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REVIEW ARTICLE



Critical review of long-term ozone exposure and asthma development

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ABSTRACT

Asthma, a chronic respiratory disorder with complex etiology and various phenotypes, is a considerable public health concern in the USA and worldwide. While there is evidence suggesting ambient ozone exposure may exacerbate asthma, information regarding the potential role of ozone in asthma development is more limited. Thus, we conducted a critical review of observational epidemiology studies to determine whether long-term ambient ozone exposure is a risk factor for asthma development. We identified 14 relevant studies; 11 evaluated asthma development in children, while three studies, based on a single cohort, assessed this outcome in adults. Studies of childhood asthma and long-term ozone exposure – including exposure *in utero*, during the first year of life and during early childhood – reported inconsistent findings, which were further weakened by critical methodological limitations in statistical analyses and in exposure and outcome assessments, such as exposure measurement error and a lack of adjustment for key confounders. For adult-onset asthma, long-term ozone exposure was associated with an increased risk in men but not women. In addition to considerable uncertainties due to potential exposure measurement error and a lack of adjustment for key confounders, this study has limited generalizability to the US general population. While experimental evidence indicates that it may be biologically plausible that long-term ozone exposure could contribute to asthma development, it does not provide insight regarding an established mode of action. Future research is needed to address the uncertainties regarding the role of long-term ambient ozone exposure in asthma development.

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Ozone; asthma development; childhood asthma; adult-onset asthma; long-term exposure; review

Introduction

Asthma is a common chronic disease and a considerable public health concern in the USA, with an estimated prevalence of 7.7% in adults and 9.5% in children between 2008 and 2010 (Moorman et al., 2012). Globally, the prevalence of asthma is increasing in many countries, particularly among children (GINA, 2017). Asthma is a multifactorial, heterogeneous disease with many clinical phenotypes, each of which involves chronic airway inflammation, reversible airway obstruction and airway hyperresponsiveness (AHR) to various triggers, as well as airway remodeling in later stages of the disease (Bates et al., 2009; Currie & Baker, 2012; Grainge & Davies, 2013; Myers & Tomasio, 2011; Noutsios & Floros, 2014; Shin et al., 2009).

The etiology of asthma is complex, and a specific cause has yet to be identified. For childhood asthma, genetics (e.g. parental asthma), respiratory infections, prenatal exposure to environmental tobacco smoke (ETS) and premature birth are well-established risk factors (Bates et al., 2009; Myers & Tomasio, 2011; Noutsios & Floros, 2014; Subbarao et al., 2009); other putative risk factors include allergens, traffic-related air pollution, breastfeeding, family size, and structure and sex (Subbarao et al., 2009). In contrast, the risk of true adult-onset asthma (i.e. not a relapse of childhood asthma in

adulthood) may be increased by allergic conditions, obesity, family history of asthma, and exposures to environmental allergens and irritants (Ilmarinen et al., 2015; Subbarao et al., 2009).

Many observational and experimental studies have investigated the potential association between short-term exposure to ozone and outcomes related to asthma severity, such as emergency department visits and hospital admissions for asthma, as well as respiratory symptoms and lung function changes in asthmatics (reviewed by Goodman et al., 2018). The evidence from these studies is suggestive of an association between short-term exposure to ambient concentrations of ozone and asthma severity (Goodman et al., 2018). By contrast, the potential impact of long-term ozone exposure on the development of asthma is unclear. The 2013 Integrated Science Assessment for Ozone and Related Photochemical Oxidants (ISA; US EPA, 2013a) reviewed observational epidemiology studies published through 2011 and concluded that the evidence supported long-term ozone exposure as a risk factor for asthma development in adults and as an effect modifier in children. Here, we conduct a critical review that includes more recently published observational studies that evaluated the association between long-term ambient ozone exposure and incident asthma.

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Methods

Literature search and study selection

We searched PubMed and Scopus for studies published through October 2017 that evaluated long-term ozone exposure and asthma development using the following terms: (“ozone” OR “air pollution”) AND (“asthma development” OR “development of asthma” OR “asthma onset” OR “onset of asthma” OR “newly onset of asthma” OR “incidental asthma” OR “incidence of asthma” OR “asthma incidence” OR “airway hyperresponsiveness” OR “bronchial hyperresponsiveness” OR “wheeze” OR “wheezing”) AND (“prospective” OR “cohort” OR “longitudinal” OR “epidemiology” OR “epidemiologic” OR “epidemiological” OR “risk factor” OR “risk factors”). In addition, we cross-referenced the ozone ISA (US EPA, 2013a) and the bibliographies of review articles to identify any studies that were not found in the literature searches.

We included peer-reviewed observational studies of humans that evaluated the associations between long-term ozone exposure (defined as approximately 30 d or longer in duration; US EPA, 2013a) and incident asthma (i.e. incidence, incidence rate or lifetime prevalence of asthma). We excluded studies that met any of our exclusion criteria: laboratory animal or *in vitro* studies; experimental studies; reviews; editorials; commentaries; correspondence/communications; letters to the editor; studies that were not published in English; studies that did not evaluate long-term exposure to ambient ozone (e.g. studies that evaluated short-term exposure or indoor exposure); studies that did not evaluate incident asthma (e.g. studies that evaluated prevalence of asthma or asthma exacerbation); and studies that did not report specific results on the associations between long-term ozone exposure and incident asthma.

Data extraction

From each selected study, we extracted and tabulated information on general and quality characteristics, such as study design, location, study population/cohort, study period, sample size, various features of the exposure assessment (e.g. metric, averaging time, estimation method), outcome ascertainment and statistical approach (e.g. regression model, confounders adjusted for, sensitivity analyses). We also extracted and tabulated detailed study results and graphically presented the study-specific results with the risk estimates standardized to a 1 part per billion (ppb) increment in ozone concentrations.

Study quality evaluation

We developed detailed study quality criteria to evaluate the internal validity of selected studies. These criteria were tailored specifically for long-term ozone exposure and asthma development, and were based on several frameworks, including the Integrated Risk Information System (IRIS) Risk of Bias (RoB) evaluation (US EPA, 2013b, 2014), the National Toxicology Program’s (NTP) Office of Health Assessment

and Translation (OHAT) approach (NTP, 2015a,b), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) system (von Elm et al., 2007a–e), the Navigation Guide (Kousta et al., 2013, 2014) and the recent ISAs for oxides of nitrogen (NO_x) and sulfur oxides (SO_x) (US EPA, 2016a,b). We did not conduct a quantitative RoB evaluation (e.g. by categorizing studies into different quality tiers like in the OHAT approach) because it was extremely difficult, if not impossible, to delineate the magnitude and direction of the biases in the available observational studies. We also considered the external validity of the studies in relation to the US general population.

The quality criteria include various methodological attributes, which we applied to individual studies to assess their quality and risk of bias. We first considered the study design: cohort or nested case-control studies had a lower risk of selection bias than case-control studies.

Next, we considered various aspects of the exposure assessment, including spatial and temporal variability, residential mobility, exposure validation, and temporality between exposure and outcome. Studies that employed inverse distance weighting (IDW) or modeling of monitoring data better accounted for spatial variability of the ozone exposure than the studies that only relied on monitoring data. Studies that used time-varying ozone exposure estimates or assessed multiple exposure windows in their analyses better accounted for temporal variability than the studies that only used time-invariant ozone exposure and assessed a single exposure window. Studies that considered residential mobility in the exposure estimates or validated the exposure estimates likely had less exposure measurement error than studies that did neither. Also, studies that clearly established the exposure-outcome temporality (i.e. the exposure occurred before the outcome) had a lower risk of bias than the studies that did not.

