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The role of socioeconomic position as an effect-modifier of the association between outdoor air pollution and children's asthma exacerbations: an equity-focused systematic review

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Abstract

Background: The role of socioeconomic position (SEP) as an effect modifier of the association between asthma exacerbations and outdoor air pollution remains unclear.

Objective: To identify and summarize the evidence regarding SEP as an effect modifier of the association between asthma exacerbations and outdoor air pollution in children.

Methods: We conducted searches in five electronic databases from January 1950 to June 2015 with no language restriction. Observational studies involving children, measuring any non-biological outdoor air pollutant exposure, resulting in any asthma-related health service use, and reporting measures of effect by individual or aggregated SEP measures were included.

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Results: Ten studies met the inclusion criteria. Five studies reported on hospitalizations, three on emergency department visits, one on ambulatory visits, and one on repeat hospital visits. Six studies identified differential effects of the effect of air pollution on asthma outcomes by SEP with stronger effects for children with a low SEP level; however, the analysis of interaction between air pollutants and SEP was significant in one study of asthma hospitalizations only. The differential effect was reported using individual and aggregated SEP measures.

Conclusion: This review reveals that there is weak evidence of SEP as an effect-modifier of the association between air pollution and children's asthma exacerbations. While stronger negative effects on asthma-related hospitalizations occur for children living in a lower SEP, the sample size of some of the original studies limited the statistical assessment of the modification effect.

Keywords: air pollution; asthma; children; health effects; socioeconomic position.

Introduction

The adverse effects of both outdoor air pollution and socioeconomic position (SEP) on respiratory-related outcomes are well documented (1–3). Outdoor air pollution can affect children with asthma, increasing the risk of exacerbations and limiting asthma control (4). A recent European study estimated that 14% of the cases of incident asthma and 15% of all exacerbations of childhood asthma were attributed to exposure to traffic-related air pollution (5). Recent evidence also suggests that outdoor air pollution might play an important role in inducing new cases of pediatric asthma, especially among children in poor socioeconomic conditions (6, 7).

SEP is a determinant of health that modifies the effect of different exposures on health (8, 9), which is referred to as effect-modification. Three main mechanisms have been

proposed to explain this effect related to air pollution exposures: 1) unequal air pollution exposure related to SEP; 2) susceptibility directly related to SEP (e.g. differential levels of health care access, nutrition, stress in low SEP populations); 3) susceptibility from predisposing health conditions or behaviors already associated with low SEP such as obesity and second-hand smoking (9). Two recent systematic reviews of the literature on socioeconomic gradients in asthma has shown that low SEP is associated with increased prevalence of severe asthma in children and adults (10) but the role of SEP as a susceptibility factor for asthma incidence is still not clear (11). Despite the availability of literature on social factors, air pollution and respiratory health (9–12), none of these reviews summarize the evidence of the modifier effect of SEP on the relationship between air pollution and health services presentations for asthma exacerbations in children or adults. Some studies have reported a strong association between air pollution and use of health services for asthma in low SEP children (13, 14), whereas other studies (15, 16) have not found a differential effect across SEP categories. To our knowledge, the evidence about the role of SEP as an effect modifier of the association between asthma exacerbations and outdoor air pollution in children has not been synthesized. If consistent evidence of such effect modification exists, it would mean that children with low SEP have higher risk of poor asthma outcomes and this could be related to their SEP and the adverse effects of air pollution. Understanding the role of SEP on this association will help identify susceptible sub-populations based on SEP and design tailored prevention and control programs (9).

The primary objective of this systematic review was to identify and summarize the evidence regarding SEP as an effect modifier of the association between outdoor air pollution and children's asthma exacerbations.

Methods

Protocol

An a priori systematic literature review protocol was registered in PROSPERO under the registration number CRD42015022166. The research question addressed in this review was: Is SEP an effect-modifier of the association between outdoor air pollution and asthma exacerbations in children? If yes, what is the magnitude of this effect? Is there any variation of the effect-modification based on SEP measure used?

Search strategy

Comprehensive searches were conducted in five electronic databases: MEDLINE, EMBASE, CAB abstracts, CINAHL, and Scopus.

The search strategy was designed by a research librarian and comprised both selected subject headings and key words related to the following terms: "air pollution", "outdoor air pollution", "asthma", "wheeze", "child", "adolescent", "youth", "SEP", "socioeconomic status", "social class", "poverty", "social disadvantage" and "deprivation" (see details in Appendix). No restrictions on language, date, or types of publication were imposed on the searches.

Study selection and data extraction

This review considered studies that evaluated the effect-modifier role of SEP on the association between asthma and outdoor air pollution in children. The review identified SEP measurements and gradients in each publication and compared children living in low SEP with children living in high SEP as defined in the original studies. A stratified analysis of the associations according to SEP level was conducted as an exploratory analysis to identify potential effect-modification; then, the assessment of the statistical significance of the interaction term between air pollutants and the SEP measure was conducted as a confirmatory analysis. The criteria for selecting studies were: 1) observational analytic designs; 2) publication date between January 1, 1950 and June 30, 2015; 3) population included and reported data separately for children up to 18 years of age; 4) environmental exposure(s) to any non-biological outdoor air pollutant, either measured directly or inferred (i.e. by proximity to roadways), with special interest in criteria air pollutants (CAP): carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃) and particulate matter $\leq 10 \mu\text{m}$ and $\leq 2.5 \mu\text{m}$ in aerodynamic diameter (PM₁₀ and PM_{2.5}); 5) outcomes related to health service use [emergency department (ED) visits, physician visits or hospitalizations]; and 6) report of measures of association or effect by individual or aggregated SEP measures for one or more SEP levels or report the results of statistical interactions between air pollutants and SEP. We used Krieger's definition of SEP for this review and considered any single or combined measure related to income, education or occupation, as a SEP measure (17). Aggregated SEP measures were defined as area-based SEP measures generally based on census data. The primary outcome was asthma-related ED visits and the secondary outcome was asthma-related hospitalizations.

