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EARLY LIFE

Meta-analysis of the effects of indoor nitrogen dioxide and gas cooking on asthma and wheeze in children

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Background Since the meta-analysis on the association between indoor nitrogen dioxide (NO_2) and childhood respiratory illness in 1992, many new studies have been published. The quantitative effects of indoor NO_2 on respiratory illness have not been estimated in a formal meta-analysis since then. We aimed to quantify the association of indoor NO_2 and its main source (gas cooking) with childhood asthma and wheeze.

Methods We extracted the association between indoor NO_2 (and gas cooking) and childhood asthma and wheeze from population studies published up to 31 March 2013. Data were analysed by inverse-variance-weighted, random-effects meta-analysis. Sensitivity analyses were conducted for different strata. Publication bias and heterogeneity between studies were investigated.

Results A total of 41 studies met the inclusion criteria. The summary odds ratio from random effects meta-analysis for asthma and gas cooking exposure was 1.32 [95% confidential interval (CI) 1.18–1.48], and for a 15-ppb increase in NO_2 it was 1.09 (95% CI 0.91–1.31). Indoor NO_2 was associated with current wheeze (random effects OR 1.15; 95% CI 1.06–1.25). The estimates did not vary much with age or between regions. There was no evidence of publication bias.

Conclusions This meta-analysis provides quantitative evidence that, in children, gas cooking increases the risk of asthma and indoor NO_2 increases the risk of current wheeze.

Keywords Asthma, wheeze, gas cooking, indoor pollution, infant, review

Introduction

The association between adverse health consequences and indoor nitrogen dioxide (NO_2) exposure has been the subject of many studies. Indoor NO_2 exposure may increase the risk of acute and chronic respiratory illnesses, reduce lung function and initiate and exacerbate asthma, especially in children.[1–4] One reason is the long periods of time that children spend indoors.[5]

In 1992, Hasselblad *et al.*[2] carried out a meta-analysis including 11 studies, which concluded that children exposed to a long-term increase of 15 ppb NO_2 indoors suffer a 20% increase in respiratory illness risk. This early quantitative analysis became a benchmark study for the relationship between indoor NO_2 and respiratory illness in children, and an important reference for the outdoor NO_2 Air Quality Guideline value established by the World Health Organization (WHO) in 1997[6] and confirmed in 2005.[7] More recently, WHO has reviewed studies on indoor NO_2 exposure, but without doing a formal meta-analysis.[8] Recent journal reviews of the issue[1,4,9–11] have also been qualitative. In view of the dearth of quantitative meta-analyses based on recent studies, we decided to review studies on asthma, wheeze, gas cooking and indoor NO_2 in children with the purpose of obtaining quantitative effect estimates.

Methods

Selection criteria

We searched for studies from which quantitative effect estimates of the relationship between gas cooking, indoor NO_2 and respiratory health effects in children could be obtained. We attempted to identify all population studies in relation to this topic. The literature was searched with PubMed and ISI Web of Knowledge from 1977 up to 31 March 2013 with the following search terms: (i) indoor nitrogen dioxide and children; (ii) personal nitrogen dioxide and children; (iii) gas cooking and children; (iv) gas appliance and children; (v) unvented and children; (vi) gas heating and children; and (vii) gas heater and children. The seven search results were combined with the Boolean operator 'or'. All of the 34 epidemiological studies included in Table 5.2 of the recent WHO guidelines for indoor air quality and citations from previous reviews and identified articles were considered as well. Duplications were removed.

To be eligible for inclusion, studies had to: (i) be published in English; (ii) be primary study, not reviews; (iii) examine respiratory disease in infancy or in childhood (defined by a maximum age of subjects $\leqslant$18 years) as outcomes; (iv) examine exposure to indoor NO_2 or household gas cooking or gas heating; (v) be conducted within family houses, not in schools or classrooms; and (vi) report an odds ratio or other effect estimator[12] or sufficient data to estimate them. Articles fulfilling all six criteria were included for further review (Figure 1).