We considered two aspects of assessing asthma development: the diagnostic accuracy in the study population and the ascertainment of asthma diagnosis. Because it is difficult to accurately diagnose asthma in small children (e.g. younger than 6 years of age; ATS, 2007; GINA, 2017), studies with participants aged 6 years or older had less potential for outcome misclassification than studies that included younger children. Studies that relied on medical records, hospital discharge records, insurance claims, or adults’ reports of physician diagnoses had less potential for outcome misclassification than the studies that used first asthma hospitalization as the surrogate for incident asthma. Asthma hospitalization, a serious exacerbation event, is a poor surrogate for incident asthma because only a small proportion of individuals with asthma are hospitalized (Akinbami et al., 2012). Also, ozone exposure may be associated with asthma severity (Goodman et al., 2018; US EPA, 2013a); therefore, the use of first asthma hospitalization, a severe exacerbation event, may bias the results regarding ozone and asthma development.

We also considered the robustness of the statistical analyses in each study. Studies that employed at least one of the following measures likely yielded more robust results than the studies that did not: used appropriate statistical models

(e.g. logistical regression models for incidence/lifetime prevalence, Cox regression models for incidence rate) with the model assumptions tested (e.g. the proportional hazard assumption for Cox regression models); adjusted for potential confounders identified from the literature including age, sex, race, socioeconomic status (e.g. income, education attainment), maternal age, gestational duration, family history of asthma or allergy, smoking, indoor environment (e.g. mold, dampness, pet ownership), traffic-related pollution (e.g. NO₂, PM_{2.5}, distance to major roadway) and other environmental covariates (e.g. surrounding greenness); evaluated non-linear dose-response relationships (e.g. quantiles, splines); and conducted sensitivity analyses.

Last, we evaluated the external validity of the study relative to the US general population. We determined that the results of childhood asthma from western populations (i.e. North American and European cohorts) are more generalizable to the USA, while results from Asian children populations are less so. For studies of adult-onset asthma, if the characteristics of the study population were similar to those of the US general population, we concluded that the findings are generalizable to the USA.

Results

Literature search and study selection

The literature searches resulted in a total of 1279 publications, and we identified 28 potentially relevant epidemiology studies by reviewing titles and abstracts. We did not identify any additional publications from cross-referencing the ozone ISA and review articles. After full-text review, we excluded 14 studies, resulting in 14 studies for review (Figure 1).

Table 1 presents the general characteristics of the selected studies. The majority of the studies were conducted in the USA and Canada in the past two decades. Out of the 14 studies, 11 evaluated asthma development in children, while three studies based on a single cohort, assessed this outcome in adults.

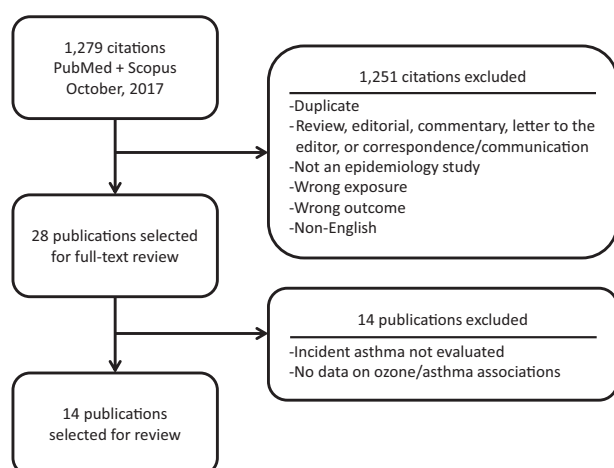


Figure 1. Selection of epidemiology studies for long-term ozone exposure and asthma development.

Study quality evaluation

We evaluated the internal and external validity of individual studies based on criteria we developed (Table 2). Thirteen out of the fourteen studies selected were cohort studies or nested case-control studies, which had a lower risk of selection bias than the one population-based case control study (Nishimura et al., 2013).

Regarding exposure assessment, there were considerable uncertainties in all of the selected studies. Several studies did not account for spatial variability or residential mobility when estimating ozone exposures. The majority of the studies did not account for the temporal variability in ozone exposure or validate the ozone exposure estimates. In addition, a source of considerable uncertainty in most of the studies with retrospective exposure assessment was a lack of temporality between the ozone exposure and the development of asthma (i.e. exposure windows covered time periods after the development of asthma).

Most studies of childhood asthma included children younger than 6 years old, in whom asthma could not be diagnosed accurately. However, these studies relied on medical records, insurance claims and parental reports of physician diagnoses to ascertain a diagnosis of asthma, which reduced the potential for outcome misclassification. Notably, Lin et al. (2008) relied solely on hospital discharge records to identify a child's first hospitalization for asthma as a surrogate for incident asthma, which, as discussed, is a poor proxy for asthma development. All of the studies of asthma development in adults ascertained incident asthma through self-reported physician diagnosis and symptoms, and thus had a low risk for outcome misclassification.

With regard to statistical analyses, most studies employed suitable statistical models and tested model assumptions when appropriate, except for those conducted by McConnell et al. (2010) and Islam et al. (2008), who did not test the proportional hazard assumption. Half of the 14 studies assessed potentially non-linear dose-response relationships by using quantiles or splines of ozone exposure in their analyses, and most conducted some form of sensitivity analysis. We also found that, while the vast majority of the 14 studies adjusted for confounders, such as age, sex, socioeconomic status and smoking, several studies did not account for race, maternal age, gestational duration, or family history of asthma or allergy, and few studies considered the potential confounding effects of indoor environment, traffic-related pollution or other environmental factors (e.g. surrounding greenness).

Regarding external validity, the majority of the studies were conducted in the USA, Canada and Europe, so their findings are more generalizable to the US population, compared to the three studies in Asia (Dong et al., 2013; Kim et al., 2013; Wang et al., 2016).

Overall, while findings from most of the selected studies are generalizable to the US population, limitations of ozone exposure assessment and the lack of adjustment for several key environmental confounders may impact the interpretation of study results.

Table 1. General characteristics of epidemiology studies of long-term ozone exposure and asthma development.