Two members of the team (LR-V; CB) conducted a pilot test to refine the selection criteria and the abstract-title screening form in a sample of 10 randomly selected papers. These two reviewers independently screened titles and abstracts generated from the search strategies to identify potentially relevant articles. Finally, the full text of the articles deemed relevant, and those whose abstracts and titles provided insufficient information were assessed for study eligibility by two independent reviewers.

Two reviewers (LR-V; CB) independently extracted data from the included studies using a standardized data abstraction form. The following information was obtained from individual studies: first author, publication year, country, data source, study aim, asthma outcome, outdoor air pollutants included, outdoor air pollution measurement, type of SEP measure, individual or aggregated level of SEP measure, sample size and population, confounders or other factors included in the analysis, results, and reported effect of the association between asthma and outdoor air pollution by SEP category.

Risk of bias assessment

Two reviewers (LR-V; CB) independently assessed the risk of bias of included studies, with disagreements being resolved by consensus. We used the risk of bias tool developed for environmental health science assessments by the US National Toxicology Program (NTP)-Office of Health Assessment and Translation (OHAT) (18). This tool includes six bias categories (selection, confounding, performance, attrition/exclusion, detection, selective reporting) and an additional category for other potential threats to internal validity. There are six individual risk-of-bias questions applicable for specific types of study designs (e.g. controlled clinical trials, cohorts) and nine common questions applicable to any study design. The common questions and the ones designed for observational studies were used. Each question of the OHAT tool is answered using one of the following options: definitely low, probably low, probably high, or definitely high risk of bias. Finally, for each outcome, studies were given a confidence rating in terms of the presence or absence of key study design features: High, moderate, low or very low.

Data synthesis

This review follows the recommendations from the PRISMA-Equity extension for systematic reviews with a focus on health equity (19, 20). Descriptive results of the included studies are provided. Agreement between reviewers on inclusion and risk of bias was measured using the κ (κ) statistic and interpreted according to the coefficient magnitude as poor (≤ 0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.00) (21). Disagreements on study selection were resolved by a third reviewer (CV-R).

Pooled quantitative measures with random effect models were planned for the analysis; however, due to heterogeneity in populations (e.g. children's age), outcomes, and designs across individual studies, pooling was not conducted. Heterogeneity also precluded meta-regression analyses to assess the effect of the type of SEP measure on the association between asthma and environmental exposures. Risk of bias assessment, data extraction, evidence tables and narrative synthesis of results were documented using Excel (Microsoft Corporation, USA). Forest plots of study results were created using GraphPad Prism version 6 (GraphPad software, San Diego CA, USA).

Results

Search results

The systematic search identified 1335 studies. After removal of duplicates and screening titles and abstracts, 98 studies were selected as potentially relevant, and 10 of them (13–16, 22–27) were included in the review (Figure 1). The complete list of excluded studies and reasons for exclusion is available upon request. Agreement between

reviewers was fair for title/abstract screening ($\kappa=0.35$; 95% CI: 0.26, 0.39) and substantial for full-text study selection ($\kappa=0.65$; 95% CI: 0.48, 0.81).

Study characteristics

The 10 papers meeting the selection criteria varied by study location, design, participants' age, number and type of air pollutants considered, SEP measure, and type of asthma outcome. Table 1 summarizes the main characteristics and results of the included studies.

The studies were mainly conducted in North America [five in the United States (US) and two in Canada], two in Korea and one in France. Most of the studies used a time-series design ($n=6$) (13, 14, 22–25); two were case-cross-over studies (15, 16), one a retrospective cohort (27) and one a cross-sectional design (26). Children's age varied widely across the studies, 0–14 years of age being the most common age range. There was also wide variation in the type and number of air pollutants assessed: NO_2 and O_3 were the air pollutants most commonly analyzed ($n=6$ for each one) (13–16, 22, 23, 26), followed by PM_{10} , SO_2 and CO ($n=4$ for each one) (14, 15, 22–24, 27), $\text{PM}_{2.5}$ ($n=3$) (13, 16, 25), and NO_x ($n=1$) (27). Asthma-related hospitalization was the most common outcome ($n=5$) (14, 22–25), followed by ED visits ($n=2$) (16, 26), phone calls made to mobile emergency physicians (hereafter ED calls $n=1$) (15), ambulatory visits ($n=1$) (13), and repeated hospital encounters ($n=1$) (27). The majority of studies used area-based SEP measures from census data and only two studies used an individual SEP measure based on health insurance premiums/status (24, 27).

Risk of bias assessment

All included studies had a *probably low risk* of selection, detection and selective reporting bias based on the OHAT risk-of-bias tool. Three studies have a *probably high risk* of confounding, as some important confounding factors were not included in the analysis (e.g. meteorological variables, influenza-related visits) (16, 23, 26). Therefore, for the asthma-related hospitalization outcome, four out of five studies showed a high level of confidence in their evidence based on the key features of the study design. For the asthma-related ED visits/calls outcome, only one of the three studies had a high level of confidence for the associations found.

