Review of the effect of air pollution exposure from industrial point sources on asthma-related effects in childhood

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Abstract: We reviewed epidemiologic studies of the association between exposure to air pollution from industries and asthma-related outcomes in childhood. We searched bibliographic databases and reference lists of relevant articles to identify studies examining the association between children's exposure to air pollution from industrial point-sources and asthma-related outcomes, including asthma, asthma-like symptoms, wheezing, and bronchiolitis. We extracted key characteristics of each study and when appropriate we performed a random-effects meta-analysis of results and quantified heterogeneity (I^2). Thirty-six studies were included in this review. Meta-analysis was generally not possible and limited to a few studies because of substantial variation across design characteristics and methodologies. In case-crossover studies using administrative health data, pooled odds ratio (OR) of hospitalization for asthma and bronchiolitis in children <5 years were 1.02 [95% confidence intervals (CI): 0.96, 1.08; $I^2 = 56\%$] and 1.01 (95% CI: 0.97, 1.05; $I^2 = 64\%$) per 10 ppb increase in the daily mean and hourly maximum concentration of sulfur dioxide (SO_2), respectively. For $PM_{2.5}$, pooled ORs were 1.02 (95% CI: 0.93, 1.10; $I^2 = 56\%$) and 1.01 (95% CI: 0.98, 1.03 $I^2 = 33\%$) per 10 µg/m³ increment in the daily mean and hourly maximum concentration. In cross-sectional studies using questionnaires, pooled ORs for the prevalence of asthma and wheezing in relation to residential proximity to industry were 1.98 (95% CI: 0.87, 3.09; $I^2 = 71\%$) and 1.33 (95% CI: 0.86, 1.79; $I^2 = 65\%$), respectively. In conclusion, this review showed substantial heterogeneity across study designs and methods. Meta-analysis results suggested no evidence of an association for short-term asthma-related effects and an indication for long-term effects, but heterogeneity between results and limitations in terms of design and exposure assessment preclude drawing definite conclusions. Further well-conducted studies making use of a longitudinal design and of refined exposure assessment methods are needed to improve risk estimates.

Introduction

There is considerable evidence that an increase in ambient air pollution is associated with both acute and chronic respiratory health outcomes.[1,2] Children are a subgroup of particular interest; early life and childhood are likely critical exposure windows because of the immaturity of the immune system and the potential for developmental disruption.[3–6] Children also typically experience a greater exposure to outdoor air pollution when compared with adults because of their higher respiratory volume relative to their body mass and because they tend to be more active and spend more time outdoors.[3–6] Several epidemiologic studies have reported positive associations between ambient air pollution and increase in the number of emergency department visits and hospitalizations for respiratory causes in children.[7–13] Others suggest that outdoor air pollution may exacerbate acute respiratory infections in children, exacerbate respiratory and asthma symptoms as well as acute changes in lung function in children.[14–17] While past evidence on the contribution of air pollution in the development of asthma have been mixed,[18,19] findings from the most recent and comprehensive systematic review and meta-analysis on the subject support that childhood exposures to air pollutants, particularly traffic-related, is associated with the development of the disease in childhood.[20]

Although air pollution studies on the respiratory outcomes in children have mostly focused on ambient urban and traffic-related air pollutants,[13,16,20–22] industrial emissions may importantly contribute to ambient air pollution experienced by some local populations. Ambient air pollution affected by industrial point-source emissions may differ to that of urban settings in terms of concentrations and composition, possibly yielding to differential toxicity.[23] We sought to investigate the effect of air pollution from

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What this study adds

This study is the first to review and summarize findings of epidemiologic studies of the association between exposure to air pollution from industries and asthma-related outcomes in childhood. This study identifies substantial heterogeneity across design and results of selected studies. As well, many studies had important limitations that make causal inference difficult. This review stresses the importance that further well-conducted studies in terms of design and methods, particularly to assess exposure, are needed to improve risk estimates. Harmonization of methods may improve comparability across studies for future meta-analysis and help to shed light on putative agents and drivers of heterogeneity.

industrial point sources on asthma in childhood. We performed a structured review of epidemiologic studies of the associations between children's exposure to air pollution from industrial point sources and the following outcomes: asthma, asthma-like symptoms, wheezing, and bronchiolitis. Specific objectives included providing a detailed description of characteristics of the selected studies, of estimates of association and, when appropriate, summarize estimates of effect using a meta-analysis of results.

Methods

Literature search

We searched EmBase, MedLine, "EBM Reviews/Cochrane," and CINAHL (Cumulative Index to Nursing and Allied Health Literature) bibliographic databases using a combination of keywords representing the following concepts: (1) air pollution; (2) industries; (3) respiratory outcomes; and (4) children. More details about the search, including the complete list of keywords, is presented in eAppendix A; http://links.lww.com/EE/A67.

Our search was restricted to articles written in English published between January 1, 2000 and September 6, 2017. Our strategy consisted of screening all titles and abstracts to assess their eligibility according to the criteria listed below. We then obtained the full-text of papers meeting our selection criteria. In the next stage, we underwent full-text read of selected articles to determine whether they should be included in the review. We completed our literature search manually through inspection of the reference list of selected articles and relevant reviews. All the process was performed by two investigators (X.G. and R.L.) and in case of discrepancy a third investigator (A.S. or S.B.) was consulted to reach a consensus.

Selection criteria

Our review was restricted to studies that reported quantitative estimates of association (thus excluding studies that reported only a *P* value, as this statistic provides no information about the magnitude of the effect) between exposures to air pollution related to industrial sources and selected asthma-related respiratory outcomes in children. Specifically, selected outcomes were asthma, asthma-like symptoms, wheezing, and bronchiolitis. Wheezing and bronchiolitis were included as they produce clinical symptoms that may be similar to those of asthma and difficult to distinguish, especially in children 5 years and younger.[24]

In terms of the study population, consistently with in another review of childhood asthma and wheezing,[25] the age range of interest was children 14 years of age and younger; thus, we excluded studies not reporting effects for participants 14 years and younger. However, we did retain a very few studies that reported findings for a group of participants that were mostly overlapping with our age group of interest, but also included some older participants as long as there were not adults (i.e., ≥18 years of age). (For example, in one study,[26] the age range was 6–15 years, with 88% of participants 6–11 years of age; thus, this study was included.)

We excluded studies in which the exposure investigated was not assessed during the aforementioned age range of interest; thus, excluding studies examining the effects of prenatal air pollution exposures. Studies that reported associations for concentrations of air pollutants measured at monitoring sites or using personal monitoring were excluded if it was not clearly specified that the study population was living in close proximity or in areas affected by emissions from industrial point sources. Studies in which the exposure was estimated by models, such as atmospheric dispersion models, were included if it was made clear that the air pollution exposure related to emissions of industrial point sources.

Extraction of the data

Data extraction from the selected articles was performed independently by at least two investigators (from X.G., R.L., and S.B.).

In case of discrepancies between the extracted information, another investigator (A.S.) reviewed the article to reach consensus. Information extracted included publication year, study design, location, sample size and age of study subjects, type of industries, method of exposure assessment, type of outcome and method of characterization, statistical analysis method, metric of exposure and effect size estimates, as well as covariates used for adjustments. When associations were reported for different age groups, we extracted the stratified results rather than for combined age groups. In instances where results were reported for the same outcome, metric of exposure and population in more than one article, we extracted the results from the latest publications (for particles with median diameter of >10 μm [PM_{10}]: Howel et al[27] vs. Pless-Mulloli et al[28]; for residential proximity: Pless-Mulloli et al[29] vs. Pless-Mulloli et al[28]) or which reported the primary results,[30] whereas another article reported sensitivity analyses.[31]

Method of analysis

With the aim to summarize effects of exposure to air pollution from industries on asthma-related outcomes by mean of a meta-analysis of results, we carefully considered a number of study design characteristics to determine whether study results can be pooled. Notably, we considered the type of outcomes, distinguishing prevalence from incidence, effects resulting from short-term exposures from those of long-term exposures, and whether the outcome was assessed from questionnaire or from administrative health data. Although we had no restriction in terms of study design, this was carefully considered to determine if studies could combined in a meta-analysis of results, as the parameters of the association being estimated may differ depending on the design used.[32] The exposure assessment methods used in the selected studies (e.g., defining exposure as living within a municipality with an industry vs. within 2 or 10 km of the industry) as well as the functional representation of the exposure variable in the statistical analysis (e.g., categorizing residential proximity to industry vs. treating it on its native scale as a continuous variable) were also of particular concern. These differences may yield to measures of associations that are not quantitatively comparable or that cannot be expressed uniformly across studies.