Study	Location	Study period	Cohort	Population	Study population ^a			Age (years, mean $\pm$ SD)	Ozone				Estimation method
					Sample size	# of cases	# of non-cases		Exposure metric	Exposure window	Averaging period	Spatial scale	
Childhood asthma													
Sbhi et al. (2016)	Canada	1999–2009	Vancouver birth cohort	Children	51,857	8659	43,198	Preschool: 2.6 ± 1.4 School age: 7.0 ± 1.2	NR	<i>In utero</i>	Months	Postal code level	Monitoring data
Tetreault et al. (2016)	Canada	1996–2011	Quebec birth cohort	Children	829,277	NR	NR	60% of follow-up occurred before the age of 6 years	NR	Early life	Months (June–August)	Postal code level	Monitoring data and land-use mixed-effects model
Wang et al. (2016)	Taipei	2010	CEAS cohort	Children	2661	336	2325	5.5 ± 1.1	8 h average, hourly	Early life	Years	District level	Monitoring data and distance to monitoring station
Machtyre et al. (2014)	Canada, Europe	Birth to 8 years old	CAPPS, LISA, GINI, PIAMA	Children	2671	534	2137	NR	NR	First year of life	Annual	Continuous spatial surface (residence level)	Monitoring data, IDW, and APMoSPHERE modeling
Dong et al. (2013)	China	2008–2009	SNEC cohort	Children	30,056	1963	28,093	8.4 ± 2.7 Range: 2–14	8 h average (daytime)	Early life	Years	District level	Monitoring data
Kim et al. (2013)	Korea	2005–2008	CHEER cohort	Children	369	NR	NR	At enrollment: 6.83 ± 0.52	NR	Early life	Years	Continuous spatial surface (residence level)	Monitoring data and ArcGIS Modeling
Nishimura et al. (2013)	USA	2006–2011	GALA II and SAGE II	Children	4320	2291	2029	Range: 8–21	8 h max, 1 h max	Early life	Years	Continuous spatial surface (residence level)	Monitoring data and IDW
Clark et al. (2010)	Canada	1999–2003	British Columbia birth cohort	Children	37,401	3482	33,919	At end of follow-up: 4 ± 0.6 range: 3–4.9 At enrollment: range: 4.8–9.0 At enrollment: ≥ 7	24 h average	<i>In utero</i> and first year of life	Months	Residential six-digit postal code	Monitoring data and IDW
McConnell et al. (2010)	USA	2002–2006	CHS cohort	Children	2497	120	2377		8 h average (10 am–6 pm)	Early life	Years	Community level	Monitoring data
Islam et al. (2008)	USA	1993–2004	CHS cohort	Children	1701	160	1541		8 h average (10 am–6 pm)	Early life	Years	Community level	Monitoring data
Lin et al. (2008)	USA	1995–2000	NYS birth cohort	Children	1,204,396	10,429	1,193,967	Range: 1–6	1 h max (10 am–6 pm)	Early life	Years	Region level	Monitoring data
Adult-onset asthma													
McDonnell et al. (1999)	USA	1977–1992	SDA cohort	Adults	2758	111	2647	Range: 27–87	8 h average (9 am–5 pm), hourly	Adult life	Years	ZIP code level	Monitoring data and interpolation
Greer et al. (1993)	USA	1977–1987	SDA cohort	Adults	3577	78	3499	Range: 26–95	Hourly	Adult life	Years	ZIP code level	Monitoring data and interpolation
Abbey et al. (1991)	USA	1977–1987	SDA cohort	Adults	6058	80	5978	NR	Hourly	Adult life	Years	ZIP code level	Monitoring data and interpolation

APMoSPHERE: Air Pollution Modeling for Support to Policy on Health and Environmental Risks in Europe; IDW: inverse distance weighting; NR: not reported; SD: standard deviation

^aThe characteristics of the study population are specific to the ozone-asthma analyses.

Table 2. Quality and generalizability of epidemiology studies of long-term ozone exposure and asthma development.

Study	Study design	Exposure assessment				Outcome assessment		Statistical analysis															
		Exposure assessment			Exposure-outcome	Physician diagnostic accuracy	Ascertainment	Appropriate statistical model employed	Confounders considered							Non-linear dose-response relationship assessed			Sensitivity analysis conducted	Generalizability to US population			
		Spatial variability considered	Temporal variability considered	Residential mobility considered	Exposure estimates validated	Exposure outcome established				Age	Sex	Race	SES	Maternal age	Gestational duration	Family history	Smoking	Indoor environment	Traffic-related pollution	Other environmental covariates			
Childhood asthma																							
Sblhi et al. (2016)	Nested case-control	Y	N	Y	N	Y	High ^a	Physician billing, hospital discharge records	Y	Y	Y	N	Y	Y	N	N	N	N	N	Y	Y	Y	High
Tetreault et al. (2016)	Cohort	Y	Y	Y	N	N	Low	Hospital discharge, two physician claims	Y	Y	Y	N	N	N	N	Y	N	N	N	N	Y	Y	High
Wang et al. (2016)	Cohort	Y	N	N	N	N	Low	Parental report of physician diagnosis	Y	Y	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	N	Low ^b
MacIntyre et al. (2014)	Cohort	Y	N	N	N	N	Low	Parental report of physician diagnosis	Y	N	Y	N	Y	N	Y	Y	N	N	N	N	N	N	High
Dong et al. (2013)	Cohort	N	N	N	N	N	Low	Parental report of physician diagnosis	Y	Y	Y	N	Y	N	Y	Y	N	N	N	N	N	N	Low ^b
Kim et al. (2013)	Cohort	Y	N	Y	Y	N	Low	Parental report of physician diagnosis	Y	Y	Y	N	Y	N	Y	Y	N	N	N	N	N	N	Low ^b
Nishimura et al. (2013)	Population-based case-control	Y	Y	Y	N	Y	High ^a	Physician diagnosis	Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	Y	High
Clark et al. (2010)	Nested case-control	Y	Y	Y	N	N	Low	Outpatient and hospital records	Y	Y	Y	N	Y	Y	N	Y	N	N	N	N	N	Y	High
McConnell et al. (2010)	Cohort	N	N	N	N	N	Low	Parental report of physician diagnosis	N ^c	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	High
Islam et al. (2008)	Cohort	N	N	Y	N	N	High ^a	Parental report of physician diagnosis	N ^c	Y	Y	Y	N	N	Y	Y	Y	N	N	N	N	N	High
Lin et al. (2008)	Cohort	N	Y	Y	N	Y	Low	Hospital discharge records ^d	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	High
Adult-onset asthma																							
McDonnell et al. (1999)	Cohort	Y	N	Y	Y	N	High ^a	Self-reported physician diagnosis	Y	Y	Y	N	Y	NA	NA	N	Y	Y	Y	N	Y	Y	Low ^e
Greer et al. (1993)	Cohort	Y	N	Y	Y	N	High ^a	Self-reported physician diagnosis and symptoms, medical records	Y	Y	Y	N	Y	NA	NA	N	Y	N	N	N	Y	Y	Low ^e
Abbey et al. (1991)	Cohort	Y	N	Y	Y	Y	High ^a	Self-reported physician diagnosis and symptoms	Y	Y	Y	N	Y	NA	NA	N	Y	N	N	N	N	N	Low ^e

SES: socioeconomic status

Grey shading indicates a higher potential for error and/or bias.

^aThe study population did not include children younger than 6 years old, for whom physicians' diagnoses of asthma may be inaccurate.

^bThe study population is Asian, so the study results may not be generalizable to the US population.

^cThe proportional hazard assumption was not tested for the Cox regression model used.

^dAsthma hospitalization was ascertained, but this is a poor surrogate for incident asthma.

^eThe Seventh-day Adventists have many lifestyle characteristics that differ from the general US population.

Table 3. Detailed results of epidemiology studies of long-term ozone exposure and asthma development.