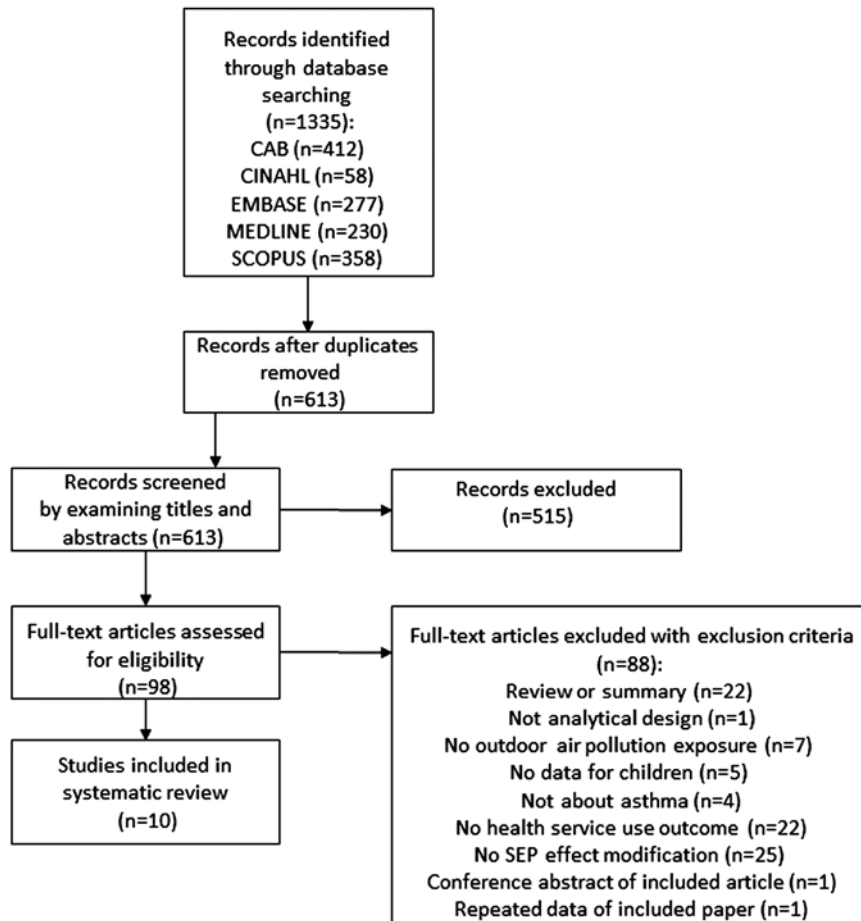


Figure 1: PRISMA flow diagram for selection of studies.

Effect-modification by SEP

The effect-modifier role of SEP was most commonly assessed for the association between air pollutants and asthma-related hospitalizations in children. Neidell (14) found that the effects of NO_2 and CO in California were larger than other CAPs; however, O_3 had a larger effect on children living in low SEP areas, especially for those aged 3–6 and 12–18 years, for which the interaction terms were statistically significant [$\beta=0.091$ ($p<0.01$) and $\beta=0.042$ ($p<0.05$), respectively]. Yap et al. (25) analyzed the effect of $\text{PM}_{2.5}$ on hospitalizations for asthma in children 1–9 years old in 12 California counties. The analysis of SEP modification-role yielded non-significant interactions; however, the associations between $\text{PM}_{2.5}$ exposure and asthma hospitalizations were stronger in areas with higher SEP in the Central Valley region (RR 0.98 95%CI 0.95–1.01 for low SEP and RR 1.07 95%CI 1.04–1.09 for high SEP).

Figure 2 shows the comparative results of the analysis of the effect modifier role of SEP for five air pollutants in three studies conducted in Canada and Korea that used

similar study designs and effect measures (22–24). When using lags between 0 and 5 days for NO_2 , O_3 and PM_{10} , the associations with asthma-related hospitalizations were higher for children living in low SEP areas; however, the 95% CI for high versus low SEP do overlap. For CO and SO_2 , there was no clear pattern of effect-modification by SEP in the included studies. From those three studies, only Lee et al. (23) assessed statistical interaction found non-significant results.

Three studies assessed the role of SEP as an effect modifier on the association between air pollutants and asthma-related ED visits/calls. Gleason et al. (16) assessed the effect of same-day $\text{PM}_{2.5}$ using the proportion of people living in poverty according to the New Jersey census as the SEP indicator. The study did not find any pattern of effect-modification by SEP level stratification and the interaction terms were not statistically significant. The effect of same day O_3 on asthma ED visits also was not modified by SEP aggregated measures in another study (Figure 3) (15, 16). In Strasbourg, France, the effects of SO_2 , PM_{10} and NO_2 on emergency calls were not different by SEP level

Table 1: Characteristics and results of included studies.