We performed a meta-analysis of results when at least three studies were deemed to be comparable according to the outcome investigated, the outcome and exposure assessment methods, and the exposure metric used in the analysis. Meta-estimates of association were calculated where appropriate using random-effects models;[33] thus, assuming that true effect size varies across studies. In instance where the air pollutant concentration (treated as continuous) was used as the metric of exposure, then effect size estimates and pooled estimates were expressed in terms of 10-unit increment in the air pollutant concentrations to facilitate comparisons. We quantified heterogeneity among estimates using the I^2 statistic, representing the percentage of the total variability explained by differences between studies rather than sampling error.[34] As rules of thumb, an I^2 value of 25%, 50%, and 75% are often used to characterize low, moderate, and high heterogeneity. In presence of high heterogeneity, no definite conclusion should be drawn from the pooled effect estimate, even if a random-effects model is used. We did not perform meta-regression analysis to investigate specific factors contributing to heterogeneity because of the limited number of studies included in each meta-analysis.

Results

Selection of studies

Figure 1 shows the selection of studies included in this review. Our initial bibliographic search yielded 308 peer-reviewed articles. Three additional studies[35–37] were identified throughout the inspection of the references of the articles selected and one
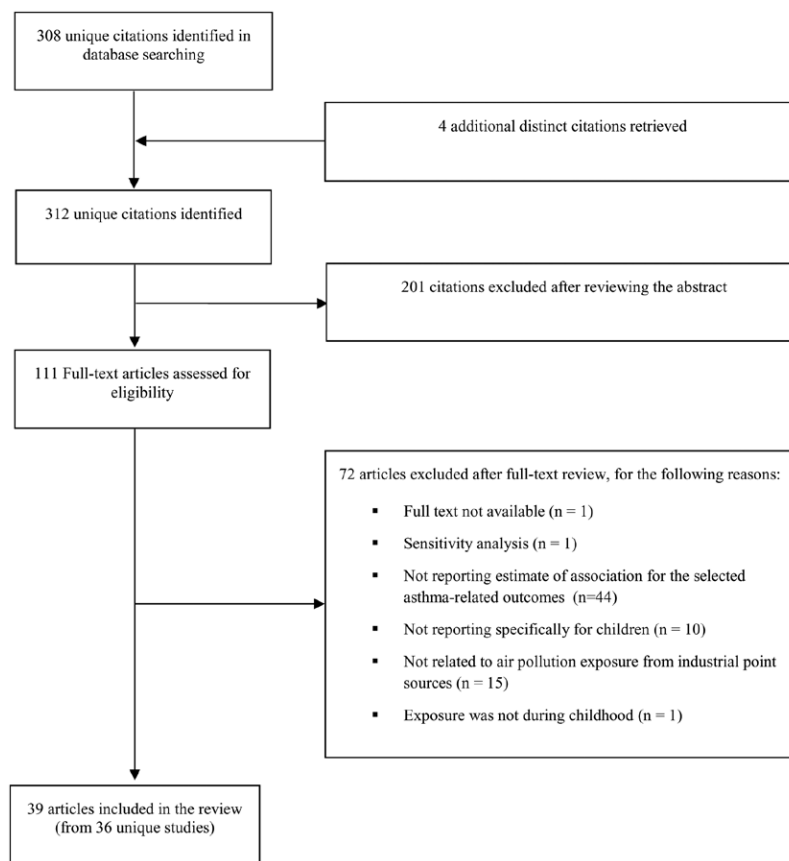
Figure 1. Flow chart presenting the selection of studies of the association between asthma-related outcomes and exposure to air pollution from industrial point sources.

study[38] by the authors was also included. One hundred eleven articles underwent full-text review, whereas one article[39] could not be retrieved. Thirty-nine articles fulfilled our inclusion criteria. This includes one study[40] that we retained although the outcome investigated was hospitalization for asthma, bronchiolitis, bronchitis, and pneumonia, as it was reported in text that sensitivity analyses restricted to asthma yielded similar results. We included five studies that reported estimates of association not strictly for children 0–14 years of age; specifically these were reported for 0–15 years,[41,42] 5–15 years,[43] 6–15 years,[26] and <17 years old.[44] We identified two studies for which multiple articles were published; more precisely, there were two articles[30,45] (another[31] was excluded as it was a sensitivity analysis) on the Viadana study and three articles[27–29] on the opencast coal mining study in England. These multiple articles were all retained for this review but considered as a single citation; therefore, this review included a total of 39 published articles from 36 unique studies.

Characteristics of the selected studies

Study settings and population

Table 1 summarizes the main characteristics of the selected studies, according to the geographic locations (eTable B1; http://links.lww.com/EE/A67, includes more information about the exposure metrics and covariates). Most studies were conducted in North America (n = 12), followed in decrease order by Europe (n = 10), Latin America and the Caribbean (n = 5), Middle East countries (n = 4), East, South, and Southeast Asia (n = 3), and southern Africa (n = 2).

The age range varied substantially across studies; some focused strictly on younger children <5 years of age,[35,36,46–52] others on children 5 years and older,[26,43,53–59] whereas some studies included both younger and older children.[28–30,40,41,45,60–63] In one study,[58] the exact age range was unclear; the methods section states that the study population is children 11–14 years old, but estimates of association are reported for children with mean age of 6.65 years (SD: 0.69 years).

Study design and outcome assessment

In terms of the outcome, it should be noted that we reported in Table 1 only information about the selected asthma related-outcomes, but other respiratory outcomes were investigated in the selected studies. In the 20 studies[26–30,41,43,45,50,53–57,59–61,64–69] that assessed respiratory outcomes through questionnaires (including diaries, questionnaire survey or interviews), the outcome frequently investigated were the prevalence of asthma (n = 16) and of wheezing (n = 14). Questionnaires were generally derived from standardized ones, notably the International Study of Asthma and Allergies in Childhood (ISAAC). In 18 studies using a questionnaire, a cross-sectional design was used to investigated the effects of long-term exposure to air pollution from industries on asthma-related outcomes. The remaining two studies were longitudinal; one short-term panel investigating short-term effects[54] and one with a longer follow-up investigating long-term effects.[50] In addition, in the opencast coal mining study in England, both a cross-sectional and panel study analysis was used to investigate long- and short-term effects, respectively.[27–29] Specifically, lifetime and period (2 and 12 months) prevalence of asthma, wheezing, and asthma-related symptoms were obtained from a questionnaire, whereas short-term effects were assessed from a daily dairy

Table 1

Main characteristics of the selected studies, ordered by geographic region and country.

