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Gas cooking and respiratory outcomes in children: A systematic review

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ABSTRACT

The most recent meta-analysis of gas cooking and respiratory outcomes in children was conducted by Lin et al. [93] in 2013. Since then, a number of epidemiology studies have been published on this topic. We conducted the first systematic review of this epidemiology literature that includes an in-depth evaluation of study heterogeneity and study quality, neither of which was systematically evaluated in earlier reviews. We reviewed a total of 66 relevant studies, including those in the Lin et al. [93] meta-analysis. Most of the studies are cross-sectional by design, precluding causal inference. Only a few are cohort studies that could establish temporality and they have largely reported null results. There is large variability across studies in terms of study region, age of children, gas cooking exposure definition, and asthma or wheeze outcome definition, precluding clear interpretations of meta-analysis estimates such as those reported in Lin et al. [93]. Further, our systematic study quality evaluation reveals that a large proportion of the studies to date are subject to multiple sources of bias and inaccuracy, primarily due to self-reported gas cooking exposure or respiratory outcomes, insufficient adjustment for key confounders (e.g., environmental tobacco smoke, family history of asthma or allergies, socioeconomic status or home environment), and unestablished temporality. We conclude that the epidemiology literature is limited by high heterogeneity and low study quality and, therefore, it does not provide sufficient evidence regarding causal relationships between gas cooking or indoor NO_2 and asthma or wheeze. We caution against over-interpreting the quantitative evidence synthesis estimates from meta-analyses of these studies.

Introduction

Nitrogen dioxide (NO_2) is commonly present in indoor air due to the presence of outdoor sources (e.g., mobile vehicles, industrial combustion) and indoor sources (e.g., tobacco use, fuel-burning stoves or heating systems) [97]. In 2010, the World Health Organization (WHO) Guidelines for Indoor Air Quality [97] recommended a 1-h indoor NO_2 guideline of 200 $\mu g/m^3$ and an annual average indoor NO_2 guideline of 40 $\mu g/m^3$, which remained in the 2021 update [96].

The annual average guideline of 40 $\mu g/m^3$ was derived from the effect estimate from a meta-analysis by Hasselblad et al. [92]. Specifically, this meta-analysis included 11 epidemiology studies published in the 1970s and 1980s that examined associations between gas (vs. electric) stove use or indoor NO_2 concentrations and lower respiratory illness (e.g., wheeze, cough, bronchitis, phlegm) in children ≤12 years old. By assuming that the health outcomes examined across studies were similar enough, that all exposure contrasts could be converted to a 30 $\mu g/m^3$ increase in NO_2 concentration, and that key confounders were properly adjusted for in all studies, the authors estimated that exposure to a long-term increase of 30 $\mu g/m^3$ NO_2 was associated with a 1.2-times higher odds of having lower respiratory illness in children (odds ratio [OR] = 1.2, 95% confidence interval [CI]: 1.1–1.3) [92].

Twenty years later, Lin et al. [93] conducted another meta-analysis to quantitatively synthesize the evidence available through 2013, with a particular focus on asthma and wheeze as health outcomes. Lin et al. [93] included a total of 41 epidemiology studies that examined the associations between indoor NO_2 or gas cooking and asthma or wheeze in children (≤18 years), including those reviewed by Hasselblad et al. [92]. The authors reported statistically significantly positive associations between gas cooking and asthma (OR = 1.32, 95% CI: 1.18–1.48) and between indoor NO_2 and wheeze (OR = 1.12, 95% CI: 1.04–1.21 for a 15-parts-per-billion [ppb] increase in NO_2) and no statistically significant associations between indoor NO_2 and asthma (OR = 1.09, 95% CI: 0.91–1.31 for a 15-ppb increase in NO_2) or between gas cooking and

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Table 1
PECOS elements and corresponding inclusion and exclusion criteria.

PECOS element	Inclusion criteria	Exclusion criteria
Population	▪ Children (≤18 years of age) from any country or region	▪ Other age groups (e.g., adults) ▪ Children are not analyzed separately (e.g., 5 years of age and older)
Exposure	▪ Long-term (months to years) or short-term (hours to days) indoor exposure to NO_2 (in a concentration unit, e.g., ppb, μg/m^3) or gas cooking in family home	▪ Outdoor NO_2 exposure only ▪ Indoor exposure to other pollutants only ▪ Indoor NO_2 exposure in schools/classrooms only ▪ Includes other combustion sources (e.g., coal, wood, kerosene) ▪ Indoor gas cooking not the main source of NO_2 ▪ Prenatal exposure only ▪ Personal NO_2 exposures that include both indoor and outdoor NO_2
Comparator	▪ Exposure to less NO_2 ▪ Use electric stove, do not have a gas stove at home, do not use gas stoves usually	▪ Exposure contrast not given ▪ Comparators were non-electric combustion sources (e.g., coal, wood, kerosene, biomass)
Outcomes	▪ Asthma (newly diagnosed, ever-diagnosed, exacerbation) ▪ Wheeze (persistent, episodes within certain time windows)	▪ Other outcomes only
Study	▪ Primary epidemiology studies with data at the individual level (e.g., cohort, case-control, cross-sectional studies) ▪ Published in English	▪ Reviews, meta-analyses, commentaries, book chapters, or conference abstracts ▪ Ecological studies ▪ Non-human studies ▪ Methodological studies ▪ Studies with secondary analyses only (e.g., based on risk estimates from existing studies) ▪ Not published in English ▪ If no results presented

Notes
NO_2 = Nitrogen Dioxide; PECOS = Population, Exposure, Comparator, Outcomes, and Study Design; ppb = Parts per Billion.
Source: Morgan et al. [83].

wheeze (OR = 1.06, 95% CI: 0.99–1.13).

Quantitative evidence synthesis through a meta-analysis can help increase the statistical power to detect underlying associations, reconcile conflicting study results due to random variation, and generate summary effect estimates that are readily usable for policy-making. However, it is no substitute for a thorough understanding of what each individual study in the literature examined, how each study addressed its own research question, and to what extent each study is equipped to contribute to the knowledge base with respect to a specific research question. It is also not necessarily informative regarding causation. Hasselblad et al. [92] narratively described the design and finding of each of the 11 reviewed studies and tabulated the main study characteristics and results; Lin et al. [93] also tabulated the main study characteristics and results. Yet, there was no systematic study quality evaluation in either meta-analysis to determine the impact of individual studies' methodological limitations on the interpretation of their respective results or the quantitative evidence synthesis results for the literature as a whole. A study quality evaluation is now recognized as an essential component of systematic reviews and meta-analyses. As neither meta-analysis assessed study quality, they could not fully address whether any statistically significant associations were likely causal.

Furthermore, since the publication of the Lin et al. [93] meta-analysis, a number of new epidemiology studies that evaluated the associations between indoor NO_2 or gas cooking and asthma or wheeze in children have been published, including a large global analysis of phase three of the International Study of Asthma and Allergies in Childhood (ISAAC) for over 500,000 children from 47 countries [34]. To synthesize the evidence to date regarding the associations between indoor NO_2 or gas cooking and asthma or wheeze in children on the basis of an in-depth and systematic examination of study characteristics, results, and methodological strengths and limitations, we conducted a systematic review of relevant epidemiology studies published through June 1, 2022, including all 41 studies that contributed to the meta-analysis by Lin et al. [93].

Methods

The protocol for this systematic review was registered with the Open Science Framework (OSF) [18] on May 4, 2022.

Eligibility criteria and literature search

Study eligibility for this systematic review was determined based on inclusion and exclusion criteria structured by population, exposure, comparator, outcomes, and study design (PECOS) elements, as shown in Table 1.

To identify eligible studies, we systematically searched the PubMed, Scopus, and Lens.org databases for publications through June 1, 2022. In order to ensure that all studies captured in the Lin et al. [93] meta-analysis were captured in the present review, we performed, in each database, a main search using terms specifically for gas cooking or indoor NO_2 in relation to asthma or wheeze (detailed search strategies in Supplemental Table 1), as well as a supplementary search using terms for indoor risk factors in relation to asthma or wheeze (detailed search strategies in Supplemental Table 2).

Study selection and data collection

Titles, abstracts, and full article texts, as appropriate, of the relevant studies identified from the systematic literature search were independently screened by one reviewer (WL) and checked for accuracy by a second reviewer (TF or EA). Eligible primary studies identified directly through screening of the literature search results, as well as any additional primary studies identified from the reference lists of relevant reviews, were included. Non-eligible studies were excluded and the reasons were documented. Any disagreement between the two reviewers was noted and resolved through discussion.

For each included study, one reviewer (e.g., TF or EA) independently extracted data (e.g., study characteristics, study results); this was checked for accuracy by the other reviewer (e.g., EA or TF). Any disagreement between the two reviewers was noted and resolved through discussion. If an included study only reported crude comparisons of exposure or outcome distributions or only generated crude effect estimates without adjusting for potential confounders, we briefly summarized the study for completeness, but did not tabulate the study information because we determined its results were unreliable for causal inference.

If a study reported multiple exposure-outcome pairs (i.e., NO_2-asthma, NO_2-wheeze, gas-asthma, gas-wheeze) of interest, each exposure-outcome pair was recorded as a separate record. If multiple effect estimates were reported for a single exposure-outcome pair, only the most fully adjusted one was extracted, unless the purpose of the most adjusted model was to evaluate potential mediation, effect modification, or sensitivity of the main study result, in which case a less adjusted one was extracted instead. In addition, if subgroup effect estimates were available and they differed meaningfully (e.g., the association was statistically significant in one subgroup but not the other), we extracted those data, as well.

Study quality evaluation

An evaluation of study quality was conducted to determine how reliable the results of each study are for addressing the corresponding research question. For each individual study included in the review and for each exposure-outcome pair, specific aspects of study quality were ranked as "high" or "low" according to a set of pre-determined criteria, as shown in Table 2. The ranking was independently performed by one reviewer (e.g., TF or EA) and then checked for accuracy by the other reviewer (e.g., EA or TF). Any disagreement between the two reviewers was noted and resolved through discussion. If an included study did not report adjusted effect estimates, its study quality was not tabulated.

Evidence synthesis

Evidence for each exposure-outcome pair was synthesized separately, taking into consideration study quality and heterogeneity across studies. Owing to the differences in the specific definitions of asthma and wheeze outcomes across studies, we classified asthma outcomes into three general categories (i.e., newly diagnosed asthma, ever-diagnosed asthma, and asthma exacerbation) and wheeze outcomes into two general categories (i.e., persistent wheeze and any wheeze). Within each exposure-outcome pair, studies that fell into the same health outcome category were considered more homogeneous (i.e., more likely to be examining the same underlying exposure-outcome relationship) than those that fell into different health outcome categories.

Evidence synthesis was performed within each health outcome category, as well as across all categories for comparison purposes. If several included studies were conducted in the same population, we primarily relied on the most recent study or the study reporting the most informative data for that population (e.g., greater population coverage, improved exposure estimates, and/or improved statistical analysis) for evidence synthesis. In addition, we explored potential heterogeneity of results by factors such as age group (e.g., $\leq$6 vs. >6–10 vs. >10 years), sex (male vs. female), study region (e.g., Europe vs. North America vs. Asia-Pacific), publication year (e.g., before 2013 vs. 2013 or later), study design (e.g., cohort vs. case-control vs. cross-sectional), and exposure contrast for gas cooking (e.g., gas vs. electric cooking, gas cooking/stove vs. not).

Guided by the Bradford Hill [4] considerations, we determined the overall plausibility of causality of the association between gas cooking or indoor NO_2 and asthma or wheeze through evaluations of strength of association, consistency, specificity, temporality, dose-response, biological plausibility, coherence, experiment, and analogy, taking into account study quality and associated possible non-causal explanations (i.e., information bias, confounding, selection bias, and reverse causation). The reporting of findings in this review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [71].

Results and discussion

Study selection

From the literature searches, we identified 1655 records from PubMed, 369 from Scopus, and 153 from Lens.org. Before title/abstract screening, 333 records were excluded because they were either duplicate records (n = 303) or records not in English (n = 30). Among the remaining 1844 records that were screened by title/abstract, 195 were kept and further screened by full-text, and 66 were eventually included in this review. Reasons for exclusion at each step are detailed in Fig. 1. The 66 studies included in this review contain all 41 studies that were previously included in the Lin et al. [93] meta-analysis, 5 studies that were published before 2013 but not captured in Lin et al. [93], and 20 new studies that were published since Lin et al. [93].

Table 2
Criteria for study quality evaluation.

Aspect		Criteria for high quality	Criteria for low quality
Exposure Assessment	NO_2	Objective, direct measure	Estimated or indirect measure
	Gas cooking	Objective measure (e.g., observed presence of gas stove)	Self-reported
Outcome Assessment	Asthma	Diagnosed, self-reported physician diagnosed, or self-reported and validated clinically	Self-reported symptoms
	Wheeze	Objective measure or short recall period (i.e., within 1 month) if self-reported	Self-reported with long (i.e., >1 month) recall period
Adjustment for Confounders		Adjusted for all key confounders, including environmental tobacco smoke, family history of asthma/allergies/atopy, SES/home environment (e.g., dust mite, cockroach, pets, mold, wood stove, dampness, heating fuels, crowdedness, pillow/quilt/mattress, form of cooling), and outdoor NO_2 (e.g., season, region, traffic) (for NO_2 studies only) ([46,69])	Failed to adjust for key confounders
Sample Selection		No obvious sources of selection bias	Had obvious sources of selection bias: cohort – lost to follow-up (>25%); case-control – control selection; cross-sectional – inclusion/exclusion criteria, missing data (>25%)
Temporality		Exposure was measured before health outcome	Exposure was measured after or at the same time as the health outcome

Notes
NO_2 = Nitrogen Dioxide; SES = Socioeconomic Status.

