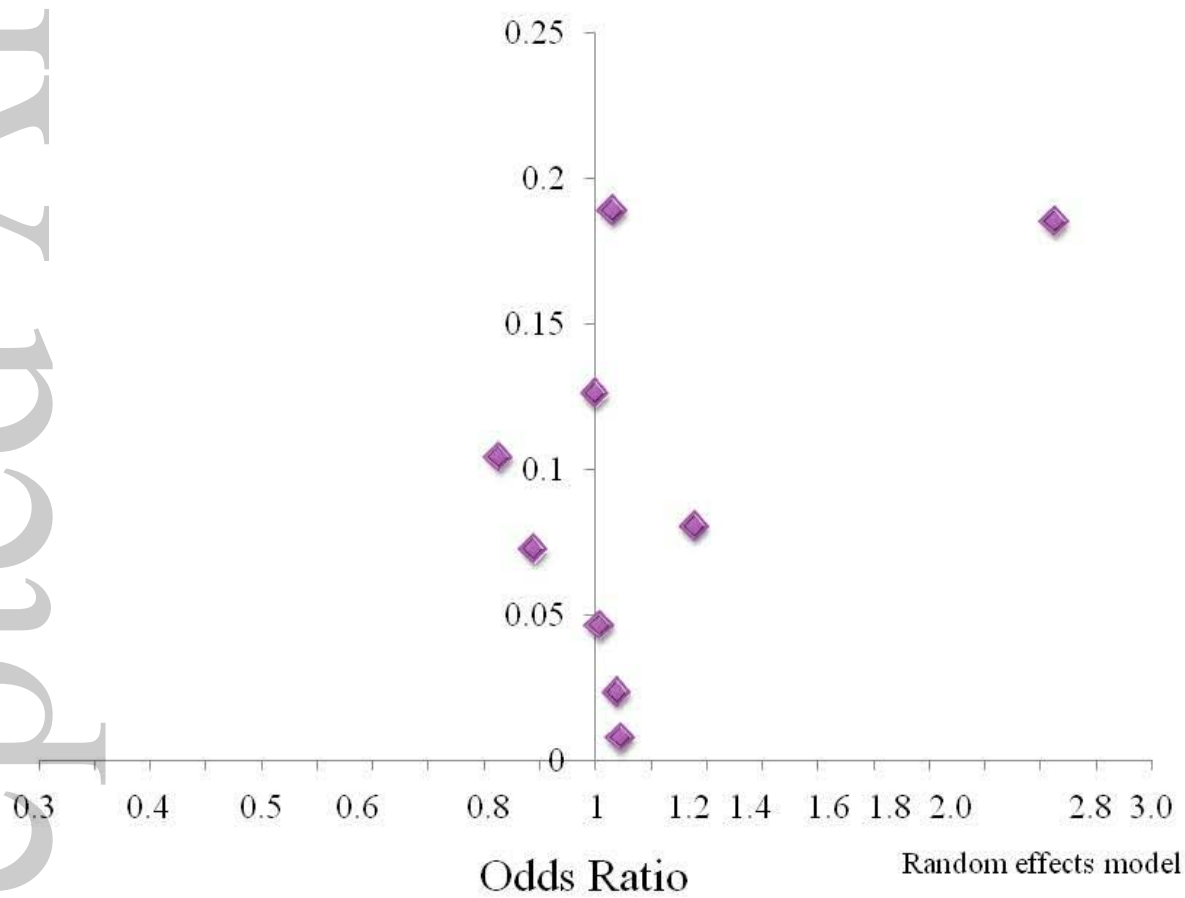


Figure 5.jpg

130 Potentially relevant articles identified

93: Citations excluded:

- 15: General reviews or report exporting the link between cohort studies and asthma.
- 10: The references by which the source of exposure is not NO₂.
- 20: These do not apply to an endpoint of there being asthma symptoms and admission or visit to hospital due to asthma
- 10: The studies cannot integrate data
- 9: The reference not appropriate by the condition of subjects
- 29: Lack of an odds ratio(OR) with 95% confidence intervals(CI)

37 Articles analyzed in detail

18: Citations excluded:

- 4: The references intended for high risk children of asthma
- 2: Repeatedly run the measurement
- 2: Duplicate studies excluded
- 1: Case crossover study
- 2: Be hard to get papers
- 7: The results are presented as relative risks

19 Concerning exposure and the subject

- 3: Outdoor NO₂ + asthmatics children
- 3: Indoor NO₂ + children in general
- 1: Indoor NO₂ + asthmatics children

12 Observational studies included in final analysis