Reference; study location and study period	Study design, study population and size	Pollutants (mean levels) and methods assessing exposure	Asthma-related outcome	SEP measure	Summary of study findings for SEP effect-modification
Lin et al., 2004 (22); Vancouver area; 1987–1998	Time series study; hospitalizations of 6–12 year olds; from British Columbia Linked Health Dataset (n=3,822)	Mean CO (960), SO ₂ (4.77), NO ₂ (18.65), O ₃ (28.02), PM ₁₀ (NS), PM _{2.5} (NS) from 1995–1998; from monitoring stations	Hospitalizations	Ecological; average household income adjusted for household size by enumeration area defined by 1991 and 1996 Canadian census	1-day lag RR (95% CI): Low SEP High SEP NO ₂ male: 1.13 (1.04–1.23) 1.04 (0.95–1.14) O ₃ female: 1.11 (0.97–1.28) 0.91 (0.78–1.05) CO male: 1.06 (0.99–1.14) 1.06 (0.98–1.14) SO ₂ female: 1.05 (0.95–1.16) 1.07 (0.96–1.19) Interaction terms were not tested.
Neidell 2004 (14); California, US; 1992–1998	Time series study; hospitalizations of 1–18 year olds from California Hospital Discharge Data (n=38,757)	Mean O ₃ (38.91), CO (1777), PM ₁₀ (34.21), NO ₂ (45.95); from monitoring stations	Hospitalizations	Ecological; percentage of high school dropouts by zip code	Linear regression beta coefficients of effect combined for 0–18 year olds: Low SEP High SEP O ₃ 0.20 –0.14 CO 0.17 –0.04 NO ₂ –0.09 0.09 PM ₁₀ –0.03 0.002 Interaction terms for CO and O ₃ were statistically significant at 5%.
Lee et al., 2006 (23); Seoul, Korea; 2002	Time series study; hospitalizations of 0–14 year olds from National Health Insurance Cooperation database (mean 8.09 patients/day)	Mean PM ₁₀ (135.18), SO ₂ (8.74), NO ₂ (6.08), O ₃ (29.83), CO (6370); from monitoring stations	Hospitalizations	Ecological; average regional health insurance rates	Higher effect from 0–5 day lag RR (95% CI): Low SEP High SEP O ₃ 1.32 (1.11–1.58) 1.12 (1.00–1.25) CO 1.02 (0.85–1.24) 1.06 (0.96–1.17) NO ₂ 1.29 (1.05–1.58) 1.13 (1.01–1.27) PM ₁₀ 1.31 (1.14–1.51) 1.16 (1.05–1.28) SO ₂ 1.29 (1.08–1.53) 1.08 (0.96–1.22) Interaction terms were not significant.
Bae 2010 (24); Seoul, Korea; 2003–2005	Time series study; hospitalizations of 0–14 year olds from National Health Insurance database (n=23,958)	Mean PM ₁₀ (62.65) from monitoring stations	Hospitalizations	Individual; based on the national health insurance premium scale and Medic Aim claim data	Percentage increase and 95% CI: Low SEP High SEP PM ₁₀ 1.78 (0.79–2.78) 0.83 (0.34–1.32) Interaction terms were not tested.
Yap et al., 2013 (25); 12 South Coast and Central Valley California counties, US; 2000–2005	Time series study; hospital admissions of 1–9 year olds from California Office of Statewide Health Planning and Development (n=146,224)	Counties mean PM _{2.5} varied between 12.75 and 24.61 from monitoring stations	Hospitalizations	Ecological; Townsend index by zip code areas from US Census 2000	3-days lag Rate ratio (95% CI): Low SEP High SEP PM _{2.5} South Coast 1.07 (1.03–1.08) 1.07 (1.05–1.09) Central Valley 0.98 (0.95–1.01) 1.07 (1.04–1.09) Interaction terms were not significant.

Table 1 (continued)

Reference; study location and study period	Study design, study population and size	Pollutants (mean levels) and methods assessing exposure	Asthma-related outcome	SEP measure	Summary of study findings for SEP effect-modification
Laurent et al.; 2008 (15); Strasbourg, France; 2000–2005	Small-area case-crossover study; emergency calls of 0–19 year olds from emergency health care network (n=954 phone calls)	Mean PM ₁₀ (22.6), SO ₂ (8.9), NO ₂ (36), O ₃ (57.7); from ADMS-urban model	Emergency calls	Ecological; deprivation index based on 1999 French Census	0–1-day lag OR (95% CI): Low SEP High SEP PM₁₀ 0.94 (0.81–1.09) 0.97 (0.71–1.33) NO₂ 0.93 (0.79–1.09) 0.76 (0.53–1.09) SO₂ 0.90 (0.67–1.22) 1.08 (0.52–2.21) O₃ 0.93 (0.81–1.08) 1.05 (0.81–1.37) Interaction terms were not significant.
Gleason et al.; 2014 (16); New Jersey, US; 2004–2007	Time-stratified case-crossover design; emergency department visits of 3–17 year olds from New Jersey Department of Health; (n=21,854 visits)	Mean O ₃ (46.18), PM _{2.5} (11.78) from monitoring stations	Emergency department visits	Ecological; proportion of population living in poverty based on 2000 US Census	Same day OR (95% CI): Low SEP High SEP PM_{2.5} 1.00 (0.98–1.03) 0.99 (0.96–1.02) O₃ 1.10 (1.07–1.13) 1.07 (1.04–1.11) Interaction terms were not significant.
Schmool et al.; 2014 (26); New York City, US; 2008–2010	Cross-sectional spatial analysis; emergency department visit rates of 0–14 year olds from the New York State Department of Health; (n=mean area-level rate 6.8%)	Mean NO ₂ (25.1) from land use regression model	Emergency department visits	Ecological; Three social stressor factors derived from factor analysis based on 29 administrative indicators at area level	Betha coefficients (SE) per IQR: Low SEP High SEP F1: “Violent crime and physical disorder” NO₂ 0.013 (0.008) 0.011 (0.014) F2: “crowding and poor access to resources” NO₂ 0.055 (0.026) –0.001 (0.008) F3: “noise complaints and poverty crime” NO₂ –0.013 (0.019) –0.016 (0.016) Interaction term was significant for F2 but not significant interaction was found by area-level poverty rates.
Burra et al., 2009 (13); Toronto, Canada; 1992–2001	Time series study; family physician and specialists service claim records for 1–17 year olds; (n=1,146,215)	Mean SO ₂ (9.7), NO ₂ (39.2), O ₃ (33.3) and PM _{2.5} (17.9); from monitoring stations	Ambulatory physician visits	Ecological; average household income at census tract level using the 1996 Canadian census	1-day lag RR (95% CI): Low SEP High SEP Females PM_{2.5} 1.01 (1.01–1.02) 1.00 (0.99–1.01) NO₂ 1.03 (1.02–1.03) 1.02 (1.02–1.03) Males SO₂ 1.02 (1.02–1.03) 1.02 (1.01–1.02) O₃ 0.96 (0.96–0.96) 0.96 (0.96–0.97) Interaction terms were not tested.