Reference	Location	Design	Age (sample size)	Health data source	Outcome	Type of effect	Exposure metrics	Exposure type	Type of industry
North America									
Smargiassi et al[46]	Montreal (Canada)	Case-crossover	2–4 yrs (n = 263 hosp; 1,579 ERV)	AHD	• Hosp for asthma • ERV for asthma	Short term	• SO_2 (dispersion model) • SO_2 (fixed-site)	•Continuous • Continuous	Refineries
Deger et al[64]	Montreal (Canada)	Cross-sectional	0.5–12 yrs (n = 842)	Quest.	• Asthma ever • Wheezing in past 12 mo. • Asthma attack in past 12 mo. • Asthma medication use in past 12 mo. • Current wheeze (≥3 times per week)	Long term	• SO_2 (dispersion model)	• Continuous	Refineries
Lewin et al[47]	Shawinigan (Canada)	Case-crossover	0–4 yrs (n = 396 hosp)	AHD	• Hosp for asthma	Short term	• PM2.5, SO2 (fixed-site) • Wind direction (continuous)	• Continuous	Aluminum smelter
Labelle et al[36]	Saguenay (Canada)	Case-crossover	0–4 yrs (n = 1006 hosp)	AHD	• Hosp for asthma and bronchiolitis	Short term	• PM2.5, SO_2 (fixed-site) • Wind direction	• Continuous	Aluminum smelter
Buteau et al[38]	Province of Québec (Canada)	Cohort	0–9 yrs (n = 722,667)	AHD	• Asthma onset	Long term	• PM2.5, SO_2, emissions • Distance • PM2.5, SO_2, emissions, weighted for distance and wind direction	• Continuous	All
Brand et al[48]	Province of Quebec and British Columbia (Canada)	Case-crossover	2–4 yrs (n = 2868)	AHD	• Hosp for asthma and bronchiolitis	Short term	• PM2.5, NO_2, SO_2 emissions, weighted for wind direction • PM2.5, SO_2, NO_2 (fixed-site)	• Continuous	Pulp mills, metal smelters and oil refineries
Clark et al[35]	Southwestern British Columbia (Canada)	Nested case-control	3–4 yrs (n = 37,401)	AHD	• Asthma onset	Long term	• Emissions, weighted for distance	• Continuous	All
Karr et al[49]	Georgia Air Basin, British Columbia (Canada)	Nested case-control	2–12 mo. (n = 68,803)	AHD	• Outpatient visit or hosp for bronchiolitis	Long term	• Emissions, weighted for distance	• Continuous	All
Liu et al[70]	New-York State (excluding New York city) (USA)	Cohort	<10 yrs (n = 21,524,390 person-yrs)	AHD	• Hosp for asthma	Long term	• Distance	• Binary (area-based)	Fuel-fired power plant, electric generators, and hazardous waste site.
Maantay et al[42]	Bronx, New York City (USA)	Ecological	0–15 yrs (n = 20,764 hosp)	AHD	• Hosp for asthma	Long term	• Distance	• Binary (1/4 mile cutoff)	All
Patel et al[50]	Northern Manhattan and the South Bronx (USA)	Longitudinal	0–5 yrs (n = 593)	Quest.	• Asthma in past 12 mo. • Wheezing in past 12 mo.	Long term	• Percentage of residential buffer area within 0.80 km of an industrial facility	• Continuous	N/S
Mirabelli and Wing[65]	North Carolina (USA)	Cross-sectional	12-14 yrs (n = 64,432)	Quest.	• Wheezing in past 12 mo.	Long term	• Distance to school • Odor • Distance and odor	• 3-level categorical • Binary • Binary	Pulp and article mill
Latin America and the Caribbean									
Loyo-Berríos et al[44]	Catano (Puerto Rico)	Nested case-control	<17 yrs (n = 6282)	AHD	• Asthma-related medical visits	Long term	• Distance • Distance, adjusted for wind direction	• Continuous • Continuous	Rum distillery, electric power plants, petroleum refineries, sewage incinerator and treatment plants, cement plants.

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Table 1
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Reference	Location	Design	Age (sample size)	Health data source	Outcome	Type of effect	Exposure metrics	Exposure type	Type of industry
Wichmann et al[53]	La Plata (Argentina)	Cross-sectional	6–12 yrs (n = 1212)	Quest.	• Asthma ever (doctor-diagnosed) • No. of asthma exacerbations in past 12 mo. • Wheezing	Long term	• Distance	• Binary (area-based)	Petrochemical complex
Lopes de Moraes et al[60]	Guamaré (Brazil)	Cross-sectional	0–14 yrs (n = 209)	Quest.	• Asthma ever • Wheezing ever • Wheezing in past 12 mo. • No. of wheezing attacks in past 12 mo. • Sleep disturbance by wheezing in past 12 mo. Speech limiting wheezing in past 12 mo	Long term	• Distance and wind direction	• Binary (<5 km, downwind)	Petrochemical complex
Herrera et al[26]	Northern Chile (Chile)	Cross-sectional	6–15 yrs (n = 288)	Quest.	• Asthma (doctor diagnosed or taking asthma medications in past 12 mo.)	Long term	Distance	• Binary (cutoff: first quartile)	Opencast mining sites (gold and copper)
Prieto-Parra et al[54]	Santiago (Chile)	Panel (12 weeks follow-up)	6–14 yrs (n = 174)	Quest., daily diary	• Wheezing • Medication for asthma crisis	Short-term	• PM2.5, PM$_{10}$, PM2.5-10, CO, NO$_2$, SO$_2$, O$_3$ (fixed-site) • PM2.5 composition • PM2.5 sources contribution (positive matric factorization)	Continuous Continuous Continuous	Copper smelter
Europe Howel et al[27], Pless-Mulloli et al[28], Pless-Mulloli et al[29]	Northern England (United Kingdom)	Cross-sectional	1–11 yrs (n = 3216)	Quest.	Lifetime prevalence: • Wheeze • Asthma Period prevalence (past 12 mo.): • >12 Wheezing in past 12 mo. • Woken child at night in past 12 mo. • Limited speech in past 12 mo. • Occurred on exercise in past 12 mo.	Long term	• Distance	• Binary (area-based)	Opencast coal mining sites
Howel et al[27], Pless-Mulloli et al[28], Pless-Mulloli et al[29]	Northern England (United Kingdom)	Panel	1–11 yrs (n = 244)	Daily diary	Daily prevalence and incidence[c] of respiratory symptoms: • Wheeze • Asthma reliever use	Short-term	• PM$_{10}$ (fixed-site)	• Continuous	Opencast coal mining sites
Aylin et al[51]	England and Wales (United Kingdom)	Ecological	0–4 yrs (n = approx. 43,932)	AHD	• ERV for asthma	Long term	• Distance	• Continuous	Coke works

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Table 1
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Reference	Location	Design	Age (sample size)	Health data source	Outcome	Type of effect	Exposure metrics	Exposure type	Type of industry
Ripabelli et al[61]	Termoli (Italy)	Cross-sectional	0.5–14 yrs (n = 95)	Quest.	• Asthma ever	Long term	• Distance	• Binary (area-based)	N/S
Rosa et al[66]	Brescia (Italy)	Cross-sectional	11–14 yrs (n = 280)	Quest.	• Asthma ever • Asthma medication use in past 12 mo. • Wheezing in the past 12 mo.	Long term	• PM_{10}, Mn, Ni, Cr, Fe, Zn, (personal monitoring)	• Continuous	Ferroalloy plants
Rusconi et al[67]	Sarroch and Brucei (Italy)	Cross-sectional	6–14 yrs (n = 489)	Quest.	• Wheezing symptoms in past 12 mo.	Long term	• Distance	• Binary (area-based)	Petrochemical refinery and liquid fuel gasification plants.
Rava et al., 2011[30], Rava et al., 2012[31], de Marco et al., 2010[45]	Viadana District (Italy)	Cross-sectional	3–14 yrs (n = 3854)	Quest.	• Doctor-diagnosed asthma ever • Asthma-like symptoms in past 12 mo. • Asthma-like symptoms score (sums of symptoms by subjects) • asthma severity index	Long term	• Distance to school and home	• 3-level categorical	Chipboard industries
Rovira et al[55]	Tarragona (Spain)	Cross-sectional	6–7 yrs (n = 2672); 13–14 yrs (n = 2524)	Quest.	• Wheezing ever • Wheezing in past 12 mo. • Wheezing with exercise in past 12 mo. • Severe wheezing • Asthma ever	Long term	• Distance	• Binary (area-based)	Oil refinery, chemical industries, petrochemical plants, incinerators, two power plants.
Hrubá et al[56]	Banska Bystrica (Slovakia)	Cross-sectional	7–11 yrs (n = 667)	Quest.	• Asthma ever (doctor-diagnosed) • Hospital admission ever for asthma or bronchitis or pneumonia. • Wheeze ever	Long term	• TSP (dispersion model)	• Continuous	Wood processing facility, cement plant, pharmaceutical company.
Câra et al[52]	Calarasi and Roseti (Romania)	Cohort	<2 yrs (n= 851)	AHD	• Wheezing (doctor-diagnosed)	Long term	• Distance • Before vs after factory closure	• Binary (area-based)	Iron, steel and coke factory
Câra et al[57]	Calarasi and Roseti (Romania)	Cross-sectional	7–10 yrs (n = 519)	Quest.	• Asthma ever (doctor-diagnosed) • Wheezing ever • Wheezing in past 12 mo. • No. of wheezing attacks in past 12 mo. • Sleep disturbance by wheezing in past 12 mo. • Speech limiting wheezing in past 12 mo. • Exercise related wheezing in past 12 mo.	Long term	• Distance • Before vs after factory closure	• Binary (area-based)	Iron, steel, and coke factory