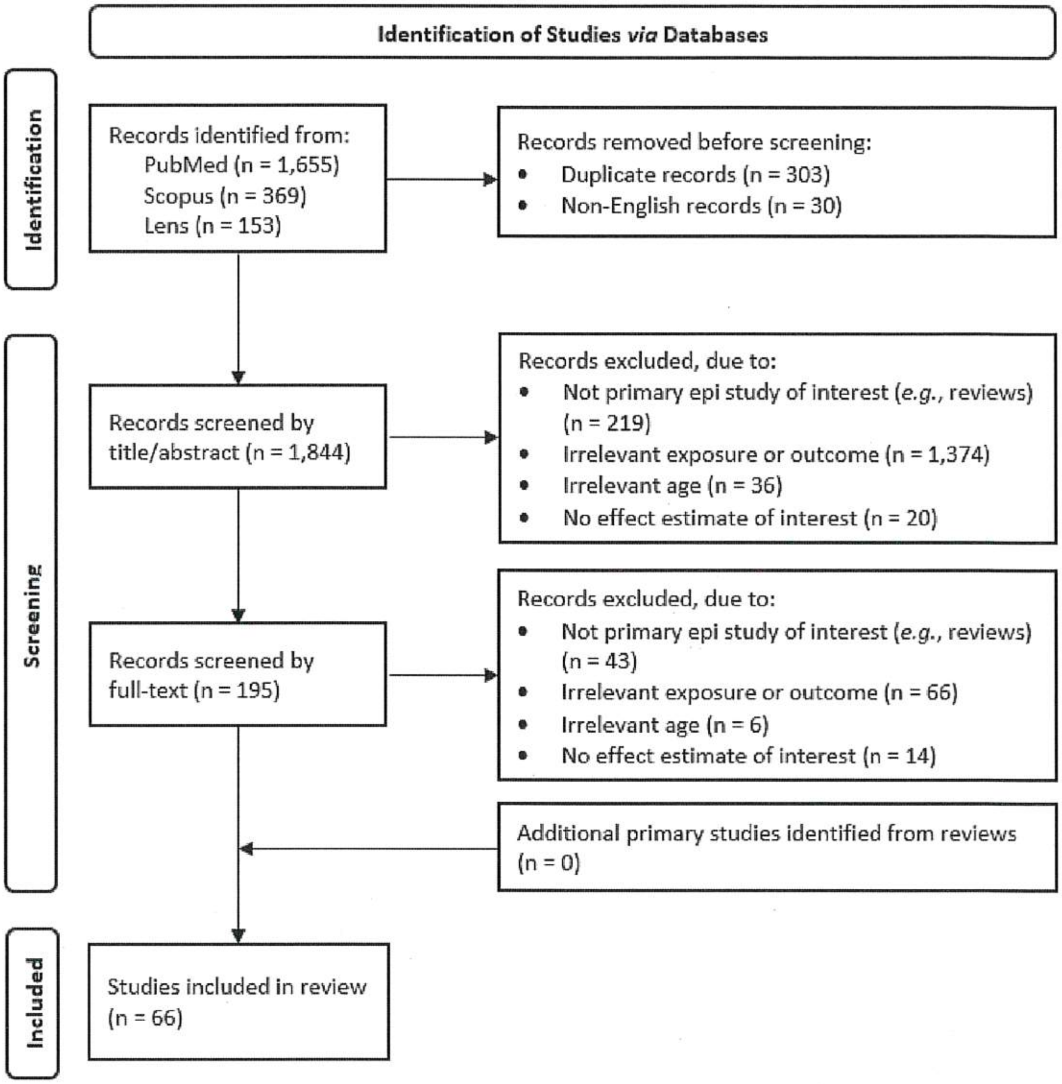

Fig. 1. Flow chart of study selection process.

Gas cooking and asthma

We identified 29 studies that evaluated the association between gas cooking and asthma. In 6 of these studies [27,31,77,82,95,98], the authors only performed crude comparisons of exposure or outcome distributions or only generated crude effect estimates without adjusting for potential confounders. Of the 6 studies, 3 [27,31,95] compared the prevalence of gas cooking exposure between children with vs. without asthma, and the authors did not find statistically significant differences. The other 3 studies [77,82,98] compared the prevalence of asthma between children in homes using gas vs. electricity for cooking, and the authors did not find statistically significant differences. These crude comparison results are not reliable for causal inference. In addition, 1 study [68] performed adjusted statistical analysis but only reported that the gas cooking-asthma association was not statistically significant (i.e., $P \geq 0.05$) without specifying either the point estimate or associated 95% CI. The following discussions focus on the remaining 22 studies that generated specific confounder-adjusted effect estimates. Of the 22 studies, 15 were included in Lin et al. [93] and 7 were published since Lin et al. [93] (Table 3, Supplemental Tables 3–4).

As shown in Table 3 and Supplemental Table 3, the 22 studies are highly heterogeneous. Most of the studies used a cross-sectional design ($n = 16$) and few used a cohort design ($n = 4$) or a case-control design ($n = 2$). Notably, all 7 studies published since Lin et al. [93] used a cross-sectional study design. Of the 22 studies, 4 were conducted in Australia, 4 in China, 3 in Canada, 3 in Germany, 2 in Netherlands, 1 in Nigeria, 1 in Russia, 1 in Uganda, 1 in the United Kingdom [UK], 1 in the United States of America [USA], and the remaining study by Wong et al. [34] was conducted globally across 47 countries. Notably, while 10 of the 15 studies captured in Lin et al. [93] were conducted in North America or Europe, the 7 studies published since Lin et al. [93] consist of 4 studies in Asia (China), 2 studies in Africa (Nigeria and Uganda), and the global study by Wong et al. [34] that covers Africa, Asia-Pacific, Eastern Mediterranean, Indian subcontinent, Latin America, North America, Northern and Eastern Europe, Oceania, and Western Europe regions. Other than the global study that included over 250,000 children, the largest study is Norbäck et al. [19], which included over 39,000 children; the sample sizes of the other studies were between 100 and 10,000. The study population overlapped between Lin et al. [94] and Willers et al. [87]. The study periods are between 1988 and 2018. The ages of children in these studies vary considerably between 0 and 19 years. While some studies (e.g., Eghomwanre et al. [5], Tavernier et al. [32], Hessel et al. [75]) examined wide ranges of ages (>10 years), other studies (e.g., Ponsonby et al. [7], Volkmer et al. [81], Willers et al. [87], Behrens et al. [88]) focused on very specific ages (within 2 years). All studies included both boys and girls. The majority of the studies were

Table 3
Epidemiology studies of gas cooking (exposed vs. unexposed) and asthma.

Citation	Study design	Country	Age (Years)	Sample size	% Exposed	Measure of association	Effect estimate	95% CI	Quality E	Quality O	Quality C	Quality S^{a}	Quality T
Ever diagnosed asthma													
Lin et al. [43]	Cross-sectional	China	5-13	2306	94	OR	3.18	0.42–24.23	L	H	H	H	L
Norbäck et al. [19]	Cross-sectional	China	3-6	39,782	75	OR	0.93	0.80–1.08	L	H	H	H	L
Casas et al. [57]	Cross-sectional	Germany	0–10	3222	12	OR	1.33	0.88–2.00	L	H	H	L^{4}	L
Garrett et al. [70]	Cross-sectional	Australia	7-14	148	NR	OR	**2.23**	**1.06–4.72**	H	H	L	L^{3}	L
Holscher et al. [10]	Cross-sectional	Germany	5-14	2162	49	OR	0.59	0.26–1.33	L	H	L	H	L
McConnell et al. [79]	Cohort	USA	9–16	3535	77	HR (Ever wheeze)	1.20	0.70–2.00	L	H	L	L^{1}	H
						HR (Never wheeze)	1.30	0.80–2.00					
Ponsonby et al. [7] [b]	Cohort	Australia	7	851	1	RR (Adj. for family history)	1.44	0.85–2.45	L	L	L	H	H
						RR (Adj. for ETS)	**1.84**	**1.06–3.17**					
Zhang et al. [67]	Cross-sectional	China	1-8	2193	58[c]	OR	1.44	0.97–2.14	L	H	L	H	L
Huang et al. [86]	Cross-sectional	China	3-6	2214	88	OR	**2.34**	**1.04–5.21**	L	H	L	L^{4}	L
Volkmer et al. [81]	Cross-sectional	Australia	4-5	8154	41	OR (Adelaide)	**1.24**	**1.07–1.42**	L	L	L	H	L
Ponsonby et al. [8]	Cross-sectional	Australia	9-10	344	32	RR	1.20	0.91–1.58	L	L	L	L^{4}	L
Wong et al. [34]	Cross-sectional	Global (47 countries)	6–7	97,726	74	OR	0.94	0.88–1.02	L	L	L	L^{4}	L
			13–14	154,287	66		0.99	0.93–1.05					
Newly diagnosed asthma													
Lin et al. [94]	Cohort	Netherlands	0–8	3590	87	OR	1.10	0.85–1.43	L	H	H	H	H
Carlsten et al. [13] [d]	Cohort	Canada	0–7	380	10	OR	1.40	0.60–3.60	H	H	L	L^{1}	H
Nantanda et al. [80] [e]	Cross-sectional	Uganda	0-5	614	2	OR	**3.80**	**1.20–13.30**	L	H	H	L^{4}	L
Tavernier et al. [32]	Case-control	UK	4-17	200	NR	OR	0.69	0.24–1.95	L	H	L	L^{2}	L
Asthma exacerbation													
Lin et al. [94]	Cohort	Netherlands	0–8	3590	87	OR	1.19	0.86–1.65	L	H	H	H	H
Behrens et al. [88]	Cross-sectional	Germany	6-7	2989	11	PR (Boys)	NE	–	L	H	H	H	L
						PR (Girls)	0.77	0.17–3.46					
Eghomwanre et al. [5]	Cross-sectional	Nigeria	≤17	304	NR	OR	2.00	0.25–15.64	L	H	H	H	L
Spengler et al. [47]	Cross-sectional	Russia	8-12	5951	80	OR (Asthma)	**2.28**	**1.04–5.01**	L	H	H	H	L
						OR (Asthma-like symptoms)	1.19	0.94–1.52					
Dekker et al. [14]	Cross-sectional	Canada	5–8	9841	5	OR	**1.95**	**1.41–2.68**	L	H	L	H	L
Garrett et al. [70]	Cross-sectional	Australia	7-14	148	NR	OR	1.73	0.77–3.90	H	H	L	L^{3}	L
Hessel et al. [75]	Case-control	Canada	5-19	1035	5–7	OR	1.70	1.00–3.10	L	H	L	L^{2}	L
Willers et al. [87]	Cross-sectional	Netherlands	4-5	2611	78	OR	1.50	0.90–2.49	L	L	H	L^{4}	L
Wong et al. [34]	Cross-sectional	Global (47 countries)	6–7	97,726	74	OR	0.97	0.87–1.09	L	L	L	L^{4}	L
			13–14	154,287	66		0.97	0.89–1.07					

Notes
– = Not Applicable; C = Adjustment of Confounders; CI = Confidence Interval; E = Exposure Assessment; ETS = Environmental Tobacco Smoke; H = High; HR = Hazard Ratio; L = Low; NE = Not Estimable; NR = Not Reported; O = Outcome Assessment; OR = Odds Ratio; PR = Prevalence Ratio; RR = Relative Risk; S = Sample Selection; SIDS = Sudden Infant Death Syndrome; T = Temporality; UK = United Kingdom; USA = United States of America.
Statistically significant results are bolded.

[a] L^{1} = cohort study, lost to follow-up (>25%); L^{2} = case-control study, control selection; L^{3} = cross-sectional study, inclusion/exclusion criteria; L^{4} = cross-sectional study, missing data (>25%).

[b] Study conducted among children at high-risk for SIDS.

[c] Calculated based on information provided in the study.

[d] Study conducted among children at high-risk for asthma (having family history of asthma or allergies).

[e] Study conducted among children with cough and/or difficulty in breathing plus fast breathing.

conducted in the general population, except three that were conducted among children with preexisting conditions (i.e., high risk for asthma in Carlsten et al. [13], high risk for sudden infant death syndrome [SIDS] in Ponsonby et al. [7], and cough and/or difficulty in breathing in Nantanda et al. [80]).

The measurement of gas cooking exposure relied on objective observation of the presence of gas cooking stove in only 2 studies [13,70]; all 20 other studies relied on self-reported information that was typically collected at one point in time. The definition of gas cooking exposure varied from ever use gas for cooking to generally/primarily use gas for cooking to presence of gas cooking stove. Few studies further specified whether "gas" was referring to natural gas (methane) or liquefied petroleum gas (LPG) (propane/butane). The prevalence of gas cooking exposure varied substantially across studies, ranging from 1.3% in Ponsonby et al. [7] to 94.09% in Lin et al. [43]. Among studies conducted in the same country, the prevalence of gas cooking exposure also varied – from 1.30% to 40.50% in Australia, from 58% to 94.09% in China, from 4.9% to 10% in Canada, from 10.90% to 48.70% in

Germany, and from 77.90% to 86.50% in Netherlands. The measurement of asthma outcome relied on physician diagnosis during the study in only 2 studies [13,80]; all of the 20 other studies relied on self-reported information, among which most were self-reported physician diagnosis. The definition of asthma outcome varied substantially across studies, with >10 different definitions used.