Study	Stratum	Ozone			Asthma	Statistical models	Effect measure	Results			P value for interaction		
		Metric	Distribution	Categories				Effect estimate	95% CI	P value for point estimate			
Sbihi et al. (2016)	Preschool	All study subjects	<i>In utero</i> average	Mean ± SD (IQR): cases: 27.7 ± 5.8 (8.6) µg/m ³ controls: 27.9 ± 5.8 (8.5) µg/m ³	Incidence	Conditional logistic regression models	OR per IQR (8.5 µg/m ³) increase	0.92	(0.87,0.97)	P < .05	NA		
								1					
								0.88	(0.81,0.95)	NR			
								0.95	(0.87,1.03)				
		Gestational duration ≥ 37 weeks	Gestational duration < 37 weeks	Birth weight ≥ 2,500 g	Birth weight < 2,500 g	Continuous	0.91	(0.86,0.96)	1.01	(0.60,1.68)	NR	NR	
													0.85
		Birth weight ≥ 2,500 g	Birth weight < 2,500 g	Continuous	0.9	(0.86,0.95)	0.59	(0.28,1.19)	1.18	(1.07,1.31)	P < .05	NA	
													1
		Tetreault et al. (2016)	School age	All study subjects	<i>In utero</i> average	cases: 27.9 ± 6.0 (8.7) µg/m ³ controls: 28.3 ± 5.9 (8.6) µg/m ³	Incidence	Conditional logistic regression models	OR per IQR (8.5 µg/m ³) increase	1			NR
										1.02	(0.87,1.20)		
1.19	(1.01,1.41)												
1.22	(1.01,1.48)												
Using ozone estimates at the birth address	Annual average		Mean: 32.07 ppb Range: 12.19 – 43.12 ppb IQR: 3.22 ppb	Incidence rate	Cox proportional hazard models	HR per IQR (3.22 ppb) increase	1.06	(1.05,1.07)	P < .001	NA			
											1.07	(1.06,1.08)	P < .001
Using ozone estimates for full residential history	Annual average		Mean: 31.97 ppb Range: 12.19 – 43.39 ppb IQR: 3.26 ppb	Incidence rate	Cox proportional hazard models	HR per IQR (3.26 ppb) increase	1.07	(1.06,1.08)	P < .001	NA			
											1		
Wang et al. (2016)	Full cohort		Long-term average	Hourly 8h mean	Mean ± SD: 27.50 ± 0.61 ppb Median: 27.62 ppb	Lifetime prevalence	Logistic regression models	OR	0.68	(0.51,0.92)	P < .05	NA	
									1		NR		
		0.79							(0.59,1.07)	P > .05			
		0.86							(0.66,1.13)	P = .277			
	Full cohort	Annual average	Mean ± SD: 36.8 ± 6.5 µg/m ³ IQR: 9.1 µg/m ³ Range: 13.3 – 55.9 µg/m ³	Lifetime prevalence	Logistic regression models	OR per 10 µg/m ³ increase	0.84	(0.62,1.12)	NR	NR			
											0.89	(0.62,1.28)	NR
	Normal weight	Overweight	Obesity	Lifetime prevalence	Logistic regression models	OR per IQR (23 µg/m ³) increase	0.73	(0.48,1.12)	NR	NR			
											0.77	(0.49,1.19)	NR
	Dong et al. (2013)	Full cohort	3-year average	Mean: 54.8 µg/m ³ Range: 34 – 89 µg/m ³	Lifetime prevalence	Logistic regression models	OR per IQR (23 µg/m ³) increase	1.25	(1.12,1.40)	NR	p = .167		
												1.53	(1.26,1.86)
1.31												(1.08,1.58)	NR
1.04												(0.83,1.30)	NR
Full cohort		5-year average	Mean: 10.32 ppb Range: 3.74 – 29.66 ppb	Lifetime prevalence	Logistic regression models	OR per 5 ppb increase	0.94	(0.61,1.46)	NR	NA			
											0.94	(0.61,1.46)	NR

(continued)

Table 3. Continued

Study	Stratum	Ozone			Asthma	Statistical models	Effect measure	Results			P value for point estimate	P value for interaction
		Metric	Distribution	Categories				Effect estimate	95% CI			
Nishimura et al. (2013)	All subjects	1-year average		Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	0.98	(0.89, 1.08)	NR	NA	
		8h max						0.96	(0.87, 1.06)			
		3-year average						0.98	(0.84, 1.14)			
	Boys	1-year average		Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	0.98	(0.87, 1.10)	NR	NR	
		8h max						0.96	(0.85, 1.09)			
		3-year average						0.96	(0.78, 1.19)			
	Girls	1-year average		Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	0.93	(0.76, 1.13)	NR	NR	
		8h max						0.95	(0.86, 1.05)			
		3-year average						0.93	(0.82, 1.04)			
	Total IgE > 200	1-year average	Mean±SD: 1-h max average in 1996 34.3±7.7 ppb 8-h max average in 1996 27.6±6.6 ppb	Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	0.96	(0.79, 1.18)	NR	NR	
		8h max						0.94	(0.74, 1.19)			
		3-year average						0.9	(0.77, 1.06)			
	Total IgE ≤ 200	1-year average		Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	0.9	(0.72, 1.12)	NR	NR	
		8h max						0.87	(0.75, 1.02)			
		3-year average						0.85	(0.69, 1.04)			
	Family history	1-year average		Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	1.03	(0.92, 1.15)	NR	NR	
		8h max						1.01	(0.90, 1.15)			
		3-year average						1.04	(0.82, 1.32)			
No family history	1-year average		Continuous	Lifetime prevalence	Two stage analysis: Logistic regression models and random-effects models	OR per 5 ppb increase	1.01	(0.77, 1.32)	NR	NR		
	8h max						0.96	(0.76, 1.21)				
	3-year average						0.97	(0.73, 1.29)				
Full cohort	1-year average	Mean±SD: Asthma cases in utero 30.05±6.39 ppb Controls in utero 30.48±6.32 ppb Asthma cases in 1st year 27.64±4.94 ppb Controls in 1st year 28.06±4.86 ppb	Continuous	Incidence	Conditional logistic regression models	OR per 10 µg/m ³ increase	0.92	(0.69, 1.21)	NR	NA		
	8h max						0.9	(0.69, 1.18)				
	3-year average						0.96	(0.82, 1.11)				
Clark et al. (2010)	Boys	1-year average		Continuous	Incidence	Conditional logistic regression models	OR per 10 µg/m ³ increase	0.94	(0.79, 1.11)	NR	NR	
		8h max						0.95	(0.76, 1.19)			
		3-year average						0.92	(0.73, 1.17)			
	Girls	1-year average		Continuous	Incidence	Conditional logistic regression models	OR per 10 µg/m ³ increase	0.83	(0.77, 0.89)	NR	NR	
		8h max						0.81	(0.74, 0.87)			
		3-year average						0.86	(0.78, 0.94)			
McConnell et al. (2010)	Full cohort	1-year average	Mean: 44.6 ppb	Continuous	Incidence rate	Cox proportional hazard models	HR across the range of ozone (30.3 ppb)	0.84	(0.76, 0.94)	NR	NA	
		2-year average						0.79	(0.70, 0.89)			
								0.74	(0.64, 0.84)			
								1.01	(0.49, 2.11)			

(continued)

(continued)