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Table 1
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Reference	Location	Design	Age (sample size)	Health data source	Outcome	Type of effect	Exposure metrics	Exposure type	Type of industry
Middle East									
Alwahaibi and Zeka[62]	Province of Sohar and Liwa (Oman)	Ecological	≤1 yr (n = 7998); 1-14 yrs (n = 12,148)	AHD	• Medical clinics visits for asthma	Long term	• Distance	• 3-level categorical	Petrochemical industrial complex, iron smelter
Kobrossi et al[43]	Districts of Koura, Batroun and Jbeil (Lebanon)	Cross-sectional	5–15 yrs (n = 486)	Quest.	• Wheezing • Wheezing after physical exercise	Long term	• Distance	• Binary (area-based)	Four cement factories, one lime and plaster factory, one asbestos-cement factory, and two fertilizer factories
Nirel et al[40]	Neot Hovav (Israel)	Case-control	0–14 yrs (n = 6666)	AHD	• Hosp for asthma	Long term	• Distance • Relative direction of the residence from the industry	• 3-level categorical • 4-level categorical	Hazardous waste treatment
Karakis et al[63]	Negev (Isreal)	Cross-sectional	0–14 yrs (n = 550)	AHD	• Asthma life prevalence (from medical clinics visits for asthma)	Long term	• Distance • Wind direction	• Binary (20-km cutoff) • Binary	Chemical, pharmaco-chemical and heavy industries, industrial hazardous waste disposal site and an incinerator.
East, South and Southeast Asia									
Deng et al[68]	Changsha (China)	Cross-sectional	3–6 yrs (n = 2490)	Quest.	• Asthma ever (doctor-diagnosed)	Long term	• SO_2 at kindergartens (IDW from fixed-site).	• Continuous	All
Awasthi et al[41]	Lucknow (India)	Case-control	≤15 yrs (n = 348)	Quest.	• Asthma symptoms from clinic record	Long term	• Distance	• Binary (1.5-km cutoff)	Smoke emitting industries
Chiang et al[58]	Taiwan	Longitudinal	11–14 yrs[a] (n = 587)	AHD	• Outpatient visit or hosp for asthma	Long term	• Distance	• Binary (10-km cutoff)	Petrochemical complex
Southern Africa									
Naidoo et al[59]	South Durban (South Africa)	Cross-sectional	9–12 yrs (n = 423)	Quest.	• Asthma ever (doctor-diagnosed) • Wheezing • Wheezing with shortness of breath • Persistent asthma	Long term	• Distance	• Binary (area-based)	N/S
White et al[69]	Cape Town (South Africa)	Cross-sectional	11–14 yrs (n = 2361)	Quest.	Prevalence of recent, frequent, and ever:[b] • Wheeze at rest • Waking with wheezing at night • Wheezing after exercise • Distressing wheeze at rest • Need to bring inhaler to school	Long term	• Distance • Distance, weighted for wind speed, wind direction	• Continuous • Continuous	Petrochemical refinery

[a] In the study by Chiang et al.[58] the methods section states that the study population was children 11–14 years old; however, some estimates of association are reported for children with mean age of 6.65 years (SD: 0.69 years).

[b] In the study by White et al.[69] "recent" was defined as in the last 12 months, whereas "frequent" as at least monthly in the last 12 months.

[c] In the study by Howel et al[27] and Pless-Mulloli et al.[28] a symptom was defined as incident if it had not been present on the previous day.

AHD, Administrative health data; ERV, emergency room visit; HR, hazard ratio; mo, month; IDW, inverse-distance weighting; N/S, not specified; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter of median diameter of <2.5 μm; Quest., questionnaire; SES, socio-economic status; SHS, secondhand smoke; SO_2, sulfur dioxide; TSP, total suspended particles; yr, year.

of respiratory symptoms collected over 6 weeks during which daily PM_{10} was concurrently measured. General Practitioner consultation records were also obtained in that study but this was not considered in the review because reasons for consultations were not reported specifically for asthma.

In 16 studies, asthma-related outcomes were assessed from administrative health data (i.e., general practitioner consultation records, hospital discharges, and emergency department visits). Four studies[36,46–48] investigated the effects of short-term exposure to air pollution from industries on asthma-related outcomes. In these four studies, a case-crossover design was used and the outcome investigated was hospitalization for asthma,[46,47] and hospitalization for asthma or bronchiolitis.[36,48] In the remaining 12 studies using health administrative data, long-term effects were investigated using different type of study designs, including cohort (n = 3[39,47,69]), nested case-control (n = 3[27,36,48]), ecological (n = 3[44,46,67]), case-control study (n = 1[41]), longitudinal (n = 1[53]) and cross-sectional (n = 1[55]). Notably, one cohort study was a natural experiment, investigating the incidence of wheezing before and after the closure of a factory among birth cohorts living in close proximity and further away from the factory.[52] Relation between exposure to industrial point sources and childhood asthma onset was investigated in one nested case-control[35] and in one population-based birth cohort study.[38]

Exposure assessment

In terms of the methods used to assess children's exposure to air pollution from industries, there was substantial variation across the selected studies. In 15 studies the proximity of the residence or school (e.g., Karakis et al[63]) to the point source, generally treated as ecological and binary, was used as a proxy measure for long-term exposure to industrial air pollution emissions. However, varying criteria were also used to define the categories of exposure; in some studies, the exposure was defined by the city or municipality of residence (or school) (such exposure assessment was referred to as "area-based" in Table 1), whereas in others it was determined according to residing within a specific distance from the industry. In the latter studies, different cutoff values, ranging from ~400 meters (quarter mile)[42] to 20 km,[63] were used to distinguish children exposed to those unexposed to emissions from the industry. In some other studies, the distance between the industrial air pollution point source and the child's residence treated as a continuous variable was used as the metric of exposure.[38,44,51,69] In the Viadana study, one of the surrogate measures used for exposure was based on the distance from home and school to the closest chipboard industries, weighted to account for the time spent at each location.[30,31,45] In addition, a three-category variable, defined as the number (i.e., none, one, two) of wood factories within 2 km from home and school, was used.

Although in most studies measurements of air pollutants concentrations were available, these were mostly used for descriptive purposes. Specifically, 10 studies used measurements from fixed-site monitors as the metric of exposure. Pollutants investigated were sulfur dioxide (SO_2),[36,46–48,54,59,64,68] PM_{10},[27,28,54,59] or of <2.5 μm ($PM_{2.5}$),[36,47,48,54] total suspended particles,[56] and nitrogen dioxide (NO_2).[48] In the only study[66] that made use of personal monitoring PM_{10} were collected for 24 hours and metals in filters were measured, including Mn, Ni, Fe, Cr, and Zn. Dispersion modeling was used to estimate exposure to ambient concentration of SO_2[46,64] and total suspended particulate matter[56] from industrial point sources. In another study, ambient $PM_{2.5}$ concentration from the industry was estimated using positive matrix factorization.[54]

In other studies, varying metrics of exposure were constructed using information about emissions of industrial point sources, distance to the industry and meteorological data. Specifically, metrics used to assess exposure of children included tons of air pollutants emitted by industries nearby the residence,[38] percentage of hours that the child's residence was downwind of the industry,[36,47]

indicators of exposure combining data on emissions and residential proximity to industries,[35] emissions and percent time that the child's residence was downwind of the industry,[48] emissions corrected for the residential proximity and wind direction,[38] and residential proximity corrected for wind direction and wind speed.[69]

Associations between exposure to emissions of industries and selected asthma-related outcomes

In the next sections, we present findings of studies included in this review, according to the outcome assessment methods and the metric of exposure used. Specifically, we have analyzed separately studies in which the outcome was assessed from administrative health data from those using a questionnaire. In view of the varying outcomes investigated and metrics of exposure used, many studies were not comparable to each other; thus a meta-analysis of results was possible in a few instances and included a limited number of studies.

Studies using administrative health data

Main findings from all studies making use of administrative health data are reported in the eTable B2; http://links.lww.com/EE/A67. The findings were organized according to the type of exposure metrics and of outcome.

Association to air pollutant concentrations

Four short-term effects studies used ambient air pollutant concentrations as the metric of exposure to pollutants from main industrial emitters to investigate the association with hospitalization for asthma or bronchiolitis in childhood.[36,46–48] All of these studies assessed exposures using measurements at fixed-site monitors, but in addition Smargiassi et al[46] used dispersion modeling. Associations for SO_2 and $PM_{2.5}$ from these studies were pooled in a meta-analysis of results. Figures 2 and 3 present forest plot showing estimates from individual primary studies together with pooled estimates and heterogeneity as measured by the I^2.