As shown in Table 3 and Supplemental Table 4, all studies examined gas cooking exposure as a binary variable, but the exposure contrast varied (e.g., gas vs. no gas, gas vs. electricity). There were 12 studies that examined ever-diagnosed asthma as the outcome type, 4 studies that examined newly diagnosed asthma, and 9 studies that examined asthma exacerbation. Overall, 15 of the 22 studies reported null results (i.e., results that are not statistically significant, regardless of the point estimate) and the other 7 studies [7,14,47,70,80,81,86] reported statistically significantly positive associations between gas cooking and asthma, with point estimates ranging from 1.24 to 3.80. Of the 7 studies that reported statistically significant findings, 3 [70,81,86] are cross-sectional studies of ever-diagnosed asthma, 1 [7] is a cohort study of ever-diagnosed asthma, 1 [80] is a cross-sectional study of newly diagnosed asthma (at time of study), and 2 [14,47] are cross-sectional studies of asthma exacerbation. Of these 7 studies, 3 [7,70,81] were conducted in Australia, whereas the other 4 studies were conducted in Russia [47], Canada [14], China [86], and Uganda [80], respectively. Of these 7 studies, 5 were captured in Lin et al. [93] and 2 were published since Lin et al. [93]. The newer studies generally adjusted for larger numbers of potential confounders than the studies captured in Lin et al. [93]. Given the high heterogeneity across the studies in this literature, we do not consider a meta-analysis to be appropriate for evidence synthesis.

The quality of studies in this literature is generally low, as a large proportion of the studies are subject to multiple sources of biases. As shown in Table 3, 20 of the 22 studies have low quality with respect to gas cooking exposure assessment, 18 studies cannot establish the temporal link between gas cooking and asthma, 13 studies have low quality with respect to confounding adjustment, 11 studies are prone to selection bias, and 5 studies have low quality with respect to asthma outcome assessment (studies that examined multiple outcome types were each only counted once). The 7 newer studies (all cross-sectional by design) are of similar quality as compared to the cross-sectional studies that were included in Lin et al. [93]. The distribution of study quality is also similar across asthma outcome types.

Temporality is a key aspect in both study quality evaluation and causal inference guided by the Bradford Hill [4] considerations (discussed below). Among the three different study designs (i.e., cohort, case-control, and cross-sectional) that have been used in this literature, the cohort study design is the only study design that could establish temporality between measured exposure vs. outcome and therefore it is the most reliable for making causal inference [51,84]. However, as noted above, only 4 of the 22 studies on which this review focused used a cohort study design that could establish temporality. These cohort studies mostly reported null results. Specifically, Carlsten et al. [13] examined the association between the presence of a gas cooking stove (yes vs. no) and newly diagnosed asthma in Canadian children aged 0–7 years and reported null result (OR = 1.40; 95% CI: 0.60–3.60) after adjusting for the key confounders (family history and socioeconomic status [SES]/home environment) as well as several other potential confounders. Lin et al. [94] examined the association between ever using gas for cooking (vs. never) and newly diagnosed asthma and asthma exacerbation, respectively, in Dutch children aged 0–8 years and reported null results (OR = 1.10, 95% CI: 0.85–1.43 and OR = 1.19; 95% CI: 0.86–1.65, respectively) after adjusting for all key confounders (environmental tobacco smoke [ETS], family history, and SES/home environment) as well as several other potential confounders. McConnell et al. [79] examined the association between the presence of a gas cooking stove (yes vs. no) and ever-diagnosed asthma in American children aged 9–16 years and reported null results (hazard ratio [HR] = 1.20; 95% CI: 0.70–2.00 among the subgroup with ever wheeze at baseline and HR = 1.30; 95% CI: 0.80–2.00 among the subgroup with never wheeze at baseline), after adjusting for the key confounder (SES) as well as several other potential confounders. Ponsonby et al. [7] examined the association between the presence of a gas cooker (yes vs. no) and ever-diagnosed asthma in Australian children aged 7 years and reported null result (relative risk [RR] = 1.44, 95% CI: 0.85–2.45) after adjusting for key confounder family history alone, but a statistically significantly positive association (RR = 1.84; 95% CI: 1.06–3.17) after adjusting for key confounder ETS exposure alone. While a positive finding (RR = 1.84; 95% CI: 1.06–3.17) was reported by Ponsonby et al. [7], it should not be overinterpreted given the fact that this positive finding was sensitive to confounder adjustment choices made within the study. It is also worth noting that the study by Ponsonby et al. [7] was conducted in a very specific subgroup of the population (children at high risk for SIDS) who were rarely exposed to gas cooking (prevalence = 1.30%), so the study results have limited generalizability to the general population. There is also large variability across the 4 cohort studies in terms of study region (four different countries), age of children (four different age ranges), gas cooking exposure definition (three measured presence of gas cooking stove vs. one measured ever use gas for cooking), and asthma outcome indicator (two effect estimates on newly diagnosed asthma, two on ever-diagnosed asthma, and one on asthma exacerbation), indicating that the only few cohort studies available to date are not necessarily examining the same underlying gas cooking-asthma relationship.

Guided by the Bradford Hill [4] considerations, we further discuss causal inference for the association between gas cooking and asthma in detail in Table 7. Overall, the epidemiology studies, including those with positive findings, largely cannot establish temporality. There are no large and precise effect estimates, and the observed associations lack consistency and specificity. An exposure-response relationship was not observed in the one study that evaluated it. No study has examined whether or how asthma risk or severity would change after removing or reducing gas cooking exposure. Experimental evidence is limited and does not sufficiently support any of the observed associations in epidemiology studies. We did not find a suitable analogy to address causality in this case. Taken together, we conclude that the evidence does not support causality.

In the meta-analysis by Lin et al. [93], all identified studies at the time were included, regardless of whether the studies reported adjusted effect estimates (vs. just performed crude comparisons), the study design, or study quality. Summarizing across these studies, Lin et al. [93] reported a statistically significantly positive association between gas cooking and asthma (OR = 1.32, 95% CI: 1.18–1.48). However, our systematic review shows that the literature to date, including the literature meta-analyzed by Lin et al. [93], is limited by the lack of reliable study designs (e.g., cohort), high heterogeneity across studies, and low study quality (primarily with respect to exposure assessment, temporality, confounding adjustment, and sample selection). Our detailed causal inference guided by the Bradford Hill [4] considerations also shows that the evidence does not support causality. As a result, the effect estimates from Lin et al. [93] should be interpreted with caution.

Gas cooking and wheeze

We identified 37 studies that evaluated the association between gas cooking and wheeze. In 6 of these studies [5,37,38,77,82,95], no adjusted effect estimates were reported. Of the 6 studies, 1 [95] compared the prevalence of gas cooking exposure between children with vs. without wheeze and did not find a statistically significant difference. The other 5 studies compared the prevalence of wheeze between gas cooking exposure groups, 4 of which [5,37,38,77] did not find statistically significant differences and 1 of which [82] observed a statistically significantly higher prevalence of wheeze among girls exposed to gas cooking (vs. electricity cooking, $P < 0.005$), but not among boys. These crude comparison results are not reliable for causal inference. In addition, 1 study [68] performed adjusted statistical analysis but only reported that the gas cooking-wheeze association was not statistically significant (i.e., $P \geq 0.05$) without specifying either the point estimate or associated 95% CI. The following discussions focused on the remaining 30 studies that generated confounder-adjusted effect estimates. Of the 30 studies, 23 were included in Lin et al. [93] and 7 were published since Lin et al. [93] (Table 4, Supplemental Tables 5–6).

As shown in Table 4 and Supplemental Table 5, the 30 studies are highly heterogeneous. Most of the studies used a cross-sectional design ($n = 25$) and a few used a cohort design ($n = 3$) or a case-control design (n = 2). Similar to the studies captured in Lin et al. [93], the newer studies were predominantly cross-sectional by design (all but 1 cohort study). Of the 30 studies, 7 were conducted in China, 5 in USA, 4 in UK, 3 in Australia, 3 in Germany, 2 in Netherlands, 1 in Austria, 1 in Canada, 1 in New Zealand, 1 in Russia, 1 in South Africa, and the remaining study by Wong et al. [34] was conducted globally across 47 countries. Notably, while 16 of the 23 studies captured in Lin et al. [93] were conducted in North America or Europe, 5 of the 7 studies published since Lin et al. [93] were conducted in China. Other than the global study that included over 250,000 children, the largest study is Norbäck et al. [19], which included over 39,000 children; the sample sizes of the other studies were between 100 and 29,000. The study population overlapped between Lin et al. [94] and Willers et al. [87] and between Norbäck et al. [19] and Norbäck et al. [20]. The study periods were between 1978 and 2018. The ages of children in these studies vary considerably, between 0 and 18 years. While some studies (e.g., Belanger et al. [53][, Casas et al. [57]) examined wide ranges of ages (≥10 years), other studies (e.g., Wong et al. [35], Belanger et al. [55]) focused on very specific ages (within 2 years). All studies included both boys and girls. The majority of the studies were conducted in the general population, except 2 that were conducted among children with preexisting conditions (i.e., high risk for asthma in Belanger et al. [55], and active asthma in Belanger et al. [53]).

Similar to the gas cooking and asthma literature, most of the studies measured gas cooking based on self-reported information that was typically collected at one point in time, and only 2 studies [50,70] used objective measurements (e.g., observed presence of gas stove). The definition of gas cooking exposure varied from ever use gas for cooking to generally/primarily use gas for cooking to presence of gas cooking stove. Few studies further specified whether "gas" was referring to natural gas (methane) or LPG (propane/butane). The prevalence of gas cooking exposure varied substantially across studies, ranging from 2.2% in Wong et al. [35] to 94.09% in Lin et al. [43]. Among studies conducted in the same country, the prevalence of gas cooking exposure also varied – from 2.2% to 94.09% in China, from 23.5% to 46.4% in USA, from 57.83% to 82.02% in UK, from 31.80% to 40.50% in Australia, from 10.90% to 48.70% in Germany, and from 77.90% to 86.50% in Netherlands. The measurements of all wheeze outcomes relied on self-reported information, and the definition of wheeze outcome varied substantially across studies. Other than "wheeze, past year" that was common across 12 studies, all other wheeze outcome definitions were unique to each study.

As shown in Table 4 and Supplemental Table 6, all studies examined gas cooking exposure as a binary variable, but the exposure contrast varied (e.g., gas vs. no gas, gas vs. electricity). Of the 30 studies, 21 examined any wheeze as the only outcome type, 4 studies examined persistent wheeze only, and 5 studies examined both any wheeze and persistent wheeze. Only a few studies examined very specific wheeze outcomes, such as duration of wheezing, speech-limiting wheeze, sleep disturbance due to wheeze, exercise-induced wheeze, wheeze with/without colds (results not shown). Overall, 23 of the 30 studies reported null results; 6 of the other 7 studies reported statistically significantly positive associations between gas cooking and wheeze [29,35,36,45,53,81], with point estimates ranging from 1.16 [81] to 2.27 [53], and 1 study reported statistically significantly inverse associations [88], with a point estimate of 0.55. All 7 studies that reported statistically significant results were cross-sectional by design and examined any wheeze as the health outcome type. None of the studies examining persistent wheeze reported statistically significant findings. Of the 6 studies that reported statistically significantly positive findings, 2 [35,36] were conducted in China, whereas the other 4 studies were conducted in USA [53], UK [29], Australia [81], and South Africa [45], respectively. All of these studies were captured in Lin et al. [93] except for Shirinde et al. [45], which was published since Lin et al. [93]. The newer studies generally adjusted for more potential confounders than the studies captured in Lin et al. [93]. Given the high heterogeneity across the studies in this literature, we do not consider a meta-analysis to be appropriate for evidence synthesis.

The quality of studies in this literature is generally low, as a large proportion of the studies are subject to multiple sources of biases. As shown in Table 4, 28 of the 30 studies have low quality with respect to gas cooking exposure assessment, 26 studies have low quality with respect to wheeze outcome assessment, 26 studies cannot establish the temporal link between gas cooking and wheeze, 18 studies have low quality with respect to confounding adjustment, and 12 studies are prone to selection bias (studies that examined multiple outcome types were each only counted once). The 7 newer studies are of similar quality as compared to the studies that were included in Lin et al. [93]. The distribution of study quality is also similar across wheeze outcome types.

Temporality is a key aspect in both study quality evaluation and causal inference guided by the Bradford Hill [4] considerations (discussed below). Among the 30 studies that this review focused on, only 3 used a cohort study design that could establish temporality, which is more reliable for making causal inference than a case-control design (used by 2 studies) or a cross-sectional design (used by the remaining 25 studies) [51,84]. These cohort studies all reported null results. Specifically, Lin et al. [94] examined the association between ever using gas for cooking (vs. never) and wheeze in the past 12 months, early transient wheeze, late onset wheeze, and persistent wheeze, respectively, in Dutch children aged 0–8 years and reported null results (OR = 1.10, 95% CI: 0.92–1.31; OR = 0.95, 95% CI: 0.74–1.23; OR = 0.75, 95% CI: 0.47–1.22; OR = 1.42, 95% CI: 0.93–2.17 respectively), after adjusting for all key confounders (ETS, family history, SES/home environment) as well as several other potential confounders. Samet et al. [50] examined the association between the presence of a gas cooking stove and wheezing during a respiratory illness episode in American children aged 1–1.5 years and reported null result (OR = 0.84, 95% CI: 0.64–1.09) after adjusting for all key confounders (ETS, family history, SES/home environment) as well as several other potential confounders. Yu et al. [40] examined the association between using gas for cooking and new onset wheeze in Chinese children aged 0–1.5 years and reported null result (HR = 3.24, 95% CI: 0.782–13.388), after adjusting for key confounders (family history and SES/home environment) as well as several other potential confounders. There is also large variability across the 3 cohort studies in terms of study region (three different countries), age of children (two different age ranges), gas cooking definition (use gas for cooking vs. presence of gas stove), and wheeze outcome indicator (three different indicators), indicating that the only few cohort studies available to date are not necessarily examining the same underlying gas cooking-wheeze relationship.