Table 3. Continued

Study	Stratum	Ozone			Asthma	Statistical models	Effect measure	Results		
		Metric	Distribution	Categories				Effect estimate	95% CI	P value for point estimate
Islam et al. (2008)	No short-allele	Long-term average	Mean (range): Higher ozone communities: 55.2 (46.5, 64.9) ppb Lower ozone communities: 38.4 (28.6, 45.5) ppb Mean: 41.06 ppb	Low	Incidence rate	Cox proportional hazard models	HR	1		p = .003
	High			0.94				(0.36, 2.43)		
	Short-allele	Long-term ozone-season average Long-term average	Mean: 50.62 ppb Mean: 41.06 ppb	Low	Incidence rate	Cox proportional hazard models	HR	1		
	High			2				(0.40, 10.17)		
Lin et al. (2008)	Full cohort	Long-term average	Mean: 9.72% Range: 1.66—26.27%	Continuous	Incidence	Logistic regression models	OR per 1 ppb increase	1.16	(1.15, 1.17)	NR
		Exceedance proportion (%) > 70 ppb	Mean: 37.51 ppb	Continuous			OR per 1 ppb increase	1.22	(1.21, 1.23)	
	New York City	Long-term average	Mean: 37.51 ppb	Low	Incidence	Logistic regression models	OR	1		NR
				Medium-High				1.43	(1.29, 1.58)	
	Other NYS cities	Long-term average	NR	Low	Incidence	Logistic regression models	OR	1.69	(1.52, 1.80)	NR
				High				1		
Medium				1.64				(1.48, 1.82)		
High				2.06				(1.87, 2.27)		
Adult-onset Asthma										
McConnell et al. (1999)	Men	Long-term average	8h mean	Tertile 1	Incidence	Logistic regression models	OR	1		NR
				Tertile 2				4.44	(1.32, 13.81)	
		Tertile 3	4.01	(1.15, 13.00)						
		Continuous	2.09	(1.03, 4.16)						
		Long-term average	Hourly Exceedance frequency (# of hours) > 60 ppb	OR per IQR (27 ppb) increase					P < .05	
				OR per IQR (11.7 ppb) increase				2.46	(1.28, 4.67)	
	Women	Long-term average	Hourly Exceedance frequency (# of hours) > 80, 100, 120, or 150 ppb	Continuous	OR per IQR (907 h) increase	1.90	(0.99, 3.64)	P < .05		
				OR per IQR increase	NR	NR	P > .05			
		Long-term average	8h mean	OR per IQR (27 ppb) increase	0.86	(0.58, 1.26)	P > .05			
				Hourly Exceedance proportion (%) > 60, 80, 100, 120, or 150 ppb	NR	NR	P > .05			
		Full cohort Men	Long-term average	Incidence	OR per IQR increase	NR	NR	P > .05		
					OR per 10 ppb increase	1.31	(0.96, 1.78)	NR		
Greer et al. (1993)	Women	Long-term average	NR	Continuous	Incidence	Logistic regression models	OR per 500 hours increase	0.94	(0.65, 1.34)	NR
Abbey et al. (1991)	Full cohort	Exceedance frequency (# of hours) > 100 ppb	NR	Continuous	Incidence	Logistic regression models	OR per 500 hours increase	1.40	(0.90, 2.34)	0.056
				Continuous	Incidence	Logistic regression models	OR per 500 hours increase	1.40	(0.90, 2.34)	0.056

CI: confidence interval; GSTP: glutathione S-transferase P; HR: hazard ratio; IgE: immunoglobulin E; IQR: interquartile range; NA: not applicable; NR: not reported; OR: odds ratio; ppb: parts per billion; SD: standard deviation; TNF: tumor necrosis factor

Bolded fonts indicate statistically significant results.

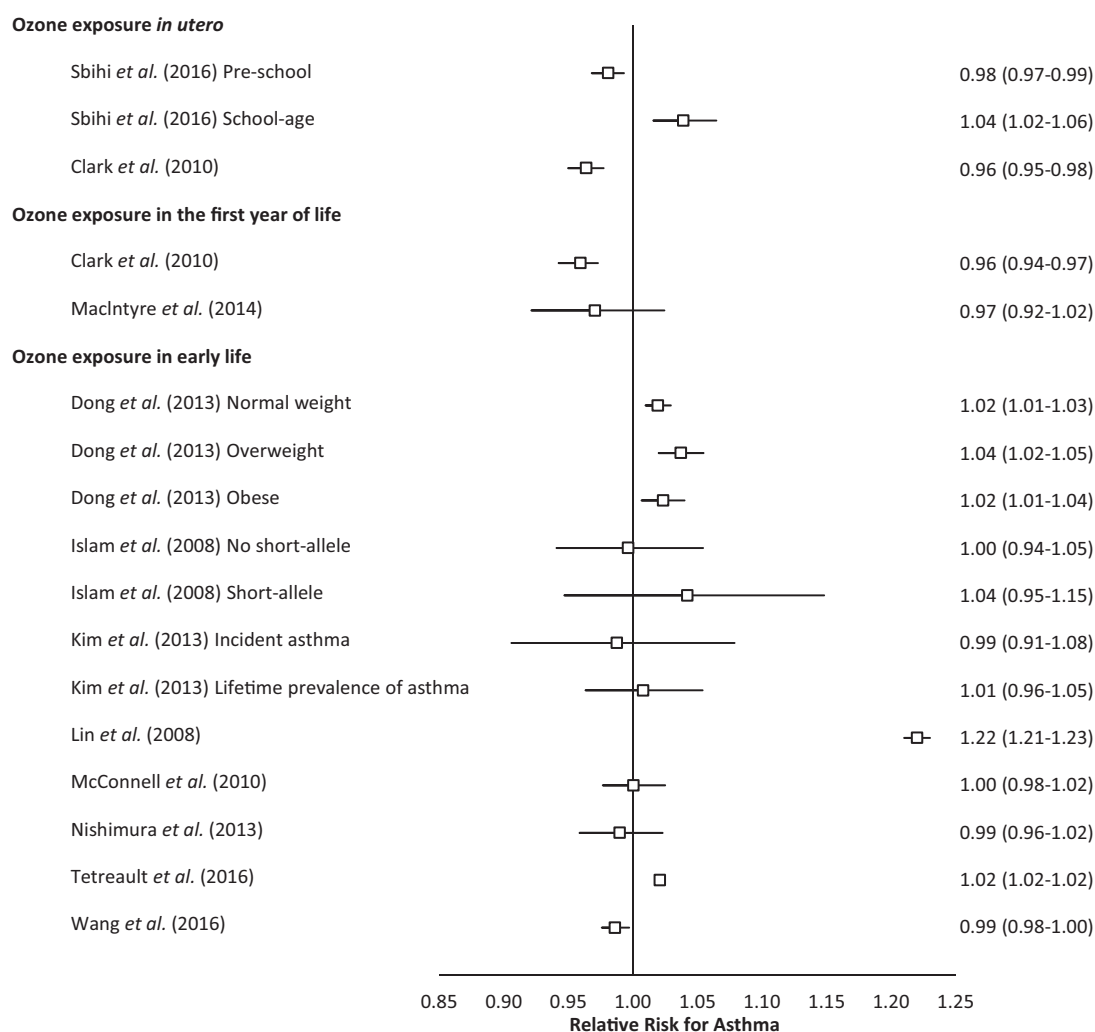


Figure 2. Study-specific results of long-term ozone exposure and childhood asthma development, by exposure window – the relative risks and their 95% confidence intervals have been standardized to a 1 ppb increment in ozone exposure.