For SO_2 (Figure 2), the meta-analyses presented in Figure 2 include findings from Smargiassi et al[46] estimated from dispersion modeling rather than measurements from fixed-site, as this method likely provide the better estimates of exposure. Pooled odds ratios (ORs) of hospitalization for asthma or bronchiolitis were 1.02 [95% confidence intervals (CI): 0.96, 1.08] and 1.01 (95% CI: 0.97, 1.05) for a 10-ppb increase in same-day daily mean and hourly maximum concentrations of SO_2, respectively. In both instances, heterogeneity was considerable (I^2 = 56% and 64%, respectively). When considering findings from Smargiassi et al[46] derived from fixed-site monitors rather than dispersion modeling (eFigure B1 and B2; http://links.lww.com/EE/A67), pooled odds ratios were 1.00 (95% CI: 0.95, 1.05) and 1.00 (95% CI: 0.97, 1.03), whereas heterogeneity was reduced (I^2 ranging between 34% and 38%).

For $PM_{2.5}$ (Figure 3), pooled odds ratios were 1.02 (95% CI: 0.93, 1.10) and 1.01 (95% CI: 0.98, 1.03) for a 10-μg/m³ increase in the 24-hour daily mean and hourly maximum concentration. Heterogeneity across results was moderate (I^2 = 56% and 32%).

In addition, ambient NO_2 was investigated in one study[48]; positive association with hospitalization for asthma or bronchiolitis was reported for the daily mean (OR per 7.4 ppb = 1.09; 95% CI: 0.65, 1.82) and hourly maximum concentration (OR per 14.6 ppb = 1.15; 95% CI: 0.64, 2.06), but confidence intervals were fairly large and included the null.

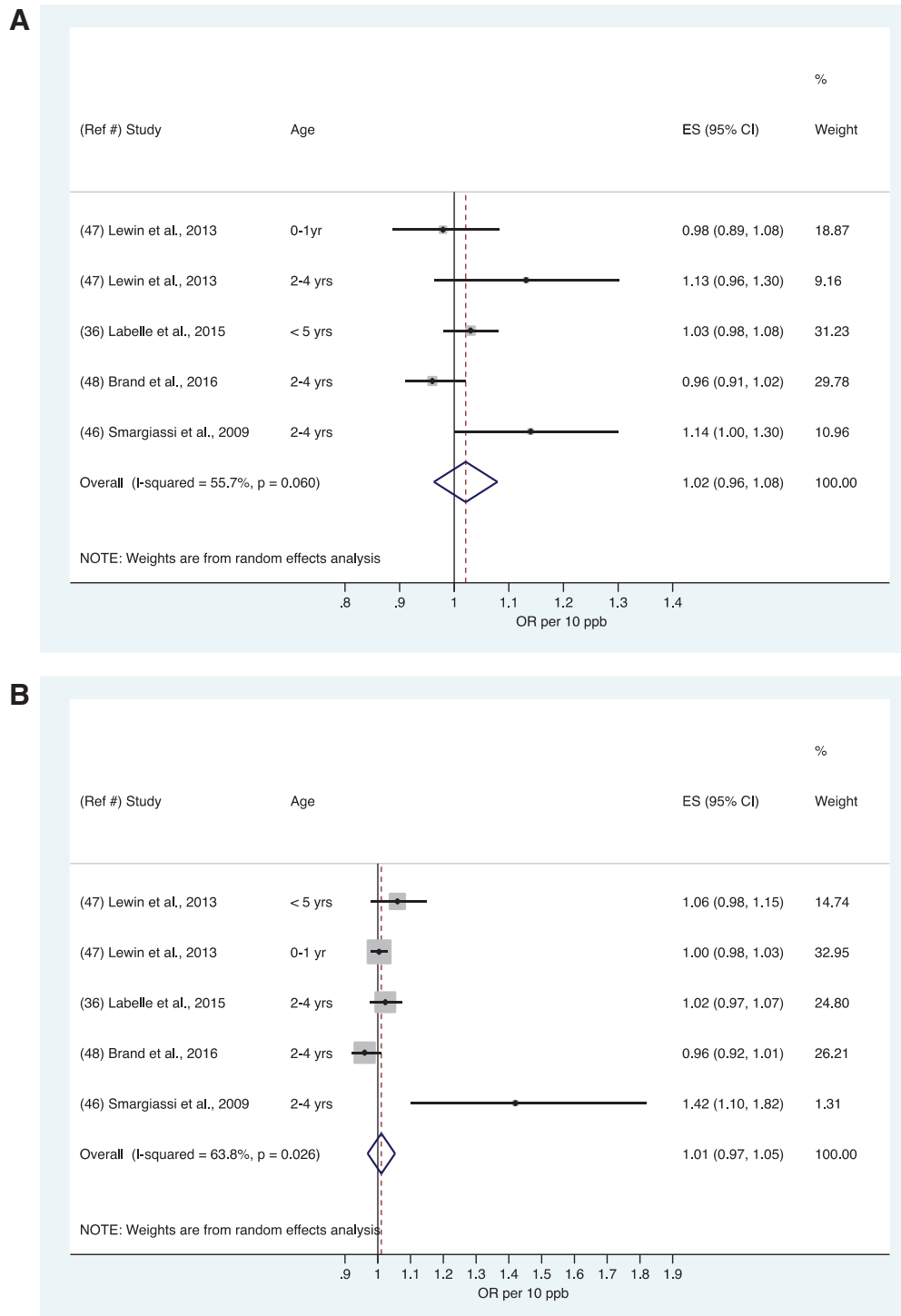### Association to residential proximity

In six studies, residential proximity to major but varied industries such as powers plants and smelters was treated as categorical (either binary or 3-level variables).[40,42,58,62,70] All of these studies reported

statistically significant associations between residential proximity and health service used for asthma, including hospitalization, emergency department visits, and clinical visits. A population-based birth cohort study found that the risk of asthma onset in children's living within 7.5 km of a major industrial air pollutant emitter (defined as emitting >100 tons per year of either $PM_{2.5}$ or SO_2) was significantly greater than in those living further than 7.5 km, whereas within 7.5 km every 1-km increase was associated with a 2.2%

(95% CI: 1.0%, 3.3%) decrease in the hazard of asthma onset.[38] In the other studies that treated the distance to the industry as a continuous variable, every 1-km decrease was found to increase the risk of hospitalization for asthma by 7% (95% CI: –2%, 18%)[51] and of asthma-related medical visits by 69% (95% CI: 50%, 91%).[44]

A meta-analysis of results was not possible because the number of studies investigating a similar outcome and using a similar metric of exposure was insufficient.

A

(Ref #) Study	Age	ES (95% CI)	% Weight
(47) Lewin et al., 2013	0-1yr	0.98 (0.89, 1.08)	18.87
(47) Lewin et al., 2013	2-4 yrs	1.13 (0.96, 1.30)	9.16
(36) Labelle et al., 2015	< 5 yrs	1.03 (0.98, 1.08)	31.23
(48) Brand et al., 2016	2-4 yrs	0.96 (0.91, 1.02)	29.78
(46) Smargiassi et al., 2009	2-4 yrs	1.14 (1.00, 1.30)	10.96
Overall (I-squared = 55.7%, p = 0.060)		1.02 (0.96, 1.08)	100.00

NOTE: Weights are from random effects analysis

OR per 10 ppb

B

(Ref #) Study	Age	ES (95% CI)	% Weight
(47) Lewin et al., 2013	< 5 yrs	1.06 (0.98, 1.15)	14.74
(47) Lewin et al., 2013	0-1 yr	1.00 (0.98, 1.03)	32.95
(36) Labelle et al., 2015	2-4 yrs	1.02 (0.97, 1.07)	24.80
(48) Brand et al., 2016	2-4 yrs	0.96 (0.92, 1.01)	26.21
(46) Smargiassi et al., 2009	2-4 yrs	1.42 (1.10, 1.82)	1.31
Overall (I-squared = 63.8%, p = 0.026)		1.01 (0.97, 1.05)	100.00