Table 1 (continued)

Reference; study location and study period	Study design, study population and size	Pollutants (mean levels) and methods assessing exposure	Asthma-related outcome	SEP measure	Summary of study findings for SEP effect-modification
Delfino et al., 2009 (27); Orange County, California, US; 2000–2003	Retrospective cohort study; admission to the hospital or visits to emergency department of 0–18 year olds; (n=2768 patients and 697 readmissions)	Mean NO ₂ cool season (5.24), NO ₂ warm season (5.66), NO _x cool (8.10), NO _x warm (6.35), CO cool (11.4), CO warm (103) from CALINE4 dispersion models	Recurrent hospitalization or emergency department visit	Ecological (poverty level and median household income based on US Census 2000 block group) Individual (insurance status)	Hazard ratios (95% CI) by IQR: By poverty level NO _x 1.12 (1.03–1.21) 1.08 (0.99–1.16) CO 1.09 (1.00–1.19) 1.06 (0.98–1.13) By median household income NO _x 1.07 (0.98–1.16) 1.14 (0.06–1.24) CO 1.04 (0.96–1.13) 1.12 (1.03–1.21) By insurance status NO _x 1.08 (1.01–1.16) 1.14 (1.04–1.25) CO 1.06 (0.99–1.14) 1.10 (1.01–1.21) Interaction terms were not significant.

^aParts per billion for gasses, µg/m³ for PM; CI, confidence interval; CO, carbon monoxide; F, factor; IQR, interquartile range; NO_x, nitrogen oxides; NO₂, nitrogen dioxide; O₃, ozone; OR, odds ratio; PM, particulate matter; RR, relative risk; SE, standard error; SEP, socioeconomic position; SO₂, sulfur dioxide; US, United States.

(Figure 3); the interaction terms for SEP and the categorical and continuous variable were not significant (15). In contrast, Shmool et al. (26) used an exploratory ecologic spatial analysis in New York City and found a statistically significant modification effect of NO₂ on asthma ED visits by SEP (i.e. defined as a factor two mainly characterized by “crowding and poor access to resources”; p-value of interaction term <0.05). The negative effect was higher in city areas in which the SEP indicator was above the median ($\beta=0.055\pm SE=0.026$ for low SEP and $\beta=-0.001\pm SE=0.008$ for high SEP). However, the authors reported non-significant interaction terms (absence of effect modification) in the association between NO₂ and asthma ED visits when using area-level poverty rates as a SEP modifier.

Two studies assessed whether SEP was an effect modifier of the relationship between air pollution exposure and other outcomes of asthma-related health services use. Burra et al. (13) measured social disadvantage and assessed the effect modification on the association between air pollution and ambulatory visits for asthma in an urban setting. For children under 18 years old, there was a significant SEP quintile ratio (Q1/Q5=1.006 95%CI 1.000–1.013) using the single day SO₂ exposure. There was also a significant difference in the SEP Q1/Q5 risk ratio using the PM_{2.5} 5-day cumulative average exposure for males and single-day exposure for females (RR=1.017 95%CI 1.002–1.031 and RR=1.012 95%CI 1.001–1.023, respectively). No significant associations were found between O₃ and ambulatory asthma visits. Delfino et al. (27) studied the effect of traffic-related air pollution on repeated hospital encounters for asthma in urban California. Using different SEP measures at census block level, they found a stronger association with NO_x among children living in higher income areas (HR=1.07, 95%CI 0.98–1.16 for low SEP vs. HR=1.14, 95%CI 0.006–1.24 for high SEP measured by median household income); however, the assessment of statistical interaction gave non-significant results and the authors suggested that this result might have been attributed to more accurate data collected in this group.