All studies were reviewed according to the six inclusion criteria. Commentaries, and studies not performed in children or exposures not relevant or without respiratory outcomes, were excluded. The remaining articles were reviewed independently by the three authors. Articles that did not report on the association between selected exposure variables and

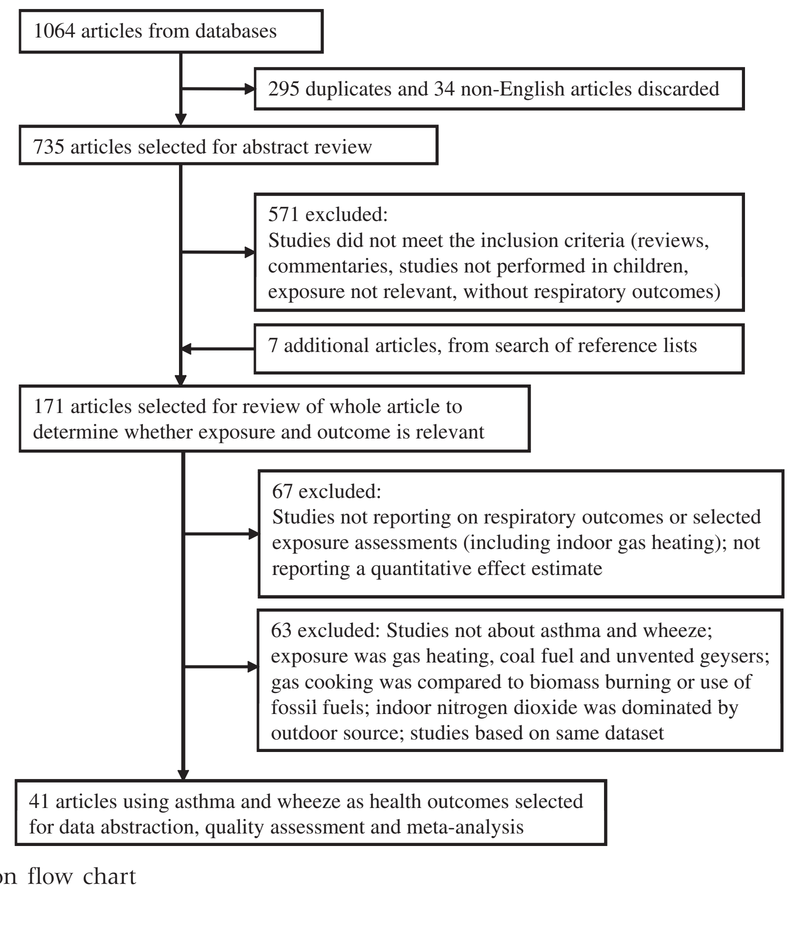

Figure 1 Study selection flow chart

respiratory outcomes in children, that could not isolate indoor gas appliances from other combustion/ energy sources (that is studies where gas, coal, wood, kerosene or fireplace cooking/heating were combined into one exposure group), that compared gas cooking with biomass burning or use of fossil fuels and that included indoor and/or personal NO_2 concentrations that were mainly affected by outdoor pollution from traffic (that is studies with personal monitoring of NO_2 where the sampling period covered both indoor and outdoor activities; and studies with indoor NO_2 measurements, in the absence of indoor sources, i.e. studies in populations with low prevalence (<10%) of gas stoves) were excluded (Figure 1).

Respiratory outcome selection

The respiratory outcomes of the studies that met the inclusion criteria included various symptoms such as rhinitis, phlegm, cough, chest illnesses, asthma and wheeze as well as lung function parameters. We restricted our review to the respiratory outcomes of wheeze and asthma, the two outcomes most frequently used in epidemiological studies among children. Both self-reported and doctor-diagnosed (either from self-reported questionnaire or clinical evaluation) asthma and self-reported wheeze were selected, in spite of the fact that the precise definition of such assessments might have some variability between studies. Furthermore, according to the occurrence time of asthma and wheeze, we categorized them into 'current asthma', 'lifetime asthma', 'current wheeze' and 'lifetime wheeze' to overcome the dilemma of various definitions of those health outcomes. 'Current' was defined as having incident asthma (or wheeze) with the symptoms occurring within the 12 months prior to the questionnaire. 'Lifetime asthma' was defined as ever having been diagnosed with asthma by a doctor; 'lifetime wheeze' was defined as wheeze ever. If studies defined wheeze in more than one way,[13] we selected wheeze without colds to avoid inclusion of symptoms related primarily to respiratory infections. We acknowledge that respiratory infections could be an interesting outcome by themselves.