NOTE: Weights are from random effects analysis

OR per 10 ppb

Figure 2. Forest plot of the association between hospitalization for asthma or bronchiolitis. A, Same-day daily mean concentration of SO_2 and (B) same-day hourly maximum concentration of SO_2, from case-crossover studies using administrative health data. Effect size and 95% CI are expressed relative to a 10-ppb increase. Pooled estimates of effect size are indicated by black squares and 95% CI are represented by horizontal lines; size of black square around point estimate is proportional to weight in calculating pooled estimate.
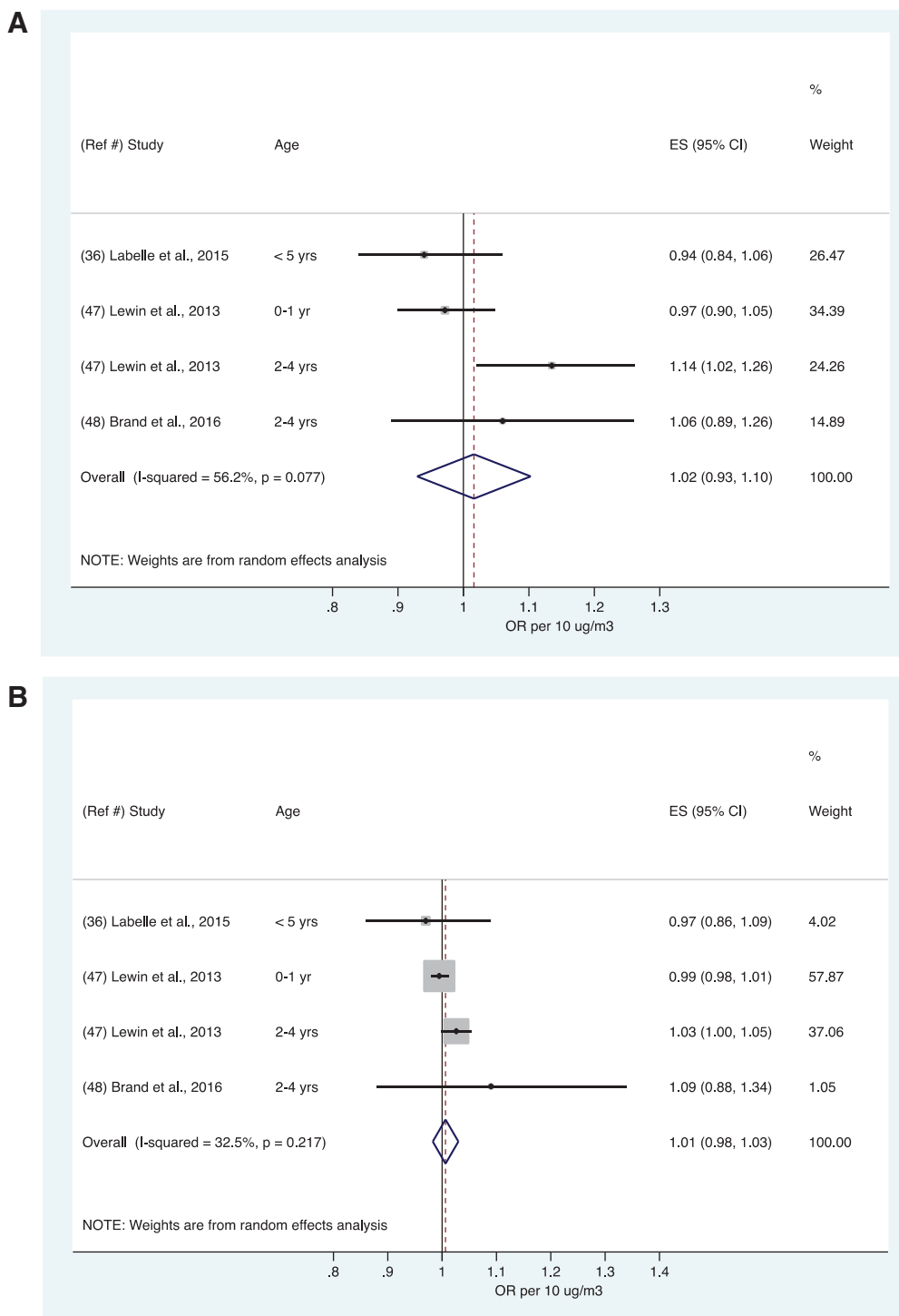
Figure 3. Forest plot of the association between hospitalization for asthma or bronchiolitis. A, Same-day daily mean concentration of PM2.5 and (B) same-day hourly maximum concentration of PM2.5, from case-crossover studies using administrative health data. OR and 95% CI are expressed relative to a 10-ppb increase. Pooled random-effect estimate of ORs is indicated by vertical points of diamonds and 95% CI are represented by horizontal points. Black squares represent individual effect size of primary studies and the bars the 95% CI; size of black squares is proportional to weight in calculating random effect summary estimate.

Association to tons emitted and wind exposure

In the two case-crossover studies[36,47] that considered as the metric of exposure the percentage of daily time that the child's residence was downwind of the point-source (in this case a smelter), associations were found with hospitalization for asthma or bronchiolitis.[36,47] More precisely, Lewin et al[47] found a positive association in children 2–4 years old (OR per 29% increment: 1.27; 95% CI: 1.03, 1.56), but no association in those <2 years old (OR per 21% increment: 1.00; 95% CI: 0.84, 1.20). As well, one cross-sectional study used a binary indicator of exposure based on wind direction from an industrial park housing various heavy industries, and found association with the prevalence of asthma (OR: 1.95; 95% CI: 1.01, 3.76).[63]

Three studies, one of short-term[48] and two of long-term effects,[49] used a metric of exposure combining tons emitted and distances. Brand et al[48] found no association for hospitalization for asthma or bronchiolitis and daily exposure to air emissions from pulp mills, oil refineries, and metal smelters, using a case-crossover analysis. Using a nested case-control design, Karr et al[49] found a positive association between hospitalization and emergency department visits for asthma or bronchiolitis (OR: 1.10; 95% CI: 1.06, 1.13) and the proximity-weighted sum of total regulated air pollutant emissions during the first year of life. In a population-based birth cohort study of long-term effects, childhood asthma onset was associated with the yearly tons emitted by industries weighted by the percentage of time downwind and the inverse distance.[38]

Association to other metrics of exposure

Using a natural-experimental design, Câra et al[52] found that the closing of a iron, steel, and coke factory was associated with a significant decrease in the occurrence of wheezing among cohorts of children <2 years old.

Studies using questionnaire

Results of associations from all studies making using a questionnaire (or a diary) to assess the outcome are presented in eTable B3; http://links.lww.com/EE/A67. Studies were organized according to the type of exposure metrics and the type of outcome.

Association to air pollutant concentration

We identified six studies investigating the association between the selected respiratory outcomes and air pollutant concentrations. A meta-analysis of results was not possible because of substantial differences across study design, outcome investigated, and exposure assessment methods.

For PM_{10}, long-term effects were investigated in two cross-sectional studies,[59,66] whereas short-term effects were investigated in two panel studies.[27,54] Notably, in one cross-sectional study, 24-hour personal PM_{10} exposure was found to be associated with lifetime asthma and asthma medication use in past 12 months; for an interquartile range (IQR) (38 g/m³), risk ratios (RR) were 1.12 (95% CI: 1.00, 1.21) and 1.21, (95% CI: 1.09, 1.35), respectively.[66] In contrast, panel studies found no association between asthma reliever use and 24-hour daily mean PM_{10} exposure from fixed-site monitors at lag 0 and 1 day,[27] and for 1 to 7 days averaging window of exposure.[54]

Prieto-Parra et al[54] investigated wheezing and reliever use in association to exposure to ambient $PM_{2.5}$ as well as ambient $PM_{2.5}$ attributable to the copper smelter. For ambient $PM_{2.5}$ they found stronger association for longer exposure; specifically associations where positive for 5- and 7-day averaging concentration [e.g., for wheezing and 7-day average exposure, RR per IQR (18.0 μg/m³) = 1.60; 95% CI: 1.15, 2.26], whereas for 1- and 3-day averaging concentration associations were null. These findings were not consistent with those for $PM_{2.5}$ attributable to the copper smelter, as for this metric associations were negative and mostly comprising the null. Hrubá et al[56] found positive associations between annual total suspended particulate matter concentrations from dispersion modeling and the lifetime prevalence of asthma and wheezing.

For SO_2, asthma prevalence was found to be associated with exposure during the first year of life in one study.[68] The two short-term effect studies investigating respiratory symptoms found no association. Specifically, one was a panel study[54] investigating the effects daily exposures related to emissions of a copper smelter, whereas the other[59] was a cross-sectional study contrasting children from a highly industrialized compared with a non-industrialized area, and using their 8-month average SO_2 exposure at school.