Study results evaluation

We identified 11 studies from 10 non-overlapping populations that evaluated childhood asthma development, and three studies from one cohort that assessed asthma development in adults. As discussed above, all of these studies had considerable uncertainties and potential for bias with regard to exposure and outcome assessments and confounder adjustment. In light of the major methodological limitations in these studies, although several studies conducted some form of sensitivity analysis, we mainly focused on the study findings from the primary and stratified analyses with a focus on the within- and between-study consistency. Detailed study results are presented in Table 3.

Childhood asthma

To aid the evaluation of study results regarding long-term ozone exposure and childhood asthma development, we graphically present the main findings from these studies in Figure 2, with the risk estimates standardized to a 1 ppb increment in ozone exposure and grouped by exposure window.

Ozone exposure in utero. Two studies, both of which were birth cohorts in Canada, evaluated the association between *in utero* ozone exposure and childhood asthma (Clark et al., 2010; Sbihi et al., 2016). Sbihi et al. (2016) reported that higher *in utero* ozone exposure was statistically significantly associated with decreased incident asthma in preschool-age children (OR = 0.92, 95% CI: 0.87–0.97). When ozone exposure was assessed as quartiles, the top three quartiles were all associated with reduced asthma risks (quartile 2: OR = 0.88, 95% CI: 0.81–0.95; quartile 3: OR = 0.95, 95% CI: 0.87–1.03; quartile 4: OR = 0.85, 95% CI: 0.77–0.94), compared to the bottom quartile. This statistically significant inverse association persisted among children with a gestational age of 37 weeks or longer (OR = 0.91, 95% CI: 0.86–0.96) or with a birth weight of 2500 g or more (OR = 0.9, 95% CI: 0.86–0.95) but was null for children with a gestational age less than 37 weeks or with a birth weight less than 2500 g. Clark et al. (2010), who assessed incident asthma only in children aged younger than 5 years, also reported a statistically significant decrease in asthma development in association with increases in *in utero* ozone exposure (OR = 0.83, 95% CI: 0.77–0.89). The observed statistically significant inverse association persisted when the

study population was stratified by sex (boys: OR = 0.86, 95% CI: 0.78–0.94; girls: OR = 0.79, 95% CI: 0.70–0.89).

In contrast, Sbihi et al. (2016) found that higher *in utero* ozone exposure was associated with a statistically significant increase in incident asthma in school-age children (OR = 1.18, 95% CI: 1.07–1.31). The analyses with quartiles of ozone exposure showed that the risk of asthma was only increased in the top two quartiles, compared to the bottom quartile (quartile 2: OR = 1.02, 95% CI: 0.87–1.20; quartile 3: OR = 1.19, 95% CI: 1.01–1.41; quartile 4: OR = 1.22, 95% CI: 1.01–1.48).

Ozone exposure in the first year of life. Two studies assessed the association between ozone exposure in the first year of life and childhood asthma (Clark et al., 2010; MacIntyre et al., 2014). MacIntyre et al. (2014), who conducted a pooled analysis of four birth cohorts in Canada and Europe, reported a null association between ozone exposure in the first year of life and the risk of ever being diagnosed with asthma up to 8 years of age. MacIntyre et al. (2014) also evaluated the potential effect modification by several single-nucleotide polymorphisms (SNPs) in the glutathione S-transferase P1 (GSTP1) and tumor necrosis factor (TNF) genes and found that the null associations between ozone exposure and asthma did not vary by any of the SNPs examined. Similar to *in utero* ozone exposure, Clark et al. (2010) observed a statistically significant inverse association between ozone exposure in the first year of life and incident asthma (full cohort: OR = 0.81, 95% CI: 0.74–0.87; boys: OR = 0.84, 95% CI: 0.76–0.94; girls: OR = 0.74, 95% CI: 0.64–0.84).

Ozone exposure in early life. Eight studies investigated the relationship between ozone exposure in early life and risk of developing asthma, and there is considerable between-study heterogeneity in the direction of observed associations.

Four studies, from three non-overlapping populations in the US and Korea, observed a null association between long-term ozone exposure in early life and risk of developing childhood asthma (Islam et al., 2008; Kim et al., 2013; McConnell et al., 2010; Nishimura et al., 2013), and the null associations did not vary by sex, family history of asthma, total IgE level, functional polymorphisms tested, the metric and averaging time of ozone exposure or measures of asthma development (Islam et al., 2008; Kim et al., 2013; Nishimura et al., 2013).

Conversely, Wang et al. (2016), a retrospective cohort study in Taipei, reported a statistically significant decrease in risk of asthma associated with higher ozone exposure based on hourly measurements (OR = 0.68, 95% CI: 0.51–0.92). The association was no longer statistically significant when the 8 h mean ozone concentrations were used (OR = 0.79, 95% CI: 0.59, 1.07).

In addition, three studies reported statistically significant positive associations between the risk of childhood asthma and ozone exposure. Tetreault et al. (2016), in a birth cohort study in Canada, found that higher ozone exposure during summer months in early life was associated with increased

risk of developing childhood asthma (HR = 1.07, 95% CI: 1.06–1.08). Tetreault et al. (2016) also evaluated the dose-response relationship using cubic splines of continuous ozone exposure but did not find any evidence for non-linearity. Dong et al. (2013), who conducted a population-based cohort study in China, observed statistically significant increases in asthma development risk associated with increases in ozone exposure, and this positive association was not modified by body weight (normal weight: OR = 1.25, 95% CI: 1.12–1.40; overweight: OR = 1.53, 95% CI: 1.26–1.86; obese: OR = 1.31, 95% CI: 1.08–1.58). Lin et al. (2008), in a cohort study in New York State, reported that higher ozone exposure in early life was associated with a statistically significantly increased risk of asthma hospitalization (OR = 1.16, 95% CI: 1.15–1.17). The results were consistent when only exposure in ozone season (April–October) was considered (OR = 1.22, 95% CI: 1.21–1.23) or when the annual percentage of hourly ozone measurements exceeding 70 ppb was considered (OR = 1.68, 95% CI: 1.64, 1.73). These increases persisted in the top two tertiles of ozone exposure when the study population was stratified by location (New York City: tertile 2: OR = 1.43, 95% CI: 1.29–1.58; tertile 3: OR = 1.69, 95% CI: 1.52–1.80 versus other New York State cities: tertile 2: OR = 1.64, 95% CI: 1.48–1.82; tertile 3: OR = 2.06, 95% CI: 1.87–2.27).

Adult-onset asthma

Three studies, all based on the Seventh-day Adventists (SDA) Cohort in California, assessed the risk of developing adult-onset asthma in association with long-term ozone exposure (Abbey et al., 1991; Greer et al., 1993; McDonnell et al., 1999).