Guided by the Bradford Hill [4] considerations, we further discuss causal inference for the association between gas cooking and wheeze in detail in Table 7. Overall, most of the epidemiology studies, including all of those with positive findings, cannot establish temporality. There are no large and precise effect estimates, and the observed associations lack consistency and specificity. An exposure-response relationship was not observed in the one study that evaluated it. No study has examined whether or how wheeze symptom would change after removing or reducing gas cooking exposure. Experimental evidence is limited and does not sufficiently support any of the observed associations in epidemiology studies. We did not find a suitable analogy to address causality in this case. Taken together, we conclude that the evidence does not

Table 4
Epidemiology studies of gas cooking (exposed vs. unexposed) and wheeze.

Citation	Study design	Country	Age (Years)	Sample size	% Exposed	Measure of association	Effect estimate	95% CI	Quality E	Quality O	Quality C	Quality S[a]	Quality T
Any wheeze													
Samet et al. [50]	Cohort	USA	0–1.5	1205	80[b]	OR	0.84	0.64–1.09	H	H	H	H	H
Lin et al. [94]	Cohort	Netherlands	0–8	3590	87	OR (Wheeze last year)	1.10	0.92–1.31	L	L	H	H	H
						OR (Early transient wheeze)	0.95	0.74–1.23					
						OR (Late onset wheeze)	0.75	0.47–1.22					
Yu et al. [40]	Cohort	China	0–1.5	544	91	HR	3.24	0.78–13.39	L	H	L	H	H
Behrens et al. [88]	Cross-sectional	Germany	6-7	2947	11	PR (Boys)	**0.55**	**0.31–0.98**	L	L	H	H	L
						PR (Girls)	1.52	0.93–2.47					
Belanger et al. [55] [c]	Cross-sectional	USA	0-1	849	34	OR (With maternal asthma)	1.03	0.59–1.79	L	H	H	L[4]	L
						OR (Without maternal asthma)	1.28	0.88–1.86					
Lin et al. [43]	Cross-sectional	China	5-13	2306	94	OR	NE	–	L	L	H	H	L
Norbäck et al. [19]	Cross-sectional	China	3-6	39,782	75	OR	1.02	0.93–1.13	L	L	H	H	L
Norbäck et al. [20]	Cross-sectional	China	3-6	17,679	75	OR (Baseline wheeze prevalence)	1.10	0.91–1.33	L	L	H	H	L
						OR (Wheeze onset)	1.03	0.86–1.22					
						OR (Wheeze remission)	0.95	0.65–1.41					
Spengler et al. [47]	Cross-sectional	Russia	8-12	5951	80	OR	1.06	0.86–1.31	L	L	H	H	L
Wong et al. [36]	Cross-sectional	China	2-6	3089	87	OR	**1.68**	**1.03–2.75**	L	L	L	H	H
Zacharasiewicz et al. [3]	Cross-sectional	Austria	6-9	28,747	NR	OR	1.16	0.92–1.46	L	L	H	H	L
Belanger et al. [53] [d]	Cross-sectional	USA	<12	728	55	OR (Multifamily housing)	**2.27**	**1.15–4.47**	L	H	L	L[4]	L
					24	OR (Single-family housing)	0.61	0.35–1.05					
Burr et al. [72]	Cross-sectional	UK	12-14	25,393	61	OR	1.03	0.97–1.10	L	L	L	H	L
Garrett et al. [70]	Cross-sectional	Australia	7-14	148	NR	OR	1.79	0.80–3.99	H	L	L	L[3]	L
Holscher et al. [10]	Cross-sectional	Germany	5-14	2061	49	OR	1.09	0.90–1.33	L	L	L	H	L
Huang et al. [86]	Cross-sectional	China	3-6	2214	88	OR	1.26	0.86–1.86	L	L	H	L[4]	L
Mitchell et al. [24]	Cross-sectional	New Zealand	6–7	10,810	16	OR	0.93	0.81–1.07	L	L	L	H	L
Shirinde et al. [45]	Cross-sectional	South Africa	13–14	1113	8	OR (Kempton Park)	**1.65**	**1.04–2.61**	L	L	L	H	L
						OR (Ever wheeze, Adelaide)	NS	Non-sig					
Volkmer et al. [81]	Cross-sectional	Australia	4-5	8154	41	OR (Wheeze last year, Adelaide)	**1.16**	**1.01–1.32**	L	L	L	H	L
				2276		OR (Current wheeze)	0.99	0.74–1.32					
				2311		OR (Transient early wheeze)	0.91	0.73–1.14					
Willers et al. [87]	Cross-sectional	Netherlands	4-5	1718	78	OR (Late-onset wheeze)	0.89	0.48–1.67	L	L	H	L[4]	L
					2	OR (Exposed during infancy but not at present)	1.53	0.61–3.80[e]					
					19	OR (Exposed at present only)	1.40	0.85–2.31[e]					
Wong et al. [35]	Cross-sectional	China	10	8323	66	OR (Exposed at present and during infancy)	**2.00**	**1.29–3.09**[e]	L	L	L	H	L
Butland et al. [12]	Case-control	UK	7.5–8.5	791	75–82	OR (Infrequent wheeze)	1.34	0.93–1.95	L	L	L	L[2]	L
				949		OR (All wheeze)	1.34	0.95–1.89					
de Bilderling et al. [29]	Cross-sectional	UK	16–18	1868	58	OR (Childhood)	**1.47**	**1.05–2.04**	L	L	L	L[4]	L
					62	OR (Adolescence)	1.06	0.74–1.50					
Ekwo et al. [25]	Cross-sectional	USA	6-12	1138	31	OR	0.70	Non-sig	L	L	L	L[4]	L
Ponsonby et al. [8]	Cross-sectional	Australia	9-10	343	32	RR	1.08	0.75–1.55	L	L	L	L[4]	L
Wong et al. [34]	Cross-sectional	Global (47 countries)	6–7	97,726	74	OR	0.96	0.89–1.03	L	L	L	L[4]	L
			13–14	154,287	66		0.99	0.92–1.07					
Persistent wheeze													
Lin et al. [94]	Cohort	Netherlands	0–8	3590	87	OR	1.42	0.93–2.17	L	L	H	H	H
Lin et al. [43]	Cross-sectional	China	5-13	2306	94	OR	1.76	0.22–14.01	L	L	H	H	L
Casas et al. [57]	Cross-sectional	Germany	0–10	3387	12	OR	1.09	0.76–1.57	L	L	H	L[4]	L

(continued on next page)

Table 4 (*continued*)

Citation	Study design	Country	Age (Years)	Sample size	% Exposed	Measure of association	Effect estimate	95% CI	Quality				
									E	O	C	S[a]	T
Dekker et al. [14]	Cross-sectional	Canada	5–8	10,185	5	OR	1.04	0.77–1.42	L	L	L	H	L
Strachan and Carey [23]	Case-control	UK	11-16	961	73–74	OR	0.86	0.61–1.23	L	L	L	H	L
Ware et al. [49]	Cross-sectional	USA	6-10	8237	46[f]	OR	0.93–1.07[g]	Non-sig	L	L	L	H	L
Willers et al. [87]	Cross-sectional	Netherlands	4-5	1923	78	OR	1.06	0.76–1.47	L	L	H	L[4]	L
Butland et al. [12]	Case-control	UK	7.5–8.5	541	75–79	OR	1.19	0.68–2.07	L	L	L	L[2]	L
de Bilderling et al. [29]	Cross-sectional	UK	16–18	1868	58	OR (Childhood)	1.02	0.77–1.36	L	L	L	L[4]	L
					62	OR (Adolescence)	0.78	0.58–1.06					

Notes

– = Not Applicable; C = Adjustment of Confounders; CI = Confidence Interval; E = Exposure Assessment; H = High; HR = Hazard Ratio; L = Low; NE = Not Estimable; NR = Not Reported; O = Outcome Assessment; OR = Odds Ratio; PR = Prevalence Ratio; RR = Relative Risk; S = Sample Selection; T = Temporality; UK = United Kingdom; USA = United States of America.

Statistically significant results are bolded.

[a] L^1 = cohort study, lost to follow-up (>25%); L^2 = case-control study, control selection; L^3 = cross-sectional study, inclusion/exclusion criteria; L^4 = cross-sectional study, missing data (>25%).

[b] Pre-determined per study design.

[c] Study was conducted among children at high-risk for asthma (having an asthmatic sibling).

[d] Study was conducted among children with active asthma.

[e] Overall $P = 0.004$ for global test across all categories.

[f] The prevalence was estimated based on numbers provided in the study.

[g] Only range was reported in the study.

support causality.

In the meta-analysis by Lin et al. [93], all identified studies at the time were included, regardless of whether the studies reported adjusted effect estimates (vs. just performed crude comparisons), the study design, or study quality. Summarizing across these studies, Lin et al. [93] reported no statistically significant association between gas cooking and wheeze (OR = 1.06, 95% CI: 0.99–1.13), consistent with our conclusion. It is worth noting that our systematic review shows that the literature to date, including the literature meta-analyzed by Lin et al. [93], is limited by the lack of reliable study designs (e.g., cohort), high heterogeneity across studies, and low study quality (primarily with respect to exposure assessment, outcome assessment, temporality, and confounding adjustment). Our detailed causal inference guided by the Bradford Hill [4] considerations also shows that the evidence does not support causality. These should be incorporated in the interpretation of any meta-analysis results for the literature.

Indoor NO_2 and asthma

We identified 20 studies that evaluated the association between indoor NO_2 and asthma. In 6 of these studies [5,28,39,41,76,78], no adjusted effect estimates were reported. Of the 6 studies, 5 compared the distribution of indoor NO_2 exposure between children with vs. without asthma, of which 3 [28,76,78] reported statistically significantly higher indoor NO_2 concentration among children with asthma and 2 [39,41] did not find statistically significant differences. The remaining study by Eghomwanre et al. [5] examined the correlation between indoor NO_2 and clinical asthma and diagnosed asthma, respectively, and in dry and wet season, respectively, and did not find a statistically significant correlation. These crude comparison results are not reliable for causal inference, so the following discussion focuses on the remaining 14 studies that generated confounder-adjusted effect estimates. Of the 14 studies, 8 were included in Lin et al. [93], 2 were published before 2013 but not included in Lin et al. [93], and 4 were published since Lin et al. [93] (Table 5, Supplemental Tables 7–8).

As shown in Table 5 and Supplemental Table 7, the 14 studies are highly heterogeneous. Specifically, 10 of the 14 studies used a cohort design, 2 used a cross-sectional design, and 2 used a case-control design. Of the 14 studies, 7 were conducted in the USA, 2 in Australia, 2 in Netherlands, 1 in Canada, 1 in Japan, and 1 in the UK. The sample sizes of the studies were between 30 and 1600, generally much smaller than the gas cooking studies. The study periods were between 1983 and 2014. The ages of children in these studies vary considerably, from 0 to 17 years of age. While some studies (e.g., Tavernier et al. [32], Lu et al. [56]) examined wide ranges of ages (>10 years), other studies (e.g., Hoek et al. [30], Shima and Adachi [64]) focused on very specific ages (within 2 years). All studies included both boys and girls. Unlike the gas cooking studies, a large proportion (8 of 14) of the indoor NO_2 studies for asthma were conducted among children with preexisting conditions, such as at high risk for asthma, active asthma, and moderate/severe asthma; only 6 studies were conducted in the general population. Notably, all 4 studies published since Lin et al. [93] were cohort studies conducted in the USA among children with preexisting conditions.

All studies measured indoor NO_2 using passive samplers, with 6 studies using the tube type samplers, 7 studies using badge type samplers, and 1 study not specifying the sampler type. Of the 14, 7 studies measured indoor NO_2 at a single location within each household, 6 studies measured indoor NO_2 at multiple locations within each household, and 1 study did not specify the measurement location. As for the specific location, 9 of the 14 studies performed measurements in children's bedroom, 6 studies in the kitchen, 6 studies in the living room/main living area, and 2 studies in activity room/dayroom (i.e., room children spent the most time awake). The averaging time for NO_2 measurements ranged from 1 day to 1 year. The mean/median concentrations of indoor NO_2 varied substantially across, as well as between subgroups within, studies, ranging from 11.6 to 109.04 $\mu g/m^3$. Among

Table 5
Epidemiology studies of NO_2 and asthma.