Association to residential proximity

In 12 studies, exposure was based on residential proximity to various types of industries including petro-chemical, chipboard, and cement plants treated as binary covariate. From these, six studies[41,43,45,53,57,59] reported positive statistically significant association with at least one of the selected outcomes. We pooled results from the 5 studies reporting an odds ratio for the association between residential proximity to industries and the lifetime prevalence of asthma and wheezing.

For asthma (Figure 4), the pooled odds ratio was 1.98 (95% CI: 0.87, 3.09), but heterogeneity across study results was substantial ($I^2 = 71\%$). Much larger effect was reported in the two studies.[57,61] When removing these two studies (one on steel iron coke plant[57] and the other unspecified[61]), the pooled odds ratio was 1.85 (95% CI: 0.78, 2.93), and heterogeneity remained substantial ($I^2 = 79\%$) (eAppendix Figure B3; http://links.lww.com/EE/A67, for the forest plot).

For wheezing (Figure 5), the pooled odds ratio was 1.33 (95% CI: 0.86, 1.79; $I^2 = 65\%$). However, two studies included in this meta-analysis used a definition of wheezing that is not entirely consistent with the others. Specifically, in one study[59] wheezing was defined as chest sounding wheezy or whistling on most days and nights, whereas in the other study[53] the occurrence of wheezing was limited to the past 12 months. When removing these two studies, the pooled OR was 1.29 (95% CI: 0.50, 2.08; $I^2 = 58\%$) (eFigure B4; http://links.lww.com/EE/A67, for the forest plot).

Other studies making use of indicators of exposure based on residential proximity included one cross-sectional study that found no association between the prevalence of asthma and asthma-like symptoms and the weighted average of minimum distances of each child's home and school from the chipboard industries.[30] In another study, exposure was represented by the percentage of a 250-m buffer from the child's residence that was within 0.80 km of an unspecified industrial point source.[50] In this study, positive association (OR: 1.30; 95% CI: 0.98, 1.52) was found between proximity to air pollution industrial point sources and parental reporting of asthma diagnosis, but not of wheezing.[50]

Association to wind and other related metrics of exposure

In one cross-sectional study a binary indicator of exposure based on wind direction from a petrochemical plant was used, and increased risk of prevalence of wheezing was reported (OR: 2.01; 95% CI: 1.01, 4.01).[60] White et al[69] found that distance weighted for wind direction and wind speed, but not simple distance from the refinery, was positively associated with asthma-related symptom prevalences.

Discussion

We reviewed and summarized 36 studies investigating the association between exposure to air pollution from industrial point source and asthma-related outcomes in childhood. Although individual studies mostly reported positive associations, there were some mixed results and our meta-analyses did not provide strong evidence about the effect of exposure to air pollution from industries on asthma outcomes in childhood. Specifically, pooled effect estimates from case-crossover studies using administrative health data suggest no effect of daily exposure to SO_2 and $PM_{2.5}$ on hospitalization for asthma and bronchiolitis in younger children (<5 years). Findings from cross-sectional studies using questionnaires suggest that residential proximity
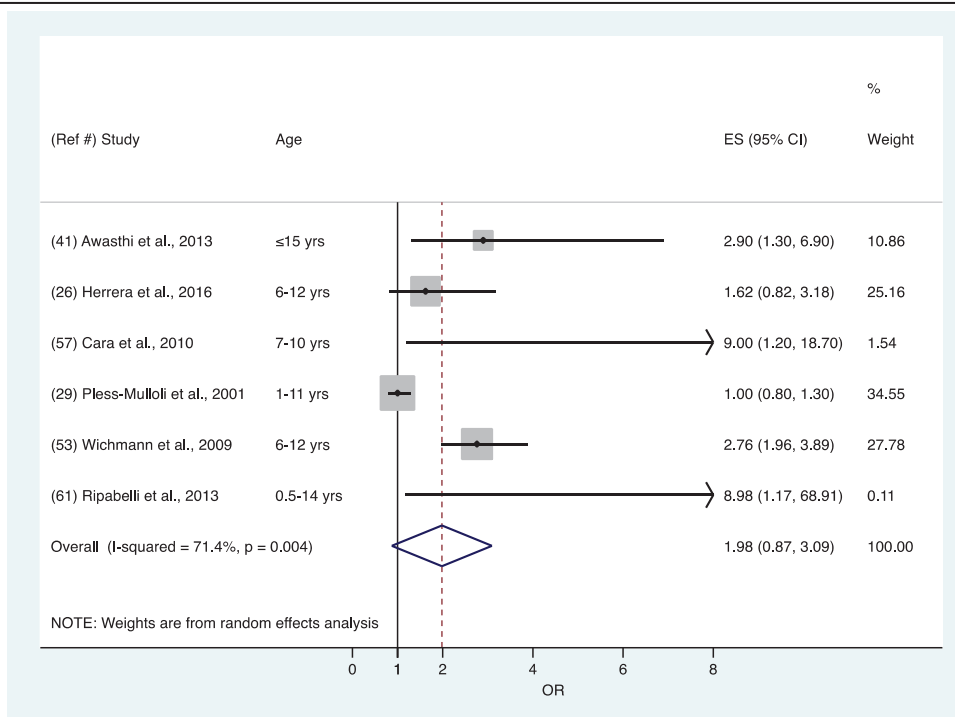
Figure 4. Forest plot of the association between residential proximity to industries and the prevalence of asthma, from cross-sectional studies using questionnaire. Pooled random-effect estimate of ORs is indicated by vertical points of diamonds and 95% CI are represented by horizontal points. Black squares represent individual effect size of primary studies and the bars the 95% CI; size of black squares is proportional to weight in calculating random-effect summary estimate. The arrows indicate that the confidence interval extends beyond the range of the value display.
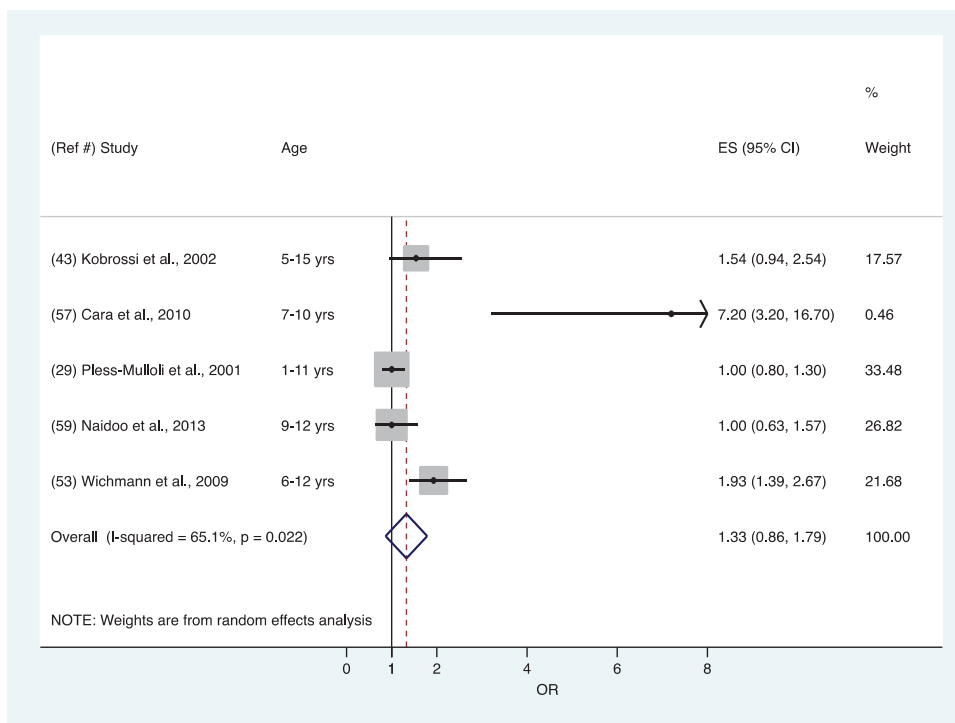
Figure 5. Forest plot of the association between residential proximity to industries and the prevalence of wheezing, from cross-sectional studies using questionnaire. Pooled random effect estimate of ORs is indicated by vertical points of diamonds and 95% CI are represented by horizontal points. Black squares represent individual effect size of primary studies and the bars the 95% CI; size of black squares is proportional to weight in calculating random-effect summary estimate. The arrows indicate that the confidence interval extends beyond the range of the value display.

to industry may be associated with the prevalence of asthma (pooled OR: 1.98; 95% CI: 0.87, 3.09) and wheezing (pooled OR: 1.33; 95% CI: 0.86, 1.79), but heterogeneity across results was considerable (I^2 = 71% and 65%).