Data abstraction

Studies on gas heating often lacked information on whether the heater was directly vented to the outside, in which case it would not be a source of indoor air pollution. For this reason, we did not include gas heating[14–19] in the meta-analysis; indoor NO_2 and gas cooking were the exposure variables that we focused on.

Ideally, meta-analysis would combine estimates only from studies with exactly the same exposure variables; we included studies for meta-analysis that were as similar as practicable with respect to these. One study about unvented kitchen geysers[20] was excluded because the reference category included gas cooking. One study[21] that compared the risk effect of gas cooking vs other cooking fuels was excluded because it compared two sources of combustion products. One study[22] that did not distinguish gas cooking from coal cooking was excluded. The concentrations of indoor NO_2 in some studies[23–26] were clearly dominated by traffic outdoors, because the percentage of study homes with household gas stoves was small; we excluded those studies as well. One panel study[27] was not included as this study provided insight only into the short-term exposure and its health effects. Two publications by Garrett *et al.*[28,29] were based on the same study population and data except for different confounder adjustment; we only included one study.[29] In this review, we refer to each population as a separate study and used the corresponding effect estimates; thus we excluded the combined risk estimates from Moshammer *et al*.[30] because we had already included the individual studies on which this paper was based. The study by von Maffei[31] was excluded because it was unclear whether it was current or lifetime asthma. In the end, 41 studies were selected for further analysis.

Selected articles were appraised using a data extraction form. Information on authors, publication year, country of origin, study design, population characteristics (gender and age), exposure definition (including proportion of gas cooking), definitions of respiratory outcomes in each reviewed article and the meta-analysis, risk measure and confounding factors was extracted.

If unadjusted and adjusted results were both reported, we extracted the one adjusted for potential confounding factors. Where more than one adjusted result was presented, we chose the one with adjustment of smoking in the family.[32] When a study reported only the number of cases and controls among the exposed and unexposed, we calculated the crude odds ratio and its corresponding 95% confidence interval (CI) following.[12] When a multi-city study provided risk estimates for single cities in addition to a combined estimate, we selected the combined estimates. If there were no combined estimates, risk estimates for single cities were used. If more than one follow-up analysis had been reported for the same population, we used results where health outcomes and exposure were measured in the same period[33–35] [e.g. questionnaire and indoor NO_2 measured in the same year; results linking childhood (adolescent) exposure to childhood (adolescent) health outcomes]. If results were presented separately for different locations of indoor NO_2 (kitchen, living room and bedroom), we extracted the results from living room, which were most frequently reported in other studies.[36] In Hoek *et al.*'s[36] study, we assumed that the majority of NO_2 concentration was in the range of 10–100 $\mu g/m^3$, based on the data that the geometric mean of NO_2 in the living room was 68.4 $\mu g/m^3$, and recalculated the effect estimates. The 95% confidence intervals were either extracted directly from the original articles or calculated by standard error transformation.

Statistical methods

We conducted meta-analyses to obtain summary risk estimates for the association between asthma, wheeze and household NO_2 exposure and its surrogate, gas cooking. For every single exposure variable, to distinguish the differing reporting times of symptoms between studies, we reported not only the overall meta-OR combining all the studies but also the subgroup meta-ORs in both 'current' and 'lifetime' asthma (or wheeze). When a study reported risk estimates for different strata of the population, e.g. for boys and girls,[34,37–39] children with asthmatic mothers or non-asthmatic mothers[40] and children living in single- or multi-family houses,[41] we included these directly into the meta-analysis without combining them first. The risk estimates for the exposure ves non-exposure categories of gas cooking were summarized.

For NO_2 exposure, we calculated two types of pooled risk estimates: (i) for the comparison of asthma and wheeze risk at high vs low exposure independently of the exact definition of high and low exposure, and (ii) for asthma and wheeze risk per 15-ppb increase in continuous NO_2 concentration. For inclusion in the meta-analysis, we converted all results in $\mu g/m^3$ to 15 ppb using standard pressure and temperature. In the high vs low exposure meta-analysis, the included studies reported different specific ranges for NO_2, which precludes a direct comparison of effect estimates from these studies. Some studies categorized NO_2 levels into more than two categories; from these, we selected ORs for the highest compared with the lowest exposure category. We appreciate that this analysis is semi-quantitative.