Discussion

This is the first systematic review summarizing the evidence regarding the role of SEP as an effect modifier of the association between air pollution and asthma-related health services outcomes in children. We identified 10 studies showing different results of SEP as an effect-modifier. Overall, five out of the 10 studies identified differential

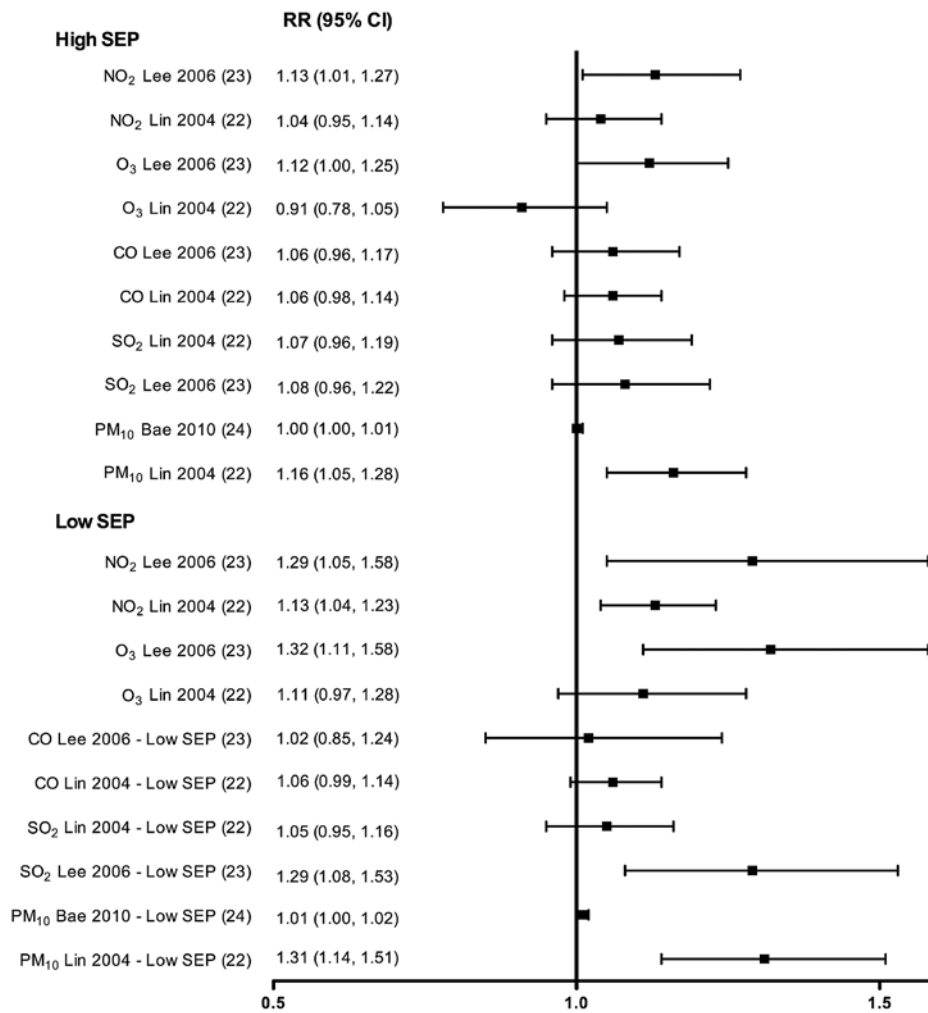


Figure 2: Effect modification by socioeconomic position on the association between air pollutants and asthma hospitalizations in children.

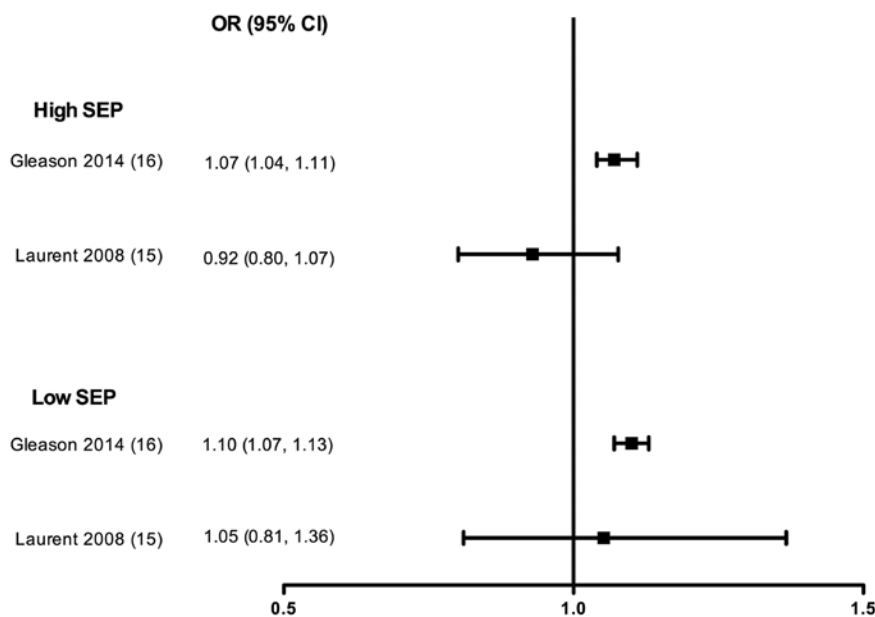


Figure 3: Effect modification by socioeconomic position on the association between ozone and asthma emergency visits/calls in children.

effects by SEP in children in important health services outcomes, with stronger negative effects among the low SEP category (14, 22–24, 26). However, an assessment of statistical interaction was conducted only in three of the five studies (14, 23, 26). Moreover, a statistically significant interaction was reported in one only of these comparisons (14). The effect of O_3 on asthma-related hospitalizations was the association with most consistent differential effects by SEP conditions in Canada, Korea and the US (14, 22, 23). In addition to O_3 , NO_2 and PM_{10} showed differential associations with asthma-related hospitalizations in children according to SEP in Canada and Korea (22–24). None of these differential effects by SEP had statistically significant interactions, however, probably related to a lack of power due to limited sample size in the original studies.