For 6058 Seventh-day Adventists with a follow-up of 10 years, Abbey et al. (1991) reported that higher ozone exceedance frequency (i.e. annual average of greater than 500 hourly ozone measurements above 100 ppb) was associated with a borderline significant increase in asthma risk (OR = 1.40, 95% CI: 0.90–2.34). Greer et al. (1993) restricted their analyses to 3577 nonsmokers, and also reported a borderline significant increase in asthma risk associated with a 10 ppb increment in ozone exposure (OR = 1.31, 95% CI: 0.96–1.78). The positive association between ozone and asthma was more pronounced in men (OR = 3.12, 95% CI: 1.61–5.85) but was null in women (OR = 0.94, 95% CI: 0.65–1.34). McDonnell et al. (1999), who analyzed 2758 nonsmokers with a follow-up of 15 years, also reported a statistically significant association between 20-year cumulative ozone exposure (based on daily 8 h mean concentrations) and asthma in men (OR = 2.09, 95% CI: 1.03–4.16) but a null association in women (OR = 0.86, 95% CI: 0.58–1.26). The results did not change meaningfully when daily hourly ozone measurements were used to calculate the 20-year cumulative ozone exposure. In addition, McDonnell et al. (1999) assessed ozone exceedance frequencies above various thresholds and found that higher exceedance frequencies above 60 ppb were associated with statistically significant increases in asthma risk among men (OR = 1.90, 95% CI: 0.99–3.64) and that the statistical significance did

not persist with higher ozone thresholds (e.g. 80, 100, 120 and 150 ppb). Ozone exceedance frequencies were not associated with asthma risk in women. When tertiles of ozone exposure were considered, men in the top two tertiles had a statistically significantly increased risk of asthma, compared to men in the bottom tertile (tertile 2: OR = 4.44, 95% CI: 1.32–13.81; tertile 3: OR = 4.01, 95% CI: 1.15–13.00).

Discussion

Overall, there is substantial between-study heterogeneity in the direction of observed associations between long-term ozone exposure and asthma development. In addition, available epidemiology studies have considerable methodological limitations, including potential exposure measurement error and a lack of adjustment for several key confounders, which further complicates the interpretation of the findings.

Childhood asthma

The observed associations between ozone exposure and development of childhood asthma varied by exposure window assessed and the age of the study population.

Ozone exposure in utero

Consistent findings from two studies (Clark et al., 2010; Sbihi et al., 2016) suggested that higher *in utero* ozone exposure was associated with reduced risk of asthma in preschool-age children. However, the effect estimates for ozone, though statistically significant, were small in magnitude. The observed dose-response relationships appeared to be linear, without any statistical evidence for non-linearity. Notably, in these two studies, ozone exposure was inversely correlated with traffic-related pollutants, a risk factor for childhood asthma. The inverse correlation between ozone and traffic-related pollutants might contribute to, at least partially, the observed inverse association between ozone exposure and asthma in preschool-age children. In addition, the diagnostic accuracy in children aged 6 years or younger (i.e. preschool) is low, and neither of the studies relied on validated ozone exposure estimates or adjusted for key confounders such as a family history of asthma (Table 2).

In contrast, Sbihi et al. (2016) reported that higher *in utero* ozone exposure was linearly associated with a small, but statistically significant, increase in asthma risk among school-age children. The observed association in school-age children was the direct opposite of that in preschool-age children in the same study, which is unlikely to be entirely explained by the better diagnostic accuracy of asthma in school-age children. Moreover, the methodological limitations of this study discussed above also applied to the analyses of school-age children (Table 2).

Ozone exposure in the first year of life

Clark et al. (2010) reported decreased risks of asthma development associated with higher ozone exposure in the first year of life, while MacIntyre et al. (2014) observed a null

association. The magnitude of the effect estimates, based on a linear dose-response relationship, was small. Both studies suffered from a high risk of bias from the exposure and outcome assessments, as well as from inadequate adjustment for confounders (Table 2).

Ozone exposure in early life

The most examined exposure window in available epidemiology studies was early life, but the results from these analyses were inconsistent with regard to the direction of observed associations. Most of the studies assumed a linear dose-response relationship between ozone and asthma development and reported ozone effect estimates that were small in magnitude. The magnitude of the ozone effect estimates observed in Lin et al. (2008) was considerably larger than that in other studies (Figure 2). As discussed above, Lin et al. (2008) assessed first asthma hospitalization, which indicates severe exacerbation and is a poor surrogate for incident asthma. Because ozone exposure may affect asthma severity (Goodman et al., 2018; US EPA, 2013a), the use of first asthma hospitalization in Lin et al. (2008) likely biased the results away from the null.

In addition, considerable uncertainty stemmed from the lack of ozone-asthma temporality in most of these studies, with the exception of Nishimura et al. (2013) and Lin et al. (2008). The ozone exposure periods evaluated overlapped with the follow-up periods for asthma; therefore, for most, if not all, of the children who developed asthma, part of their estimated ozone exposures occurred after the outcome occurred. Because of the continuing downward trend of ambient ozone concentration in the USA between 1998 and 2010 (US EPA, 2013a), this lack of temporality might have led to an overestimation of the association between early life ozone exposure and asthma development.

Similar to studies that evaluated ozone exposures *in utero* and in the first year of life, studies of early life ozone exposure were also limited by considerable measurement error and uncertainties in exposure and outcome assessments (Table 2). Several studies did not adjust for key confounders, such as a family history of asthma, and most did not control for preterm birth, exposure to traffic-related air pollutants or the indoor environment (Table 2). Findings from Asian children populations were less generalizable to the USA than those from the Western populations (Table 2).

Because the natural and anthropogenic sources of ozone precursors differ in urban and non-urban areas (US EPA, 2013a), it is conceivable that urbanicity could modify potential associations between long-term ambient ozone concentrations and asthma development. However, more than half of the studies of childhood asthma were conducted only in urban areas (Clark et al., 2010; Dong et al., 2013; Kim et al., 2013; Nishimura et al., 2013; Sbihi et al., 2016; Wang et al., 2016), while the rest of the studies included children living in both urban and non-urban areas (Islam et al., 2008; Lin et al., 2008; MacIntyre et al., 2014; McConnell et al., 2010; Tetreault et al., 2016). There were no apparent patterns in the observed associations between ozone and childhood asthma development with regard to whether the studies

were conducted only in urban areas or in urban and non-urban areas combined. Because there were no studies conducted only in non-urban areas, we were unable to examine the association between long-term ozone exposure and childhood asthma development in rural settings.

Adult-onset asthma

Adult-onset asthma was only evaluated in one population, the California Seventh-day Adventists cohort (Abbey et al., 1991; Greer et al., 1993; McDonnell et al., 1999). Long-term ozone exposure was associated with increased asthma risk in men but not women (Greer et al., 1993; McDonnell et al., 1999). The magnitude of the observed association was large, with the ORs greater than 2. The increased risk in men was persistent when ozone exposure was analyzed linearly, in tertiles, or with exceedance frequencies above various thresholds.

The ozone ISA relied on these studies to conclude that long-term ozone exposure is a risk factor for adult-onset asthma. However, there does not seem to be a biologically plausible reason for the different associations between men and women. Men, on average, had more severe asthma, and thus might have been more likely to get diagnosed with asthma than women in this cohort. Because ozone exposure may be associated with asthma severity, the observed association between ozone and asthma development in men could be partially attributable to the difference in asthma severity (i.e. men appear to have an increased incidence, but it is actually a reflection of men with more severe asthma being diagnosed). Also, in the analyses by Greer et al. (1993) and McDonnell et al. (1999), the exposure periods overlapped with the follow-up periods for asthma (Table 2); as discussed above, this might have biased the results away from the null. In addition, these studies did not consider temporal variability when estimating ozone exposure and did not adjust for key confounders, such as a family history of asthma and exposure to other environmental allergens and irritants (Table 2).