Heterogeneity

We used standard chi-square tests to examine the heterogeneity among studies; results were defined as heterogeneous for $P < 0.10$.[42] The I^2 statistic was used to quantify the extent of inconsistency among the studies. The I^2 values <25% reflect low inconsistency, values of 25–75% reflect moderate inconsistency, whereas values >75% indicate high inconsistencies among studies.[43] Due to the heterogeneity among studies which were performed independently by different researchers in different populations, pooled risk estimates were calculated by random-effect models with inverse-variance weights.[44] Summary estimates from fixed-effect models were also presented in the Forest plots for comparison.

Influence analysis

To evaluate the influence of individual studies on the summary effect estimate, we performed influence analysis. This method recalculated the summary estimate, omitting one study at a time.

Sensitivity analysis

Sensitivity analyses were employed to test whether the risk estimates varied by study region and age of the participants. Age was categorized into $\leqslant$6 years, 6–10 years and >10 years. Further subdivision of the youngest category was not possible because of the number of studies performed within that age range. Study regions were divided into Europe, North America, and Asian and Pacific area.

We noticed that the proportion of gas cooking varied considerably between studies. In order to examine whether observed exposure health relationships of a study were associated with the percentage exposed to gas cooking, stratified analyses were performed using 30% of cooking with gas stoves as a cut-off.

In our database, there were some studies which were conducted a long time ago. Since then, the actual use and the emissions of gas cookers as well as disease management strategies may have changed. To examine the influence of older studies, we compared risk estimates between older and newer studies as part of a sensitivity analysis. For operational purposes, the publication year 2000 was used as the cut-off.

Subsequently, exploratory univariate meta-regressions were performed to assess whether heterogeneity in associations between gas cooking and asthma and wheeze between studies was related to age of the participants, study region, proportion of gas cooking and year of publication.

Furthermore, random effects models were performed to determine the potential impact by asthmatic subjects. Asthmatic children may be more sensitive to the effects of indoor NO_2. Therefore, we repeated analyses of the associations of gas cooking and indoor NO_2 with wheeze by excluding two studies which focused on asthmatic children only at the initial recruitment.

Assessing publication bias

Publication bias was evaluated with funnel plots and the Egger's and Begg's tests.[45]

All statistical analyses were performed using STATA (version 10; StataCorp LP, College Station, TX, USA), employing the 'metan', 'metabias' and 'metainf' commands for meta-analyses and bias evaluation. 'Metareg' was used to test differences in effect size between subgroups of studies.

Results

A flow chart of the selection stages of the studies for analysis is shown in Figure 1. We extracted data from 41 studies published since 1977 assessing the relationship between household NO_2 or gas cooking and asthma and wheeze (Supplementary Table 1, available as Supplementary data at IJE online).[13,29,32–41,46–74] Among those 41 studies, 19 studies were conducted in Europe (UK, Austria, Germany, Netherlands, Czech Republic, Spain and Russia), 14 in North America (USA and Canada), 3 in Asia (China and Japan), 4 in Australia and 1 in New Zealand. Among them, four studies contributed information on infants[32,40,65,75] and two studies on asthmatic children;[41,46] the rest were studies on general populations of school-age children. There were 16 cross-sectional, 18 cohort, and 7 case-control studies. However, most of the reports from cohort studies were based on cross-sectional rather than longitudinal analysis. Three studies included the association between previous gas cooking exposure and the development of respiratory symptoms: De Bilderling *et al.*[33] and Ponsonby *et al.*[32] used a cohort design to link early exposure estimates to subsequent risk of wheeze and asthma, and Wong *et al*.[35] used a survey study with a retrospective questionnaire. The other reviewed studies focused mainly on whether the presence of respiratory symptoms was associated with current exposure