Despite numerous studies assessing the effects of outdoor air pollution on ED visits in adults and children (28), only a few have assessed the effect modification of SEP, especially in children. Overall, we found three studies failing to demonstrate any SEP differential effect on the association between pollutant exposure and asthma-related ED visits/calls (15, 16, 26). There are several possible explanations for these findings. First, ED visits may reflect issues related to access to primary health care more than a setting for the delivery of care for severe cases (29). From a severity perspective, ED visits are heterogeneous (range in severity from mild to severe exacerbations), whereas hospitalizations are more homogeneous (moderate-severe exacerbations). Finally, it may be that the effect of pollution is to increase airway inflammation in already inflamed airways (perhaps related to poverty, living conditions, access to medications, etc.) and result in those patients being disproportionately affected.

The current evidence points out a differential effect by SEP on more severe asthma outcomes such as hospitalizations. Furthermore, O_3 , NO_2 and PM_{10} are also consistently associated with outdoor air pollution-related mortality (1, 30), including differential effects by SEP conditions (2). As suggested by O'Neill (9), this might support the theory that SEP differentially influences patients through chronic poor living conditions, higher pollution exposures and poor asthma control associated with low SEP. Conversely, these results counter the hypothesis that the gradients are related to differential access to health services during acute asthma episodes, particularly in countries without financial barriers to health care access (e.g. Canada). This hypothesis, however, needs to be verified through additional studies conducted in countries with different health systems and social conditions.

As SEP is a complex construct, its measurement in these studies requires further discussion. One can define

SEP as social and economic factors influencing the position that individuals or groups hold within the societal structure. SEP can be estimated using measures of occupation, education and income at individual level, or using area-based indices at the aggregated (area) level (17, 31–33). Most of the studies in this review used aggregated SEP measures at area-level and found differential but non-statistically significant interaction effects by SEP. Only two studies reported individual SEP measures and they also failed to find significant modifier effects by SEP (24, 27). In this regard, Kim et al. compared the role of SEP as an effect modifier on the association between outdoor air pollution and asthma-related ED visits using individual and regional variables from the general population of Seoul, Korea (34). The authors found a modifier effect using only regional-level variables, suggesting that contextual area-level conditions might have a stronger and differential effect than income-related individual conditions. Interestingly, they also reported that all regions included in their study had similar pollutant concentrations and therefore, exposure to higher levels of outdoor air pollution in low SES regions was not the potential mechanism behind the SEP differential effect. Similarly, a nation-wide Canadian mortality study reported that areas with higher percentages of individuals with high education, income and employment have longer exposure to low concentrations of $PM_{2.5}$ (35); still Canadian studies have also reported stronger effects of air pollution on mortality and respiratory health in populations with lower income and education (36, 37).

Many factors have been proposed to explain the differential effect of air pollution on health outcomes by SEP. Children in low SEP conditions may face important barriers accessing health care services; higher exposure to air pollution sources, violence and stressor factors, poor hygiene and housing conditions, and differential dietary patterns, among others (9). Health care use and access may differ by country depending on different factors and, especially, the characteristics of the health care systems. Some studies in this review were conducted in Canada (13, 22), where there is universal health care coverage. Still, they showed consistent differential effects by SEP categories, suggesting that universal health care may not guarantee equity in access to health care services (38) or that access is not major determinant of the differential effect by SEP in some settings. For the purpose of this systematic review we do not consider that differences in access to health care introduced a bias in the results. Even in the case of settings with recognized unequal access to health care by SEP conditions (i.e. US jurisdictions), the analysis of effect modification is valid since its purpose is assessing the relationship between air pollution and asthma

exacerbations within a given SEP group, and not the frequency/prevalence of health services visits. While the low SEP population seeking health care might be underrepresented in those settings, it is important to note that in the included studies, the number of visits are large in both SEP groups, and frequently higher for people in the low SEP, including the studies from the US (14, 16, 27).

Shmool et al. (26) assessed the effect modification of stressor factors (e.g. the measure of SEP) on the association between area-average NO_2 and asthma-related ED visits, identifying a differential effect, albeit non-statistically significant modification effect. Effects were mainly related to factors representing “crowding and poor access to resources”, but not to those representing “violent crime or property crime” (26). Therefore, as suggested by Forno, (3) a more practical approach to address inequalities in asthma and environmental health practice may include the use of robust SEP measures to promote interventions in social susceptible populations. Having identified those populations, the mechanisms behind the modifier role of SEP could be addressed locally in order to introduce public health interventions targeting more specific sub-populations.

Strengths and limitations

Some strengths and limitations of this review need to be addressed. The strengths of this systematic review pertain to its rigor in searching the literature, the criteria-based selection of relevant evidence, the rigorous appraisal of study risk of bias and the evidence-based inferences. The statistical quality of the included studies is also worth mentioning. For example, the commonly used generalized additive models (GAM) for the analysis of time-series studies of air pollution tended to overestimate the relative risk of air pollution on health outcomes. The problem resided in the use of default convergence criteria included in the biostatistics software S-PLUS that lead to the development of alternative techniques to model GAM convergence (39, 40). Interestingly, the five papers included in this review using GAM described the correction of the convergence criteria; therefore, the results are not likely to be affected by the GAM overestimation (13, 22–25). There are, however, some limitations. First, the small number of available studies and their heterogeneity precluded the calculation of pooled estimates of the differential effects of SEP. This was particularly true for the ED visits/calls data. Similarly; we were not able to analyze variations by geographical location. It is well known that the effect-modifier phenomenon is not a condition related to

a study design or analysis, but a property of the association between exposure and health outcome that may vary geographically (41). Therefore, it is recommended that SEP differential effects should be routinely assessed in environmental health analyses and if the SEP differential effect is present, the mechanism behind the SEP differential effect should be addressed at local level.