Citation	Study design	Country	Age (Years)	Sample size	NO^2 exposure		Exposure contrast ($\mu g/m^3$)[a]	Measure of association	Effect estimate	95% CI	Quality				
					Concentration ($\mu g/m^3$)[a]	Location					E	O	C	S[b]	T
Ever diagnosed asthma															
Neas et al. [61]	Cohort	USA	7–11	1567	16–44 (M)	B, D/A, K	per 28.20	OR	0.91	0.60–1.36	H	H	H	H	L
Garrett et al. [70]	Cross-sectional	Australia	7-14	148	12 (Mdn)	B, LR, K	per 10 (B)	OR	1.01	0.75–1.37	H	H	L	L^3	L
							per 10 (Indoor mean)	OR (Overall)	1.00	0.75–1.31					
								OR (Winter)	0.99	0.84–1.16					
								OR (Summer)	2.52	0.99–6.42					
Hoek et al. [30]	Case-control	Netherlands	6	80	59–67 (M)	B, LR, K	per 10-fold	OR (K)	1.29	0.40–5.40[c]	H	H	L	L^2	L
								OR (LR)	5.83	0.70–34.90[c]					
								OR (B)	2.68	0.40–16.20[c]					
Newly diagnosed asthma															
Shima and Adachi [64]	Cohort	Japan	9–10	842	35–61 (M)	LR	per 18.80	OR	0.87	0.51–1.43	H	H	H	H	L
Carlsten et al. [13] [d]	Cohort	Canada	0–7	155	21 (M)	B	>18.80 (vs. ≤18.80)	OR	1.80	0.70–4.80	H	H	L	L^1	H
Tavernier et al. [32]	Case-control	UK	4-17	200	NR	B, LR	Not specified	OR (LR)	0.85	0.51–1.44	H	H	L	L^2	L
								OR (B)	0.92	0.49–1.71					
Asthma exacerbation															
O'Connor et al. [33] [d]	Cohort	USA	0–7	442	38 (Mdn)	NR	Not specified	OR	0.97	0.75–1.26	H	H	L	H	H
Shima and Adachi [64]	Cohort	Japan	9–10	842	35–61 (M)	LR	per 18.80	OR (4th grade, males)	0.77	0.48–1.20	H	H	H	H	L
								OR (4th grade, females)	**1.63**	**1.06–2.54**					
								OR (5th grade, males)	0.92	0.60–1.39					
								OR (5th grade, females)	**1.67**	**1.06–2.66**					
								OR (6th grade, males)	0.78	0.45–1.30					
								OR (6th grade, females)	1.18	0.62–2.18					
Paulin et al. [62] [e]	Cohort	USA	5–12	30	109 (M)	K	per 10-fold	OR	0.63	0.08–4.72	H	H	L	H	L
Dijkstra et al. [58]	Cross-sectional	Netherlands	6-12	775	20–60 (M)[f]	B, LR, K	21–40 (vs. 0–20)	OR	0.67	0.32–1.41	H	L	L	H	L
							41–60 (vs. 0–20)		0.34	0.08–1.54					
							>60 (vs. 0–20)		0.56	0.15–2.06					
Garrett et al. [70]	Cross-sectional	Australia	7-14	148	12 (Mdn)	B, LR, K	per 10 (B)	OR	1.06	0.77–1.46	H	H	L	L^3	L
Hansel et al. [73] [g,h]	Cohort	USA	2-6	150	56 (M)	B	per 37.60	RR	1.04	0.97–1.12	H	L	L	H	L
Lu et al. [56] [e]	Cohort	USA	5–17	142	39 (Mdn)	B	per 10-fold	OR (Normal weight)	1.34	0.83–2.14	H	L	L	H	L
								OR (Overweight)	1.42	0.65–3.11					
								OR (Obese)	1.93	0.77–4.82					
Nitschke et al. [63] [g,h]	Cohort	Australia	5-12	174	71 (M of Max)	K	per 18.80	RR (Daytime)	1.00	0.95–1.05	H	L	L	H	L
Schachter et al. [26] [i]	Cohort	USA	6–14	36	45–62 (M)	LR	Not specified	OR (Summer)	1.20	0.40–3.65	H	L	L	H	L
								OR (Winter)	**2.82**	**1.10–7.24**					
							11.32- ≤ 16.69 (vs. ≤11.32)		1.15	0.94–1.42					
							16.69- ≤ 26.88 (vs. ≤11.32)		**1.31**	**1.04–1.66**					
Belanger et al. [54] [e]	Cohort	USA	5–10	1342	20 (M)	B, D/A	>26.88 (vs. ≤11.32)	OR	**1.43**	**1.08–1.88**	H	L	L	L^1	L
							per 5-fold (if >11.32 threshold)		**1.37**	**1.01–1.89**					

Notes
B = Bedroom; C = Adjustment of Confounders; CI = Confidence Interval; D/A = Dayroom/Activity Room; E = Exposure Assessment; H = High; K = Kitchen; L = Low; LR = Living Room; M = Mean; Max = Maximum; Mdn = Median; NO_2 = Nitrogen Dioxide; NR = Not Reported; O = Outcome Assessment; OR = Odds Ratio; ppb = Parts per Billion; RR = Relative Risk; S = Sample Selection; T = Temporality; UK = United Kingdom; USA = United States of America.
Statistically significant results are bolded.
[a] Converted if ppb was originally used as the unit in the paper.
[b] L^1 = cohort study, lost to follow-up (>25%); L^2 = case-control study, control selection; L^3 = cross-sectional study, inclusion/exclusion criteria; L^4 = cross-sectional study, missing data (>25%).
[c] 90% CI.
[d] Study was conducted among children at high-risk for asthma (i.e., having family history of asthma or allergies).
[e] Study was conducted among children with active asthma.
[f] Estimated from figure in the study.
[g] Published before but not included in Lin et al. [93].
[h] Study was conducted among children with physician-diagnosed asthma.
[i] Study was conducted among children with moderate/severe asthma.

studies conducted in the same country, indoor NO_2 concentrations also varied – from 16.17 to 109.04 μg/m^3 in the USA and from 20 to 67 μg/m^3 in Netherlands. The measurement of asthma outcome relied on physician diagnosis during study in only 1 study [13]. All 13 other studies relied on self-reported information, among which 4 relied on self-reported physician diagnosis and 3 relied on confirmed/validated clinically. The definition of asthma outcome varied substantially across studies, with 14 distinct definitions used.

As shown in Table 5 and Supplemental Table 8, the exposure contrast for which the effect estimates were calculated varied substantially across studies. Of the 14 studies, 6 calculated effect estimates from a set increment of indoor NO_2 concentration on the original scale, but the actual magnitude varied from 10 μg/m^3 to 37.6 μg/m^3; 5 studies examined indoor NO_2 concentration on the log scale; 3 studies categorized indoor NO_2 concentration, each in a unique way; and 3 studies did not specify the exposure contrast. Only 1 study [54] examined the operationalization of indoor NO_2 concentration in more than one way (categorical and continuous). Notably, only 1 study [63], which was captured by our literature search but not included in Lin et al. [93], focused on the examination of maximum rather than average indoor NO_2. In general, 3 of the 14 studies examined ever-diagnosed asthma, 3 studies examined newly diagnosed asthma, and 10 studies examined asthma exacerbation. Few studies examined very specific asthma outcome indicators (e.g., exercise-related asthma, medication use) (results not shown).

Overall, 11 of the 14 studies reported null results; 3 studies reported statistically significantly positive associations between indoor NO_2 and asthma [26,54,64], among which 2 [54,64] were included in Lin et al. [93] and 1 [26] was published since Lin et al. [93]. The magnitudes of the three statistically significant point estimates were not directly comparable with each other, given the different exposure contrasts used. Belanger et al. [54], a cohort study in the USA, reported a 1.37 (95% CI: 1.01–1.89) times higher risk of asthma exacerbation per 5-fold increase in NO_2 if greater than a prespecified threshold of 11.32 μg/m^3. Shima and Adachi [64], a cohort study in Japan, reported a 1.63 (95% CI: 1.06–2.54) times and 1.67 (95% CI: 1.06–2.66) times higher risk of asthma exacerbation per 18.8 μg/m^3 increment of indoor NO_2 among girls in 4th and 5th grades, respectively. However, null result was observed for 6th grader girls or among boys. Schachter et al. [26], a cohort study in the USA, reported a statistically significantly positive association between each interquartile range (not specified) increase of indoor NO_2 concentration and asthma exacerbation in winter (OR = 2.82, 95% CI: 1.10–7.24), but not in summer. Notably, all 3 studies were cohort by design and the statistically significant findings were all for asthma exacerbation as the outcome type. Compared to the studies included in Lin et al. [93], the newer studies generally adjusted for fewer potential confounders. Given the high heterogeneity across the studies in this literature, we do not consider a meta-analysis to be appropriate for evidence synthesis.

The quality of this literature is generally low. Although all studies have high quality with respect to exposure assessment, a large proportion of them are subject to multiple sources of biases. As shown in Table 5, 12 of the 14 studies have low quality with respect to confounding adjustment, 12 studies cannot establish temporality, 6 studies have low quality with respect to asthma outcome assessment, and 5 studies are prone to selection bias (studies that examined multiple outcome types were each only counted once). All 4 studies published since Lin et al. [93] have low quality with respect to confounding adjustment and high quality with respect to sample selection; although all 4 studies are cohort by design, three cannot establish temporality because the measurements of indoor NO_2 in the cohort were not necessarily taken prior to the measurements of asthma outcomes. The distribution of study quality is similar across asthma outcome types, except that, among studies of asthma exacerbation, a larger proportion are of low quality with respect to outcome assessment and a larger proportion are less prone to selection bias.

Temporality is a key aspect in both study quality evaluation and causal inference guided by the Bradford Hill [4] considerations (discussed below). Compared to the gas cooking studies, a much larger proportion (i.e., 10 of 14) of indoor NO_2 studies for asthma used a cohort design, which is in general more reliable for making causal inference than a case-control or cross-sectional design [51,84]. However, 8 of these 10 studies were of low quality with respect to temporality, despite the cohort design, due to the fact that the measurements of indoor NO_2 in the cohort were not necessarily taken prior to the measurements of asthma outcomes. Only the remaining 2 cohort studies [13,33] were of high quality with respect to temporality. Carlsten et al. [13] examined the association between indoor (bedroom) NO_2 and newly diagnosed asthma in Canadian children aged 0–7 years and reported null result after adjusting for key confounders (family history, SES/home environment, and outdoor NO_2) as well as several other potential confounders. O'Connor et al. [33] examined the association between indoor (location not specified) NO_2 and asthma exacerbation in American children aged 0–7 years and reported null result, after adjusting for the key confounder (family history) as well as several other potential confounders. While these 2 cohort studies both focused on children aged 0–7 years in North America region, their health outcomes varied, indicating that the only cohort studies that could establish temporality to date are not necessarily examining the same underlying indoor NO_2-asthma relationship.

Guided by the Bradford Hill [4] considerations, we further discuss causal inference for the association between indoor NO_2 and asthma in detail in Table 7. Overall, most of the epidemiology studies, including all of those with positive findings, cannot establish temporality. There are no large and precise effect estimates, and the observed associations lack consistency and specificity. An exposure-response relationship has not been well-characterized. No study has examined whether or how asthma risk or severity would change after reducing indoor NO2 exposure. Experimental evidence is limited and does not sufficiently support any of the observed associations in epidemiology studies. We did not find a suitable analogy to address causality in this case. Taken together, we conclude that the evidence does not support causality.

In the meta-analysis by Lin et al. [93], all identified studies at the time were included, regardless of whether the studies reported adjusted effect estimates (vs. crude comparisons), the study design, or study quality. Summarizing across these studies, Lin et al. [93] reported no statistically significant association between indoor NO_2 and asthma (OR = 1.09, 95% CI: 0.91–1.31 for a 15-ppb [i.e., 28.2 μg/m^3] increase in NO_2), consistent with our conclusion. It is worth noting that our systematic review shows that the literature to date, including the literature meta-analyzed by Lin et al. [93], is limited by the lack of consistent findings among studies with reliable study design (e.g., cohort), the high heterogeneity across studies, and the low study quality (primarily with respect to confounding adjustment and temporality). Our detailed causal inference guided by the Bradford Hill [4] considerations also shows that the evidence does not support causality. These should be incorporated in the interpretation of any meta-analysis results for the literature.

Indoor NO_2 and wheeze

We identified 16 studies that evaluated the association between indoor NO_2 and wheeze. In 2 of these studies [5,28], no adjusted effect estimates were reported. Eghomwanre et al. [5] examined the correlation between indoor NO_2 and wheeze in dry and wet season, respectively, and did not find a statistically significant correlation. Cibella et al. [28] compared indoor NO_2 concentrations in spring and winter, respectively, between children with vs. without wheeze and reported statistically significantly higher indoor NO_2 concentrations in each season among children with wheeze (vs. without wheeze, $P = 0.003$). These crude comparison results are not reliable for causal inference. As a result, the following discussion focuses on the remaining 14 studies that generated confounder-adjusted effect estimates. Of the 14 studies, 11 were included in Lin et al. [93], 1 was published before 2013 but not included in Lin et al. [93], and 2 were published since Lin et al. [93]

Table 6
Epidemiology studies of NO_2 and wheeze.