It is notable that while the Seventh-day Adventists cohort is in California, this population is characterized by markedly lower risks of certain chronic diseases than the US general population, which was hypothesized to be attributable to the lifestyle and diet in the Seventh-day Adventists. The observed association between ozone and asthma in Seventh-day Adventist men, and the effect modification by sex may not be entirely generalizable to the US general population.

Study quality evaluation

A study quality evaluation (i.e. assessing internal validity of individual studies) is a key component in the systematic review process (NRC, 2014). There are many study evaluation frameworks available for most realms of evidence, several of which formed the theoretical basis for our study quality criteria (Koustas et al., 2013, 2014; NTP, 2015a,b; US EPA, 2013b, 2014, 2016a,b; von Elm et al., 2007a–e). However, while many of these frameworks provide guidance

on key considerations in study quality evaluation, they do not stipulate detailed criteria specific to the exposure and outcome of interest. For example the OHAT RoB approach considers three key domains: exposure characterization, outcome assessment and adjustment for confounding, and several other RoB criteria for observational studies (NTP, 2015a,b). Studies with definitely or probably low risk of bias in all three key domains are categorized in the 1st study quality tier and those with definitely or probably high risk of bias in any of the three key domains are categorized in the 2nd or 3rd study quality tiers (NTP, 2015a,b). Studies are then evaluated in tiers, but the impact of specific aspects of study quality may not be considered when interpreting study results.

In contrast, our quality criteria address more detailed and distinct characteristics that are specific to long-term ambient ozone exposure and asthma development, resulting in a comprehensive and in-depth assessment of the quality of the overall evidence. We found that all of the available studies had substantial uncertainties in exposure and outcome assessments and in adjustments for confounders, which is consistent with categorizing these studies in 2nd and 3rd tiers using the OHAT approach. The overall low quality of the available studies reduces our confidence in the body of evidence.

Biological plausibility

Some of the reported effects of ozone exposure on the respiratory system are common features of asthma, providing biological plausibility for long-term ozone exposure as a contributor to asthma development. For example when ozone exposure concentrations are high enough and of sufficient duration to overwhelm antioxidant defenses in the respiratory tract, ozone reacts with macromolecules to form secondary oxidation products that can induce respiratory tract inflammation and epithelial cell injury with subsequent airway remodeling (Mudway & Kelly, 2000; US EPA, 2013a). Inflammation contributes to oxidative stress and reactive oxygen species (ROS) generation, which may cause increased bronchial reactivity (indicating AHR) observed as both an immediate and persistent response to ozone exposure in humans and experimental animals, respectively (US EPA, 2013a).

Asthma development also involves alterations in the immune system, and T-cells play a central role in asthma pathogenesis (Wu et al., 2014). Development of the allergic asthma phenotype is associated with a skewing of T-cell responses toward a T helper 2 (Th2) immune response instead of a T helper 1 (Th1) response. Th2 responses include several features of asthma, such as increased production of inflammatory cytokines, eosinophils and immunoglobulin E (IgE) antibodies in the respiratory tract, which induces a state of allergic sensitization (Bates et al., 2009; Marino et al., 2015; Noutsios & Floros, 2014). Exposure of children to ozone has been shown to increase eosinophils and proinflammatory cytokines in the respiratory tract (Noutsios & Floros, 2014) and short-term ozone exposure

studies in rodents and primates have reported enhanced IgE production (US EPA, 2013a). Short-term ozone exposure has also been shown to enhance antigen presentation in humans, which contributes to exaggerated T-cell responses and promotes Th2-mediated inflammation and an allergic phenotype (US EPA, 2013a). The persistent nature of these short-term responses contributes to the biological plausibility of an association between long-term ozone exposure and development of allergic asthma (US EPA, 2013a). We note, however, that although ozone exposure has been linked with Th2-related responses in several studies, there are no direct experimental studies associating ozone exposure with the initial polarization of Th1–Th2 responses (Auten & Foster, 2011).

Studies in non-human primates exposed repeatedly to ozone, with or without exposure to house dust mite antigen (an inhaled allergen), provide a model of allergic asthma in humans, as these studies reported reversible impaired air-flow, elevated IgE levels in serum and airways, increased eosinophils and other immune cells in the airways and development of AHR (US EPA, 2013a). Long-term exposure of infant rhesus monkeys to 0.5 parts per million (ppm) ozone and an antigen-induced greater than additive changes in airway resistance and AHR, and exposure to ozone alone increased eosinophil levels and induced effects related to airway obstruction and AHR, including decreased growth of the distal conducting airways that persisted at least six months after cessation of ozone exposure (Fanucchi et al., 2006; Plopper et al., 2007; Schelegle et al., 2003). This indicates that long-term exposure to ozone and allergens in early life can disrupt growth and differentiation processes in the airways and provides plausibility that ozone could contribute to asthma development in children.

Several genetic factors that confer susceptibility to asthma development have been identified (Gowers et al., 2012; US EPA, 2013a). Some of these factors may modify asthma risk by affecting the internal dose of ozone reaction products or their response in the respiratory tract, providing biological plausibility for ozone exposure having a role in asthma development. For example variation in genes for antioxidant or anti-inflammatory enzymes could increase susceptibility to ozone-induced oxidative stress, inflammation and subsequent airway remodeling (Gowers et al., 2012). Another hypothesis is that in those with a genetic predisposition to atopy (i.e. a tendency to develop allergic diseases, such as asthma), there is a dominant Th2 inflammatory phenotype, and continuous exposure to ozone and allergens could cause atopic bronchial hyperresponsiveness and lead to asthma (Gowers et al., 2012; Marino et al., 2015).

Variability of asthma phenotypes has also been hypothesized to be attributable to epigenetic influences from early life environmental exposures (such as to ozone). In *in vitro* studies, histone modification and DNA methylation of Th lymphocyte genes have been induced by perinatal exposure to environmental insults, such as oxidative stress, leading to polarization toward Th2 responses associated with development of allergic asthma (Noutsios & Floros, 2014). Thus, it is plausible that ozone exposure may induce epigenetic changes associated with development of certain asthma

phenotypes, although there are no studies available to support this directly.

Overall, the experimental evidence discussed above indicates that ozone exposure can induce many persistent respiratory effects that are also involved in asthma pathogenesis, suggesting that long-term ozone exposure could plausibly contribute to asthma development. However, the underlying mechanisms of asthma development in humans are poorly understood, so it is unclear whether the ozone-induced effects are direct contributors to asthma onset.

Conclusion

Available epidemiology studies of long-term ozone exposure, including *in utero* exposure, and development of childhood asthma reported inconsistent findings, which were further weakened by considerable methodological limitations in exposure and outcome assessments, and in statistical analyses. Epidemiology findings regarding long-term ozone exposure and adult-onset asthma, from one unique population with limited generalizability to the general population, were also limited by considerable uncertainties due to exposure measurement error and a lack of adjustment for key confounders. While experimental evidence suggests that it may be biologically plausible that long-term ozone exposure could contribute to asthma development, it has not established a definitive mode of action. Future research is needed to address key uncertainties regarding the role of ambient ozone exposure in asthma development.

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