While some previous reviews of the association between air pollution and asthma have focused on urban and traffic-related air pollution,[15,18–20,71,72] this review is the first to focus on the effects of air pollution from industrial point sources. Despite that our quantitative analysis did not provide strong evidence of an association, we consider that this should not be interpreted as air pollution emitted by industries has no effect on asthma-related outcome in children. The body of evidence from epidemiologic studies strongly support the association between ambient air pollution and asthma exacerbation as well as asthma onset in childhood; therefore, it is very difficult to envision that emissions from industries would not contribute to such adverse respiratory effects. Rather, we consider that the mixed associations from primary studies and the lack of evidence from our meta-analyses are due to important limitations that we discuss below.

Notably, although we did not exclude studies based on quality assessment, we consider that many of the selected studies were not of high quality. Particularly, almost half of the studies used a cross-sectional design. This type of design provides a snapshot of the outcome and exposure at a specific point in time; therefore, prevalence can be measured but not incidence.[73] The lack of information about temporality is an important limitation to infer causality.

The exposure assessment, which is a critical component of air pollution studies, was a major limitation in many of the selected studies. Assessing the contribution of point sources to air pollution experienced by individuals is challenging. Point source characteristics, including the amount of emissions, stack height, and plume properties, as well as other parameters influencing dispersion in the atmosphere such as meteorological conditions (e.g., wind speed and direction) and topography are among factors determining the contribution of point sources to ambient air pollution.[74] Most studies that account for wind data have found positive association.[36,38,44,47,60,69] Especially, findings from White et al[69] showed that in adding wind adjustments (speed, direction, and proportion of time blown) to the distance may make an appreciable difference to the inference of association between point source emissions exposure and respiratory symptoms. However, in many studies (n = 15), the exposure was treated as binary based on the community of residence or using an arbitrarily cutoff distance, thus neglecting to account for factors influencing the spatial dispersion of emissions, such as wind direction. Furthermore, the exposure was time-invariant, thus assuming that the current residential location is an adequate proxy of the children long-term (or historical) exposure. Such exposure assessment is subject to substantial exposure misclassification, making it difficult to ascertain whether the observed associations were indeed attributable to air pollution and to what extent emissions from industrial point sources contributed to the observed effects. If misclassification in exposure were non-differential, this would bias effect estimates toward the null and could explain some of the mixed results. For the investigation of the short-term effects, the use of personal monitoring is typically recommended to better quantify the exposure of participants to air pollution, as it allows to account for mobility and time-activity patterns. However, distinguishing the contribution of industries from that of other sources remains very challenging, particularly for air pollutant emitted by multiple sources such as PM. In the only study that made use of personal monitoring, which was limited by a cross-sectional design, the contribution of PM attributable to industries was not determined.[66] Alternatively, atmospheric dispersion modeling making use of reliable and sufficient data accounting for characteristics of point source, meteorological conditions and topography, can provide spatiotemporally refined estimates of exposure (both short and long term) to industrial emissions at participants' residence when compared with fixed-site monitoring.[75,76] For short-term exposure to SO_2, stronger association with hospitalization for asthma and bronchiolitis was found when using dispersion modeling when compared with measurements at fixed-site monitors.[46] Fixed-site monitors may not be specifically located to capture the influence of industrial point source emissions. The ability of a fixed-site monitoring station to represent the exposure of individuals will depend on its location, particularly in terms of distance to the point source and wind direction, and will likely be limited to individuals residing in very close proximity to the station. Additionally, the use of dispersion modeling can be refined when combined with other air pollution estimates, such as background regional ambient concentrations of air pollutant from satellite-based or land use regression models.[76] However, because emissions data are rarely available on daily basis, the variation of estimates of pollution from dispersion modeling may be limited to the use of meteorological factors (e.g., wind direction and speed) when investigating the short-term effects of air pollution exposure.

Another limitation of this review relates to the substantial variation across study design and characteristics that made pooling findings generally not possible. These variations likely contributed to the statistical heterogeneity (reflected by the I^2 statistic) observed in the meta-analyses conducted, which make interpretation of findings challenging. Particularly, the exposure assessment was a main source of heterogeneity, as a variety of exposure metrics were used. In studies in which the outcome was collected from a questionnaire, many used a binary indicator of exposure based on residential proximity to industries; however, varying distances or definitions were used across studies limiting our ability to compare results across studies. In addition to being subject to important exposure misclassification, such qualitative indicators of exposure do not allow to account for the quantitative magnitude and type of exposure in the analysis, making impossible to derive an exposure-response functions that would support causality.

The fact that studies were conducted in different countries of the world, where ambient air pollution concentration and emission standards may also substantially differ, is likely another source of heterogeneity. In addition, studies covered a wide range of industrial activities, emitting complex mixtures of pollutants that likely vary in composition and toxicity. Evidence from toxicologic, controlled human exposure, and epidemiologic studies suggests that adverse health effects of particulate matter likely depend on the size, composition, and solubility of the particulate matter.[2] This was our motivation for extracting information about the types of industrial source, but it was not possible to consider this in our meta-analysis because of the very few number of studies included and the relatively large variety of industrial activities. To address possible drivers of heterogeneity, putative agents and differential toxicity by type of point source, a greater standardization of future study design and methods may be desirable, including greater harmonization of methods and definitions for the outcome and for the exposure, as well as harmonization of confounders included in the analysis. However, because the air pollution mixture may importantly differ across geographical location and depending on the type of industry, any evidence base as defined by non-heterogeneous meta-analysis may be difficult to achieve. In our meta-analysis of case-crossover studies of the association between air pollutants and hospitalization for asthma and bronchiolitis, statistical heterogeneity was substantial despite all studies[36,46–48] used a similar design, were conducted in Canada, among children of similar age, using similar methods of exposure and outcome assessment, and of statistical analysis. This inherent heterogeneity implies that evidence may have to rely on findings from a very limited number of studies rather than meta-analyses, thus stressing the importance of having high quality and well-conducted studies.

In this review, a large number of the cross-sectional studies used questionnaire surveys to assess respiratory symptoms and doctor-diagnosed respiratory outcomes. Although studies mostly used standardized questionnaires, these are subject to recall bias; we may suspect that people leaving in proximity to industries will have a tendency to overreport, thus yielding to overestimated effect size. In addition, standardized questionnaires, including the ISAAC and the ATS, are subjected to between-country and between-language variation that have been shown to influence the results and may limit comparison of findings across studies.[77,78] Administrative health data using ICD codes is also not free of possible outcome misclassification, but this method appears less prone to biases as compared with questionnaire. However, administrative health data are influenced by healthcare access, which is an issue in several countries worldwide. This may be an additional source of heterogeneity in this review.

Although our review focus on children, age groups varied across studies and this may also be a source of uncertainty and heterogeneity. The diagnosis of asthma is particularly difficult in children <5 years old due to developmental limitations, which may lead outcome misclassification, particularly if this diagnosis is from emergency room visits.[79] Age is a risk factor for asthma and possibly an effect modifier of the association with air pollution from industries; however, this could not be addressed in this review because too few studies were comparable.

Conclusions and recommendations

This review highlighted substantial heterogeneity across study design and methods, limiting the conduct of a meta-analysis to a few instances and including very few studies. Results from meta-analyses suggested no evidence for short-term asthma-related effects, whereas for long-term effects there was an indication of an association; however, limitations in terms of design (i.e., cross-sectional) and exposure assessment (i.e., binary exposure based on residential proximity) preclude drawing definite conclusions. Further high quality and well-conducted studies are needed to improve our understanding of the effects of industrial air pollution emissions on asthma and other respiratory outcomes. Specific recommendations include the use of a longitudinal study design, of methods of outcome assessment beyond reporting of doctor-diagnosis (e.g., using prescribed medication from prescription registry and/or diagnosis codes), of refined exposure assessment methods (e.g., atmospheric dispersion modeling) that capture local influence of point sources and that may allow distinguishing the contribution of industries from that of other sources, of continuous rather than categorical exposure analysis and, the inclusion of all important confounders in the analyses.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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