Citation	Study design	Country	Age (Years)	Sample size	NO_2 Exposure		Exposure contrast (μg/m³)[a]	Measure of association	Effect estimate	95% CI	Quality				
					Concentration (μg/m³)[a]	Location					E	O	C	S[b]	T
Any wheeze															
Samet et al. [50]	Cohort	USA	0–1.5	1205	19–38 (Mdn)[c]	B, D/A, K	37.60–75.20 (vs. 0–37.60)	OR (Unlagged)	0.92	0.73–1.15	H	H	H	H	H
							>75.20 (vs. 0–37.60)		0.88	0.56–1.37					
							37.60–75.20 (vs. 0–37.60)	OR (Lagged)	0.95	0.75–1.19					
							>75.20 (vs. 0–37.60)		0.98	0.66–1.48					
Yu et al. [40]	Cohort	China	0–1.5	544	42 (M)	B	Not specified	HR	0.99	0.979–1.003	H	H	L	H	H
Belanger et al. [55] [d]	Cross-sectional	USA	0-1	849	>19 (46%)	LR	per 18.80	OR (With maternal asthma)	1.10	0.87–1.40	H	H	L	L[4]	H
								OR (Without maternal asthma)	1.10	0.96–1.25					
Li et al. [9]	Cohort	China	0–1.5	963	NR	NR	Not specified	HR	1.00	0.995–1.001	H	H	L	L[1]	H
Nitschke et al. [63] [e,f]	Cohort	Australia	5-12	174	71 (M of Max)	K	per 18.80	RR (Daytime)	0.98	0.92–1.04	H	H	L	H	L
Shima and Adachi [64]	Cohort	Japan	9–10	842	35–61 (M)	LR	per 18.80	OR (4th grade, males)	0.98	0.68–1.39	H	L	H	H	L
								OR (4th grade, females)	**1.90**	**1.30–2.83**					
								OR (5th grade, males)	0.88	0.59–1.29					
								OR (5th grade, females)	**1.60**	**1.06–2.44**					
								OR (6th grade, males)	0.91	0.58–1.41					
								OR (6th grade, females)	1.23	0.78–1.92					
								OR (Incident wheeze)	0.73	0.45–1.14					
Belanger et al. [53] [g]	Cross-sectional	USA	<12	728	19–43 (M)	LR	per 37.60	OR (Any wheeze, multifamily housing)	**1.52**	**1.04–2.21**	H	H	L	L[4]	L
								OR (Any wheeze, single-family housing)	0.99	0.71–1.38					
								RR (No. wheeze days, multifamily housing)	**1.33**	**1.05–1.68**					
								RR (No. wheeze days, single-family housing)	0.98	0.78–1.22					
Belanger et al. [54] [g]	Cohort	USA	5–10	1342	20 (M)	B, D/A	11.32- ≤ 16.69 (vs. ≤11.32)	OR	1.15	0.90–1.45	H	H	L	L[4]	L
							16.69- ≤ 26.88 (vs. ≤11.32)		**1.44**	**1.11–1.86**					
							>26.88 (vs. ≤11.32)		**1.53**	**1.16–2.02**					
							per 5-fold (if >11.32 threshold)		**1.49**	**1.09–2.03**					
Dijkstra et al. [58]	Cross-sectional	Netherlands	6-12	775	20–60 (M)[c]	B, LR, K	21–40 (vs. 0–20)	OR	0.75	0.40–1.41	H	L	L	H	L
							41–60 (vs. 0–20)		0.36	0.11–1.26					
							>60 (vs. 0–20)		0.94	0.37–2.40					
Esplugues et al. [2]	Cross-sectional	Spain	0-1	352	20 (M)	NR	per 10	OR	1.07	0.86–1.33	H	H	L	L[4]	L
Hoek et al. [30]	Case-control	Netherlands	6	124	59–63 (M)	B, LR, K	per 10-fold	OR (K)	1.45	0.50–4.00[h]	H	H	L	L[2]	L
								OR (LR)	1.57	0.38–6.20[h]					
								OR (B)	1.45	0.37–5.50[h]					
Garrett et al. [70]	Cross-sectional	Australia	7-14	148	12 (Mdn)[i]	B	per 10	OR	1.15	0.85–1.54	H	L	L	L[3]	L

(continued on next page)

Table 6 (*continued*)

Citation	Study design	Country	Age (Years)	Sample size	NO_2 Exposure		Exposure contrast (μg/m³)[a]	Measure of association	Effect estimate	95% CI	Quality				
					Concentration (μg/m³)[a]	Location					E	O	C	S[b]	T
Persistent wheeze															
Neas et al. [61]	Cohort	USA	7–11	1567	16–44 (M)	B, D/A, K	per 28.20	OR	1.16	0.89–1.52	H	L	H	H	L
Venn et al. [6]	Case-control	UK	9-11	416	21–50 (M)	K	22.1–34 (vs. 0–22)	OR	0.66	0.38–1.16[j]	H	L	L	H	L
							34.1–58 (vs. 0–22)		0.87	0.50–1.50[j]					
							>58 (vs. 0–22)		0.67	0.38–1.18[j]					

Notes

B = Bedroom; C = Adjustment of Confounders; CI = Confidence Interval; D/A = Dayroom/Activity Room; E = Exposure Assessment; H = High; HR = Hazard Ratio; K = Kitchen; L = Low; LR = Living Room; M = Mean; Max = Maximum; Mdn = Median; NO_2 = Nitrogen Dioxide; NR = Not Reported; O = Outcome Assessment; OR = Odds Ratio; ppb = Parts per Billion; RR = Relative Risk; S = Sample Selection; T = Temporality; UK = United Kingdom; USA = United States of America.

Statistically significant results are bolded.

[a] Converted if ppb was originally used as the unit in the paper.

[b] L^1 = cohort study, lost to follow-up (>25%); L^2 = case-control study, control selection; L^3 = cross-sectional study, inclusion/exclusion criteria; L^4 = cross-sectional study, missing data (>25%).

[c] Estimated from study figure.

[d] Study was conducted among children at high-risk for asthma (having an asthmatic sibling).

[e] Published before but not included in Lin et al. [93].

[f] Study was conducted among children with physician-diagnosed asthma.

[g] Study was conducted among children with active asthma.

[h] 90% CI.

[i] The median also takes into account concentrations in living room and kitchen.

[j] $P = 0.4$ for global test across all categories; P-trend = 0.3.

(Table 6, Supplemental Tables 9–10).

As shown in Table 6 and Supplemental Table 9, the 14 studies are highly heterogeneous. Specifically, 7 of the 14 studies used a cohort design, 5 used a cross-sectional design, and 2 used a case-control design. While the studies published prior to Lin et al. [93] used varied study designs, both of the studies published since Lin et al. [93] used a cohort design. Of the 14 studies, 5 were conducted in the USA, 2 in Australia, 2 in China, 2 in Netherlands, 1 in Japan, 1 in Spain, and 1 in the UK. Notably, both of the studies published since Lin et al. [93] were conducted in China. The sample sizes of the studies were between 100 and 1600, generally much smaller than the gas cooking studies. The study periods were between 1983 and 2014. The ages of children in these studies vary considerably between 0 and 14 years. While some studies (e.g., Belanger et al. [53], Garrett et al. [70]) examined wide ranges of ages (>5 years), other studies (e.g., Hoek et al. [30], Shima and Adachi [64]) focused on very specific ages (within 2 years). All studies included both boys and girls. Most of the studies were conducted in the general population, except 4 that were conducted among children with preexisting conditions (i.e., high risk for asthma in Belanger et al. [55], active asthma in Belanger et al. [53,54], and physician-diagnosed asthma in Nitschke et al. [63]).

Similar to the indoor NO_2 and asthma literature, all studies measured indoor NO_2 using passive samplers, with 9 studies using tube type samplers, 2 studies using badge type samplers, and 3 studies not specifying the sampler type. Of the 14 studies, 7 measured indoor NO_2 at a single location within each household and 5 studies measured indoor NO_2 at multiple locations within each household; 2 studies did not specify the measurement location. As for the specific location, 7 of the 14 studies performed measurements in children's bedroom, 6 studies in the kitchen, 5 studies in the living room/main living area, and 3 studies in activity room/dayroom (i.e., room children spent the most time awake). The averaging time for NO_2 measurements ranged from 1 day to 1 year. The mean/median concentrations of indoor NO_2 varied substantially across, as well as between subgroups within, studies, ranging from 11.6 to 63 μg/m³. Among studies conducted in the same country, indoor NO_2 concentrations also varied – from 16.17 to 44.18 μg/m³ in the USA and from 20 to 63 μg/m³ in Netherlands. Similar to the gas cooking studies, all of the wheeze outcomes relied on self-reported information, except that Hoek et al. [30] additionally relied on physician-reported information. The definition of wheeze outcome varied substantially across studies, with 12 distinct definitions used across the 14 studies.

As shown in Table 6 and Supplemental Table 10, the exposure contrasts for which the effect estimates were calculated varied substantially across studies. Of the 14 studies, 7 calculated effect estimates for a set increment of indoor NO_2 concentration on the original scale, but the actual magnitude varied from 10 μg/m³ to 37.6 μg/m³; 2 studies examined indoor NO_2 concentration on the log scale; 4 studies categorized indoor NO_2 concentration, each in a unique way; and 2 studies did not specify the exposure contrast. Only 1 study [54] examined the operationalization of indoor NO_2 concentration in more than one way (categorical and continuous). Notably, only 1 study [63], which was captured by our literature search but not included in Lin et al. [93], focused on the examination of maximum rather than average indoor NO_2. Of the 14 studies, 12 examined any wheeze as the only outcome type, and 2 studies examined persistent wheeze only. Few studies examined very specific wheeze outcomes (e.g., duration of wheezing) (results not shown).

Overall, 11 of the 14 studies reported null results; 3 studies reported statistically significantly positive associations between indoor NO_2 and wheeze [53,54,64], all of which were included in Lin et al. [93]. The magnitudes of the three statistically significant point estimates were not directly comparable with each other, given the different exposure contrasts used. Belanger et al. [53], a cross-sectional study in the USA, reported a 1.52 (95% CI: 1.04–2.21) times higher risk of wheeze symptoms and a 1.33 (95% CI: 1.05–1.68) times greater number of days of wheeze symptoms per 37.6 $\mu g/m^3$ increment of indoor NO_2 for participants in multi-family housing; however, null result was reported for participants in single-family housing. Belanger et al. [54], a cohort study in the USA, reported a 1.49 (95% CI: 1.09–2.03) times higher risk of wheeze per 5-fold increase in NO_2 if greater than a prespecified threshold of 11.32 $\mu g/m^3$. Shima and Adachi [64], a cohort study in Japan, reported a 1.9 (95% CI: 1.30–2.83) times and 1.6 (95% CI: 1.06–2.44) times higher risk of wheeze per 18.8 $\mu g/m^3$ increment of indoor NO_2 among girls in 4th and 5th grades, respectively. However, null result was observed for 6th grader girls or among boys. All 3 studies examined any wheeze as the health outcome type. Compared to the studies included in Lin et al. [93], the newer studies generally adjusted for similar numbers of potential confounders. Given the high heterogeneity across the studies in this literature, we do not consider a meta-analysis to be appropriate for evidence synthesis.

The quality of this literature is generally low. Although all studies have high quality with respect to indoor NO_2 exposure assessment, a large proportion of them are subject to multiple sources of biases. As shown in Table 6, 11 of the 14 studies have low quality with respect to confounding adjustment, 10 studies cannot establish temporality, 7 studies are prone to selection bias, and 5 studies have low quality with respect to wheeze outcome assessment (studies that examined multiple outcome types were each only counted once). Both of the studies published since Lin et al. [93] have low quality with respect to confounding adjustment, high quality with respect to wheeze outcome assessment, and, as cohort studies, have high quality with respect to temporality. The distribution of study quality is similar across wheeze outcome types.

Temporality is a key aspect in both study quality evaluation and causal inference guided by the Bradford Hill [4] considerations (discussed below). Compared to the gas cooking studies, a larger proportion (i.e., 7 of 14) of indoor NO_2 studies for wheeze used a cohort study design, which is in general more reliable for making causal inference than a case-control or cross-sectional design [51,84]. However, 4 of the 7 studies [54,61,63,64] were of low quality with respect to temporality, despite the cohort design, due to the fact that the measurements of indoor NO_2 in the cohort were not necessarily taken prior to the measurements of wheeze outcomes. Only the remaining 3 cohort studies [9,40,50] were of high quality with respect to temporality. These 3 cohort studies all reported null results. Samet et al. [50] examined the association between indoor (bedroom) NO_2 and any wheezing during lower respiratory tract illness in American children under 1.5 years old and reported null results comparing across three exposure categories, after adjusting for all key confounders (ETS, family history, SES/home environment, and outdoor NO_2) as well as several other potential confounders. Li et al. [9] and Yu et al. [40] both examined the association between indoor NO_2 and new onset wheeze in Chinese children under 1.5 years old, and both studies reported null results (HR = 1.00, 95% CI: 0.995–1.001 and HR = 0.99, 95% CI: 0.979–1.003, respectively), after adjusting for key confounders (family history and SES/home environment) as well as several other potential confounders. While these 3 cohort studies all focused on children under 1.5 years old, their health outcome and study region varied, indicating that the only cohort studies that could establish temporality to date are not necessarily examining the same underlying indoor NO_2-wheeze relationship.

Guided by the Bradford Hill [4] considerations, we further discuss causal inference for the association between indoor NO_2 and wheeze in detail in Table 7. Overall, most of the epidemiology studies, including all of those with positive findings, cannot establish temporality. There are no large and precise effect estimates, and the observed associations lack consistency and specificity. An exposure-response relationship has not been well-characterized. No study has examined whether or how wheeze symptom would change after reducing indoor NO2 exposure. Experimental evidence is limited and does not sufficiently support any of the observed associations in epidemiology studies. We did not find a suitable analogy to address causality in this case. Taken together, we conclude that the evidence does not support causality.

In the meta-analysis by Lin et al. [93], all identified studies at the time were included, regardless of whether the studies reported adjusted effect estimates (vs. crude comparisons), the study design, or study quality. Summarizing across these studies, Lin et al. [93] reported a statistically significantly positive association between indoor NO_2 and wheeze (OR = 1.12, 95% CI: 1.04–1.21 for a 15 ppb [i.e., 28.2 $\mu g/m^3$] increase in NO_2). However, our systematic review shows that the literature to date, including the literature meta-analyzed by Lin et al. [93], is limited by the lack of consistent findings among studies with reliable study design (e.g., cohort), the high heterogeneity across studies, and the low study quality (primarily with respect to confounding adjustment, temporality, and sample selection). Our detailed causal inference guided by the Bradford Hill [4] considerations also shows that the evidence does not support causality. As a result, the effect estimates from Lin et al. [93] should be interpreted with caution.

Implications for meta-analyses

As discussed, we do not consider a meta-analysis to be appropriate for evidence synthesis in this review, due to the high heterogeneity across studies. A key source of heterogeneity is the differences in gas cooking practices (e.g., cooking methods, frequency, and duration; stove type and condition; ventilation; kitchen layout; natural gas vs. LPG) in different countries/regions. For example, we have discussed how a number of the post-2013 epidemiology studies have been conducted in China. As compared to typical USA cooking methods that consist of boiling, frying, roasting, and baking, traditional Chinese stir-frying/wok cooking methods rely on higher temperatures and gas combustion rates [59]. Ventilation practices can also differ between USA and Chinese residences; Chinese residences continue to heavily rely on natural ventilation modes (e.g., infiltration, windows) rather than mechanical ventilation systems [42]. It has also been shown that ventilation standards/regulations, as well as actual ventilation measurements in dwellings, vary across European countries [15]. Few studies in the current literature examined the details associated with gas cooking practices.