Second, the findings of this systematic review are likely to be affected by the confounding identified in some studies. We did not exclude studies with probably high risk of confounding in the analysis as they still provide important information for the review. Moreover, the main finding of this review related to the weak evidence of SEP as an effect-modifier in children’s asthma-related hospitalizations is robust even after excluding the study with potential high risk of confounding. The findings are likely to be affected also by the SEP variable measurement. Measuring SEP is a complex endeavor (32, 42) SEP aggregated indicators based on adults’ characteristics might facilitate comparison across the studies but not accurately reflect the SEP of children. Further work needs to be performed on SEP measurement in children living in different social settings.

Finally, selection and publication bias are potential limitations of this review. Although we conducted a comprehensive electronic search and identified an important number of potentially eligible studies, many of them were excluded either because SEP was used as a confounding variable, or the analyses were not available specifically for children (Figure 1). We contacted some authors of studies in which SEP modification analyses were conducted; however, data was not published for children and re-analysis of data was not possible in most cases.

Conclusion

This systematic review synthesized the evidence on the role of SEP as an effect-modifier of the association between air pollutants (mainly O_3 , followed by NO_2 , and PM_{10} , using lags between 0 and 5 days) and important asthma-related outcomes. The results revealed that associations between hospitalizations and air pollutants seem to have a stronger negative influence on children living in low SEP conditions. However, confirmation of the effect modification by statistically significant interactions between air pollutants and SEP was evident only in one out of five studies, probably related to sample size limitations of the original studies. Three studies failed to identify effect modification by SEP for asthma-related ED visits. The SEP modifier role was mainly assessed using

aggregated measures; however, differential effects by SEP were also observed in the two studies that used individual SEP measures. Future studies assessing the association between air pollution exposure and health effects in children should address the differential effect of SEP and, if present, the potential mechanisms behind this phenomenon should be addressed at local level as mechanisms might vary geographically.

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the selection process and contributed to the data interpretation. MO, AO-V and BR contributed to study design, and data interpretation. All authors contributed in writing and editing the manuscript and approved the final version for publication.

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Appendix

MEDLINE SEQUENCE AND TERMS

1. Air Pollution/
2. air pollutants/ or particulate matter/ or sulfur dioxide/ or nitrogen dioxide/ or ozone/ or carbon monoxide/ or polycyclic hydrocarbons, aromatic/ or volatile organic compounds/
3. ("air pollution" or "air pollutant").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. ("ambient air pollution" or "outdoor air pollution").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. 1 or 2 or 3 or 4
6. asthma/
7. ("respiratory sounds" or "asthma").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. ("respiratory symptoms" or "wheez*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. 6 or 7 or 8
10. Child/
11. ("child*" or "adolesc*" or "teen*" or "youth" or "pediat*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. 10 or 11
13. socioeconomic position/ or socioeconomic factors/ or exp poverty/ or social class/ or exp Social Marginalization/
14. (social adj (class* or disadvantage*)).mp.
15. (deprivation or poverty or "socioeconomic status" or "socioeconomic*").mp.
16. 13 or 14 or 15
17. 5 and 9 and 12 and 16
18. limit 17 to yr="1950 -Current"

EMBASE SEQUENCE AND TERMS

1. exp Air Pollution/
2. exp air pollutant/ or particulate matter/ or nitrogen dioxide/ or ozone/ or carbon monoxide/ or sulfur dioxide/ or polycyclic aromatic hydrocarbons/ or volatile organic compound/
3. ("air pollution" or "air pollutant").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. ("ambient air pollution" or "outdoor air pollution").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Appendix (continued)

5. 1 or 2 or 3 or 4
6. asthma/
7. ("respiratory sounds" or "asthma").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. ("respiratory symptoms" or "wheez*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. 6 or 7 or 8
10. Child/
11. ("child*" or "adolesc*" or "teen*" or "youth" or "pediat*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. 10 or 11
13. socioeconomic position/ or socioeconomic factors/ or exp poverty/ or social class/ or exp Social Marginalization/ or exp social status/
14. (social adj (class* or disadvantage*)).mp.
15. (deprivation or poverty or "socioeconomic status" or "socioeconomic*").mp.
16. 13 or 14 or 15
17. 5 and 9 and 12 and 16
18. limit 17 to yr="1950 -Current"

CAB ABSTRACTS, CINAHL, AND SCOPUS

air pollut* OR "ambient air pollution" OR "outdoor air pollution") AND TOPIC: (asthma* OR wheez* OR "respiratory symptoms") AND TOPIC: (child* OR adolesc* OR teen* OR pediat*) AND TOPIC: ("socioeconomic position" OR "socioeconomic status" OR "social class" OR "socioeconomic factors" OR "poverty" OR "social class" OR "social status" OR "social marginalization" OR "socioeconomic*") Timespan: 1950-2015.

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