Changes in cooking practices and policy over time is another key source of heterogeneity. For example, from 1990 to 2020, when the majority of the studies in the present review were conducted, the percentage of the population mainly cooking with more polluting fuels (i.e., unprocessed biomass [wood, crop residues, and dung], charcoal, coal, and kerosene) dropped from over 75% to <50% in Central Asia and Southern Asia and from about 60% to about 30% in Eastern Asia and South-eastern Asia, indicating significant progress in transitioning towards universal use of clean fuels (i.e., gaseous fuels [LPG, natural gas, biogas], electricity, alcohol, and solar energy) as the main fuel for cooking; whereas during the same period, the percentage of population mainly cooking with polluting fuels only dropped from 90% to 84% in Sub-Saharan Africa and were consistently low (<10%) in North America and Europe [74]. Among the studies included in the present review, some defined gas cooking exposure as any or ever using gas for cooking in the home, whereas others defined it as primarily using gas for cooking; some compared children in homes with gas cooking to no gas cooking (but that could include other cooking fuels such as biomass cooking or electricity cooking, see Nantanda et al. [80] for example), whereas other studies compared children in homes with gas cooking strictly to electricity cooking. This further complicates the comparison and synthesis of study findings.

Studies in the current literature were also conducted among children of various age ranges for which the susceptibility and presentation of asthma vary [65]. Both global and USA analyses show that childhood asthma incidence rates were the highest among children under age 4, second highest among children aged 5–9 years, and lower among older children [17,21]. Pakkasela et al. [44] classified asthma into allergic (i.e., asthma with allergic rhinitis) vs. non-allergic types (asthma without allergic rhinitis) and showed that, throughout childhood, the incidence

Table 7
Causal inference guided by the Bradford Hill [4] considerations.

Definition	Evaluation			
	Gas – Asthma	Gas – Wheeze	NO_2 – Asthma	NO_2 – Wheeze
Consistency *Consistent associations (*i.e., *associations, especially statistically significant associations, mostly in the same direction [e. g., ORs > 1]) are observed by different authors, under different study designs, and in different study regions, populations, and time periods.*	The 22 reviewed studies were conducted by different authors in different countries/ regions and time periods. The studies mostly used a cross-sectional design (n = 16), with a few using a cohort or case-control design (Main Table 3, Supplementary Tables 3 and 4). Overall, only a small proportion (*n* = 7) of the 22 studies reported statistically significantly positive associations, among which the majority (*n* = 6) used the same (cross-sectional) design. Some of the limited positive findings lack internal consistency (e.g., Ponsonby et al. [7], Spengler et al. [47]). The remaining 15 studies reported null results, with point estimates in both directions. When examined within more homogeneous study subgroups, the positive findings do not concentrate around a particular health outcome type, study region, or age group. Consistent associations were not observed in different study settings.	The 30 reviewed studies were conducted by different authors in different countries/ regions and time periods. The studies mostly used a cross-sectional design (n = 25), with a few using a cohort or case-control design (Main Table 4, Supplementary Tables 5 and 6). Overall, only a small proportion (n = 6) of the 30 studies reported statistically significantly positive associations and 1 study reported a statistically significantly inverse association. All of these 7 studies used the same (cross-sectional) design. Some of the limited positive findings lack internal consistency (e.g., Belanger et al. [53], Volkmer et al. [81], Behrens et al. [88]). The remaining 23 studies reported null results, with point estimates in both directions. When examined within more homogeneous study subgroups, the positive findings do not concentrate around a particular study region or age group, although they are all for any wheeze as the health outcome type. Consistent associations were not observed in different study settings.	The 14 reviewed studies were conducted by different authors in different countries/ regions and time periods. The studies mostly used a cohort design (*n* = 10), with a few using a cross-sectional or case-control design (Main Table 5, Supplementary Tables 7 and 8). Overall, only a small proportion (*n* = 3) of the 14 studies reported statistically significantly positive associations. All of these 3 studies used the same (cohort) design. Some of the limited positive findings lack internal consistency (e.g., Shima and Adachi [64]). The remaining 11 studies reported null results, with point estimates in both directions. When examined within more homogeneous study subgroups, the positive findings do not concentrate around a particular study region or age group, although they are all for asthma exacerbation as the health outcome type. Consistent associations were not observed in different study settings.	The 14 reviewed studies were conducted by different authors in different countries/ regions and time periods. Half (n = 7) of the studies used a cohort design, 5 used a cross-sectional design, and 2 used a case-control design (Main Table 6, Supplementary Tables 9 and 10). Overall, only a small proportion (n = 3) of the 14 studies reported statistically significantly positive associations. Of these 3 studies, 2 used a cohort design and 1 used a cross-sectional design. Some of the limited positive findings lack internal consistency (e. g., Shima and Adachi [64]). The remaining 11 studies reported null results, with point estimates in both directions. When examined within more homogeneous study subgroups, the positive findings do not concentrate around a particular study region or age group, although they are all for any wheeze as the health outcome type. Consistent associations were not observed in different study settings.
Strength *The effect estimates are large and precise (e. g., narrow 95% CI). Small and imprecise effect estimates could be driven by bias, confounding, or chance.*[a]	The point estimates of the 7 studies that reported statistically significant associations ranged from 1.24 to 3.80, with all but one effect estimate being below 2.40 (Main Table 3, Supplementary Table 4). The larger the point estimate was, the less precise its 95% CI was, indicating that the point estimate was less stable. It is also notable that a large proportion of these studies (5 out of 7) did not fully adjust for key confounders. Many potential confounders (e.g., indoor factors such as dampness and mold) are positively associated with both gas cooking and asthma risk. Had these confounders been accounted for, magnitudes of the observed associations may have been attenuated. As for the 15 studies that reported null results, the lower 95% confidence limits ranged from 0.17 to 1.00, with all but 5 being 0.60 or greater; the upper 95% confidence limits ranged from 1.02 to 24.23, with all but 5 being 3.10 or lower. This indicates that if there were associations that were missed due	The point estimates of the 6 studies that reported statistically significantly positive associations ranged from 1.16 to 2.27 (Main Table 4, Supplementary Table 6). The larger the point estimate was, the less precise its 95% CI was, indicating that the point estimate was less stable. It is also notable that none of these 6 studies fully adjusted for key confounders. Many potential confounders (e. g., indoor factors such as dampness and mold) are positively associated with both gas cooking and asthma-associated wheeze symptoms. Had these confounders been accounted for, magnitudes of the observed associations may have been attenuated. As for the 23 studies that reported null results, the lower 95% confidence limits ranged from 0.22 to 0.97, with all but 4 being 0.58 or greater; the upper 95% confidence limits ranged from 1.03 to 14.01, with all but 4 being 2.47 or lower. This indicates that if there were associations that were missed due to insufficient statistical power, they would	The point estimates of the 3 studies that reported statistically significantly positive associations ranged from 1.31 to 2.82, with all but 1 effect estimate being below 1.70, although they are not directly comparable across studies given the different exposure contrasts used (Main Table 5, Supplementary Table 8). The larger the point estimate was, the less precise its 95% CI was, indicating that the point estimate was less stable. It is also notable that 2 of the 3 studies did not fully adjust for key confounders. Many potential confounders (e.g., indoor factors such as dampness and mold) are positively associated with both indoor NO_2 exposure and asthma risk. Had these confounders been accounted for, magnitudes of the observed associations may have been attenuated. As for the 11 studies that reported null results, the lower 95% confidence limits ranged from 0.08 to 0.99, with all but 4 being 0.40 or greater; the upper 95%	The point estimates of the 3 studies that reported statistically significantly positive associations ranged from 1.33 to 1.90, with all but 1 effect estimate being 1.60 or lower, although they are not directly comparable across studies given the different exposure contrasts used (Main Table 6, Supplementary Table 10). The larger the point estimate was, the less precise its 95% CI was, indicating that the point estimate was less stable. It is also notable that 2 of these 3 studies did not fully adjust for key confounders. Many potential confounders (e. g., indoor factors such as dampness and mold) are positively associated with both indoor NO_2 exposure and asthma-associated wheeze symptoms. Had these confounders been accounted for, magnitudes of the observed associations may have been attenuated. As for the 11 studies that reported null results, the lower 95% confidence limits ranged from 0.11 to 0.995, with all but 1

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Table 7 (*continued*)

Definition	Evaluation			
	Gas – Asthma	Gas – Wheeze	NO_2 – Asthma	NO_2 – Wheeze
	to insufficient statistical power, they would have been relatively close to the null value (e.g., OR = 1). There are no large and precise effect estimates.	have been relatively close to the null value (e.g., OR = 1). The only statistically significantly inverse association reported by Behrens et al. [88] is likely a chance finding. This finding lacked internal consistency, as the study reported a statistically significantly inverse association among boys (PR = 0.55, 95% CI: 0.31–0.98) but a null result (PR = 1.52, 95% CI: 0.93–2.47) among girls. Further, the point estimate (0.55) of the reported statistically significantly inverse association is below most of the lower 95% confidence limits reported by the 23 studies with null results. There are no large and precise effect estimates.	confidence limits ranged from 1.05 to 34.9, with all but 4 being 4.82 or lower. This indicates that if there were associations that were missed due to insufficient statistical power, they would have been relatively close to the null value (e.g., OR = 1). There are no large and precise effect estimates.	being 0.37 or greater; the upper 95% confidence limits ranged from 1.001 to 6.20, with all but 3 being 2.40 or lower. This indicates that if there were associations that were missed due to insufficient statistical power, they would have been relatively close to the null value (e.g., OR = 1). There are no large and precise effect estimates.
Specificity *The observed associations are limited to a specific exposure and to a specific health outcome.*[b]	Asthma has multiple known risk factors and thus cannot be linked specifically to gas cooking exposure. For example, increased risk of asthma has been associated with family history of asthma, respiratory infections, ETS exposure, and indoor allergen exposure (e.g., dust mite, cat, dog, mouse, cockroach, and molds) [46,69]. Gas cooking in itself is not a very specific exposure, as the associated exposures to chemicals and their mixtures vary by a number of factors such as gas composition, stove type and condition, ventilation, cooking frequency and duration, as well as cooking methods. The health outcomes associated with each individual chemical also vary. As a result, gas cooking exposure cannot be linked specifically to asthma. The observed associations lack specificity.	In most of the reviewed studies, wheeze was examined as a symptom of asthma, which has multiple known risk factors, such as family history of asthma, respiratory infections, ETS exposure, and indoor allergen exposure (e.g., dust mite, cat, dog, mouse, cockroach, and molds) [46,69]. As a result, wheeze as a symptom of asthma cannot be linked specifically to gas cooking exposure. Gas cooking in itself is not a very specific exposure, as the associated exposures to chemicals and their mixtures vary by a number of factors such as gas composition, stove type and condition, ventilation, cooking frequency and duration, as well as cooking methods. The health outcomes associated with each individual chemical also vary. As a result, gas cooking exposure cannot be linked specifically to wheeze. The observed associations lack specificity.	Asthma has multiple known risk factors and thus cannot be linked specifically to indoor NO_2 exposure. For example, increased risk of asthma has been associated with family history of asthma, respiratory infections, ETS exposure, and indoor allergen exposure (e.g., dust mite, cat, dog, mouse, cockroach, and molds) [46,69]. While indoor NO_2 is a specific exposure, it cannot be linked specifically to asthma. For example, indoor NO_2 exposure has been associated with cardiovascular health outcomes such as coronary artery disease, arrhythmia, heart failure, and ischemic heart disease [22,89]. The observed associations lack specificity.	In most of the reviewed studies, wheeze was examined as a symptom of asthma, which has multiple known risk factors, such as family history of asthma, respiratory infections, ETS exposure, and indoor allergen exposure (e.g., dust mite, cat, dog, mouse, cockroach, and molds) [46,69]. As a result, wheeze as a symptom of asthma cannot be linked specifically to gas cooking exposure. While indoor NO_2 is a specific exposure, it cannot be linked specifically to wheeze. For example, indoor NO_2 exposure has been associated with cardiovascular health outcomes such as coronary artery disease, arrhythmia, heart failure, and ischemic heart disease [22,89]. The observed associations lack specificity.
Temporality *Causality can only exist if the exposure precedes the occurrence of the health outcome with a sufficient lag time, if any is expected.*	Of the 22 studies in this literature, 16 used a cross-sectional design, including 6 of the 7 studies that reported statistically significantly positive associations; only the remaining 1 study used a cohort design. As a result, temporality cannot be established in most of the studies in this literature, including the majority of the studies with positive findings. The lack of temporality prevents any causal inference.	Of the 30 studies in this literature, 25 used a cross-sectional design, including all 7 studies that reported statistically significant associations. As a result, temporality cannot be established in most of the studies in this literature, including all of the studies with positive findings. The lack of temporality prevents any causal inference.	Of the 14 studies in this literature, 10 used a cohort design, including all 3 studies that reported statistically significantly positive associations. However, the majority (n = 8) of these 10 cohort studies, including all 3 studies with positive findings, cannot establish temporality despite the cohort design. Temporality cannot be established in any of the 4 studies that used a cross-sectional or case-control design. The lack of temporality prevents any causal inference.	Of the 14 studies in this literature, 7 used a cohort design, including 2 of the 3 studies that reported statistically significantly positive associations. However, 4 of these 7 cohort studies, including both of the cohort studies with positive findings, cannot establish temporality despite the cohort design. Temporality cannot be established in either of the 2 case-control studies. Except for Belanger et al. [55], the cross-sectional studies, including that by Belanger et al. [53] with positive findings, cannot establish temporality.

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Table 7 (*continued*)

Definition	Evaluation: Gas – Asthma	Gas – Wheeze	NO_2 – Asthma	NO_2 – Wheeze
				The lack of temporality prevents any causal inference.
Dose-Response *There exists a well-characterized exposure-response relationship (e.g., increased disease risk at higher exposure level).*	All studies examined gas cooking exposure as a binary variable (e.g., gas vs. electricity, ever vs. never), preventing the characterization of potential exposure-response relationship. We only identified 1 study that explored potential exposure-response relationships. Specifically, Lin et al. [94] examined the association across different frequency levels of gas cooking exposure (never, intermittent, and always). However, the observed association was not statistically significant in either the intermittently exposed or the always exposed group (vs. never exposed), with the point estimate being very similar but slightly greater in the intermittently exposed group than the always exposed group (adjusted ORs both between 1 and 2 but not specified). An exposure-response relationship has been assessed only in 1 study and is not supported by its results.	All studies examined gas cooking exposure as a binary variable (e.g., gas vs. electricity, ever vs. never), preventing the characterization of potential exposure-response relationship. We only identified 1 study that explored potential exposure-response relationships. Specifically, Lin et al. [94] examined the association across different frequency levels of gas cooking exposure (never, intermittent, and always). However, the observed association was not statistically significant in either the intermittently exposed or the always exposed group (vs. never exposed), with the point estimate being greater in the intermittently exposed group than the always exposed group (adjusted ORs both between 1 and 2 but not specified). An exposure-response relationship has been assessed only in 1 study and is not supported by its results.	All but 1 study [13] addressed dose-response by examining indoor NO_2 exposure as a continuous variable or categorical variable with ≥ 3 levels. However, only 1 study [54] explored multiple potential shapes of the exposure-response relationship (log-scale vs. categorical); all other studies each examined one assumed shape and lag structure. Overall, only 3 studies observed a statistically significant exposure-response relationship, 2 of which [26,64] are linear and 1 [54] of which is linear on the log-scale or categorical. An exposure-response relationship has not been well-characterized.	All studies addressed dose-response by examining indoor NO_2 exposure as a continuous variable or categorical variable with ≥ 3 levels. However, only 1 study [54] explored multiple potential shapes of the exposure-response relationship (log-scale vs. categorical); 1 study [50] explored different lag structures (lagged vs. unlagged); and all other studies examined one assumed shape and lag structure. Overall, only 3 studies observed a statistically significant exposure-response relationship, 2 of which [53,64] are linear and 1 of which is linear on the log-scale or categorical. An exposure-response relationship has not been well-characterized.
Biological Plausibility *Causality is more scientifically defensible if there exists evidence for a plausible biological mechanism by which the exposure may lead to the health outcome, although the existing evidence may be limited.*	US EPA [91] concluded from experimental studies (e.g., animal and controlled human exposure studies) that short-term NO_2 exposure may induce asthma exacerbation via increased airway responsiveness or allergic inflammation, despite some mixed findings and that long-term NO_2 exposure may lead to asthma development via airway hyperresponsiveness or development of an allergic phenotype, although experimental evidence was limited. Notably, experimental studies evaluated high exposures (e.g., >100 ppb) that may not be relevant to those generally experienced by children in homes with gas cooking. It is currently not established that childhood NO_2 exposures associated with gas cooking are of sufficient duration, frequency, or concentration to cause or contribute to asthma (or associated wheeze symptom).			
Experiment *There exists experimental or semi-experimental evidence (e.g., reduced disease risk resulting from reduced exposure).*	We did not find interventional studies addressing asthma after removing or reducing gas cooking exposure.	We did not find interventional studies addressing wheeze after removing or reducing gas cooking exposure.	We did not find interventional studies addressing asthma after reducing indoor NO_2 exposure.	We did not find interventional studies addressing wheeze after reducing indoor NO_2 exposure.
Analogy *A similar exposure is an established causal factor for a similar health outcome.*	We did not find a suitable analogy in this case.	We did not find a suitable analogy in this case.	We did not find a suitable analogy in this case.	We did not find a suitable analogy in this case.
Coherence *The observed associations in epidemiology studies can be interpreted logically along other realms of evidence (e.g., animal studies).*[c]	Experimental evidence on the plausible biological mechanisms by which NO_2 exposure may lead to asthma (or associated wheeze symptom) is limited to high-level NO_2 exposures that may not be relevant to the exposure levels experienced by children in homes with gas cooking examined in epidemiology studies. The observed associations in epidemiology studies are not sufficiently supported by, although not contradicting, the experimental evidence.			
Causal Conclusion	Taken together, the evidence does not support causality.	Taken together, the evidence does not support causality.	Taken together, the evidence does not support causality.	Taken together, the evidence does not support causality.

Notes

CI = Confidence Interval; ETS = Environmental Tobacco Smoke; NO_2 = Nitrogen Dioxide; OR = Odds Ratio; ppb = Parts per Billion; PR = Prevalence Ratio; US EPA = United States Environmental Protection Agency.

[a] Small effect estimates in themselves do not undermine the likelihood of causality.

[b] The lack of specificity does not undermine the likelihood of causality.

[c] The lack of other realms of evidence does not undermine the likelihood of causality.

of non-allergic asthma remained low, whereas the incidence of allergic asthma was highest in early childhood and decreased towards older age.

Regarding the results of existing meta-analyses, it is crucial that the high heterogeneity and its sources are recognized in their interpretation. Of equal importance is the consideration of study quality. It is well-recognized that a meta-analysis performed using risk estimates from studies of low quality will be prone to bias and incorrect results [16,99]. Given our findings that show the relatively low quality of the epidemiology literature used in the Lin et al. [93] meta-analysis, we caution against over-interpretation of its results. Consistent with our words of caution, Vrijheid [66] stated in a contemporaneous commentary on the Lin et al. [93] meta-analysis concerns related to residual confounding by "asthma and wheeze risk factors such as dampness, mould, pets and environmental tobacco smoke" that "may be closely related to the use of gas cookers and indoor NO_2" and heterogeneity due to varying levels of adjustment for these confounders among studies.

Recently, Gruenwald et al. [90] relied on the North American- and European-specific risk estimates for gas cooking and current asthma that were reported in the Lin et al. [93] meta-analysis, among other data sources and a series of statistical assumptions, and estimated that "12.7% (95% CI = 6.3-19.3%) of current childhood asthma in the US is attributable to gas stove use." This population attributable fraction (PAF) calculation used the quantitative evidence synthesis estimates from Lin et al. [93] at face value without considering the underlying high heterogeneity or low quality among the individual studies. More importantly, a key underlying assumption of any PAF calculation is that there is a clear causal relationship between the risk factor(s) and disease [11]; in this case, the Gruenwald et al. [90] PAF calculation is predicated on there being a clear causal association between gas stove use and current childhood asthma.[1] However, our in-depth evaluation of heterogeneity and study quality in the present review reveals that, although the quantitative evidence synthesis from Lin et al. [93] reported a statistically significantly positive association between gas cooking and asthma, the epidemiology literature is limited and a causal conclusion is not supported. The Gruenwald et al. [90] calculation is a clear example of over-interpretation of the Lin et al. [93] meta-analysis results, and the calculated PAF value is not valid. This echoes the conclusion of a recently published commentary by Cox Jr. [60] that "the projections of Gruenwald *et al.* that about 13% of childhood asthma in the US could be prevented by reducing or eliminating gas stove emissions have no known validity. They are not supported by the data and analyses performed."

Strengths and limitations

A major strength of this review is that we used transparent, systematic, rigorous methods. This included the fact that we registered our protocol before we began the review and that we only made minor changes during the review process, which we indicated in protocol amendments. We determined study eligibility based on PECOS elements and two reviewers were involved in selecting studies and extracting data to help ensure accuracy. We took study quality and heterogeneity across studies into account when synthesizing evidence across studies. We did not conduct a meta-analysis because of the heterogeneity of study designs, which would have produced meta-risk estimates that would have been difficult to interpret. We used Bradford Hill considerations to guide our overall evaluation, and followed PRISMA guidelines when reporting our results.

As noted by Goodman et al. [48], "When reviewing individual studies in the context of study quality, we found that it is most helpful to first determine what aspects of study quality are likely to have the most impact on the interpretation of results, instead of spending time and resources on sometimes up to dozens of aspects that ultimately may not have much impact." However, it is simply not possible to choose study quality criteria without some level of subjectivity. For example, we had to make decisions on what to classify as key confounders and what criteria needed to be satisfied for a study to be considered high quality with respect to confounding.

Other researchers may have made different choices than we did, but our choices are all fully transparent, and we also note that even though we categorized studies as high or low for each aspect, we discussed the results of all studies in the context of each aspect. That is, we did not merely check a box as overall high or low quality, and summarize results according to the boxes checked. Rather, we discussed study results in light of those individual aspects.

Future research

To better address the question of whether gas cooking exposure or indoor NO_2 can increase asthma or wheeze risk in children, the most reliable observational epidemiology study would be a cohort study that meets all key study quality criteria, including for sample selection, temporality, exposure assessment, outcome assessment, and confounder adjustment. We found that only 1 cohort study conducted over 30 years ago [50] was high quality in all of the major categories we consider to be important. A future study will require considerable resources to complete, but will be better able to address causation than any other study conducted to date.

With regard to sample selection, future cohort studies should be conducted with an adequate sample size to allow for the detection of any true underlying association and the adjustment of all potential confounders. Researchers should minimize loss to follow up, and determine whether any individuals who drop out of the study likely differ from those remaining.

With regard to gas cooking exposure assessment, researchers should confirm the type of stove in each home, and record information on the specific fuel used, the frequency and duration of use, and whether and what type of ventilation is used. They should also record information on when children are in the home, and their locations and activities in the home, particularly with respect to when gas stoves are used. For studies evaluating NO_2 exposure, NO_2 should be measured using a validated method (e.g., passive dosimeters) and over a sufficient period of time and over different seasons to ensure that measurements are representative of typical exposures. Ideally, personal NO_2 measurements should be made, with sensors capable of collecting time-resolved (e.g., minute-by-minute or hour-by-hour) data to capture both short-term peak exposure levels as well as time-averaged exposure levels [85]. In addition, the study should consider what the sources of NO_2 are in the home (e.g., gas stoves, gas heaters, other appliances, ETS) and children's NO_2 exposure outside of home (e.g., at school, in traffic).

With regard to outcome assessment, asthma can be particularly difficult to study, as both over-and underdiagnoses are common [1]. It can also be challenging to study wheeze since it is hard to define. Both asthma and wheeze should be clearly defined, and timing of events should be recorded. Health professionals associated with the study should confirm all diagnoses in the study to minimize misclassification.

With regard to confounder adjustment, researchers should make an effort to measure and adjust for all potential confounders. The present review considers as key confounders ETS, family history of asthma/allergies/atopy, SES/home environment (e.g., dust mite, cockroach, pets, mold, wood stove, dampness, heating fuels, crowdedness, pillow/quilt/mattress, form of cooling), and outdoor NO_2 (for NO_2 studies), all of which are known risk factors for asthma, and therefore asthma-associated wheeze symptoms [46,69]. ETS, some home environment

[1] As further discussed in a commentary prepared by several of this paper's authors (Goodman et al., submitted), Gruenwald et al. (2023) also did not address other assumptions that must be met for the calculation of a PAF for gas stove use and current childhood asthma, including that having a gas stove is independent of other asthma risk factors, and that eliminating gas stoves would immediately reduce asthma risk.

factors (e.g., heating systems), and outdoor NO_2 are known sources of indoor NO_2 [97]; ETS and SES/home environment (e.g., poverty/substandard housing) may be closely related to the use of gas cookers [52,66]. Having a family history of asthma/allergies/atopy may affect parents' choices of cooking appliances or other indoor factors that could affect indoor NO_2 levels. Other potential confounders include additional factors that may be associated with asthma, such as obesity, indoor and outdoor co-pollutants including ozone (O_3) and fine particulate matter ($PM_{2.5}$), and environmental parameters including temperature and relative humidity [46,69].

In addition to observational studies, interventional and experimental studies can be conducted to directly address causation. These studies are very resource-intensive, but can more directly address causation. These studies will need to involve families with similar home environments and other asthma or wheeze risk factors. Ideally, all residences will have similar gas stoves at the beginning of the study, and some (ideally, a random subgroup of) stoves will be replaced with other types of stoves (e.g., electric or induction). Ventilation should also be considered (e.g., enforce controlled ventilation, comparing with and without ventilation under the same gas stove use pattern). All of the study quality aspects discussed above for observational studies (e.g., exposures, health outcomes, potential confounders) apply to interventional studies. Further, researchers will need to record any noncompliance to the intended intervention and evaluate its potential impact on the study results. Only then would this type of study provide results that could be informative regarding causation.

Conclusion

We conducted the first systematic review of gas cooking or indoor NO_2 and asthma or wheeze in children that included an in-depth evaluation of study heterogeneity and study quality. We reviewed 66 relevant studies, including those in the most recent meta-analysis by Lin et al. [93]. We found that most of the studies are cross-sectional by design. The few cohort studies that could establish temporality largely reported null results. There is large variability across studies in terms of study region, age of children, gas cooking exposure definition, and asthma or wheeze outcome definition, precluding clear interpretations of meta-analysis estimates such as those reported in Lin et al. [93]. Furthermore, a large proportion of the studies are subject to multiple sources of bias and inaccuracy, primarily due to self-reported gas cooking exposure or respiratory outcomes, insufficient adjustment for key confounders and unestablished temporality. We conclude that the epidemiology literature is limited by high heterogeneity and low study quality and, therefore, it does not provide sufficient evidence regarding causal relationships between gas cooking or indoor NO_2 and asthma or wheeze. We caution against over-interpreting the quantitative evidence synthesis estimates from meta-analyses of these studies.

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Declaration of Competing Interest

Gradient has worked with several organizations in the past that have an interest in gas stoves and NO_2 science. None of these clients was involved with the conception or drafting of this paper.

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Appendix A. Supplementary data

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