The meta-analysis of findings from 19 studies on the association between gas cooking and asthma (Figure 2) demonstrates an increased odds of current asthma [random effects meta-odds ratio (OR) 1.42; 95% CI, 1.23–1.64, $P = 0.000$, $n = 11$ studies) and lifetime asthma (1.24; 95% CI, 1.04–1.47, $P = 0.014$, $n = 8$ studies) in children exposed to gas cooking. The overall odds ratio was 1.32 (95% CI, 1.18–1.48, $P = 0.000$; $I^2 = 19.8\%$, heterogeneity P-value = 0.204) for the association between asthma and gas cooking (Figure 2a) and 1.09 (95% CI, 0.91–1.31, $I^2 = 35.5\%$, heterogeneity P-value = 0.185) per 15-ppb increase in NO_2 exposure (Figure 2b). Indoor NO_2 was positively associated with the odds of current wheeze (random effects meta-OR 1.15 per 15 ppb, 95% CI, 1.06–1.25, $P = 0.001$) (Figure 3b). There was only one study reporting lifetime wheeze in children exposed to indoor NO_2; combining it into the meta-analysis yielded a pooled random effects OR of 1.12 (95% CI, 1.04–1.21, $P = 0.002$, $I^2 = 11.3\%$, heterogeneity P-value = 0.337). The combined analysis of 28 studies, including >11 000 children with wheeze, demonstrated no increased risk in children who had ever been exposed to gas cooking (random effects meta-OR = 1.06, 95% CI, 0.99–1.13, $I^2 = 42.8\%$, heterogeneity P-value = 0.006) (Figure 3a). Results for current wheeze (random effects meta-OR = 1.07, 95% CI, 0.99–1.15, heterogeneity P-value = 0.002) were similar to results for all wheeze. We observed heterogeneity among those studies, with I^2 of 50.4% and 42.8% for current and all wheeze, respectively. Therefore, the combined estimates for lifetime wheeze based on the random effects model were likely to represent the effect more accurately. The Forest plots ordered by publication date (Figures 2 and 3) show that there was no obvious trend in risk estimates over time. An influence analysis showed that no single study dominated the combined estimates.

Four of the 41 studies compared children exposed to high $NO_2$with children exposed to low NO_2.[49,53,65,69] We did not find an increase in asthma[49,53] (random effects meta-OR = 1.10, 95% CI, 0.35–3.40, $I^2 = 49.5\%$, heterogeneity P-value = 0.159) and in wheeze[53,65,69] (random effects meta-OR = 0.81, 95% CI, 0.59–1.12, $I^2 = 0.0\%$, heterogeneity P-value = 0.715) among children with the highest compared with the lowest NO_2 exposure. The results, however, should be interpreted with caution because the number of studies included was small.

We performed additional analyses to examine the pooled estimates for wheeze when restricted to general populations of children, excluding studies based on asthmatic children.[41,46] Restricting the analysis to general populations of children did not change the effect estimates (Table 1). When we excluded crude effect estimates from five studies[38,39,52,59,68] without confounder adjustment, the summary effect of gas cooking exposure on asthma in children became somewhat stronger (Table 1).

Risk estimates for asthma were not different in children aged ⩽6 years,[32,52,60,70,72] 6–10 years[37,49–51,58,59,64] or >10 years[29,39,54,56,57,66,68] (Table 2). Stratification by study region showed that the ORs for the association of all asthma with gas cooking exposure tended to be higher in Europe (random effects meta-OR = 1.34, 95% CI, 1.15–1.57) and the Asian-Pacific region (random effects meta-OR = 1.29, 95% CI,1.15–1.45), and lower in North America (random effects meta-OR = 1.12, 95% CI, 0.73–1.73). However, the ORs did not differ significantly between regions. The trend was similar for all wheeze (Table 3).Taking the proportion of participants using gas for cooking into account (Table 2), there was a tendency for the risk estimates to be higher in the studies which had less than 30% of participants using gas cooking. No stratified analyses by age, study region, proportion of gas stoves or year of publication were performed for indoor NO_2 as the numbers of studies in the different strata were too small to obtain enough statistical power.

Almost half of the included studies were published before 2000. The estimated effects of gas cooking on asthma were higher in studies that were published before the year 2000; however, the estimates did not differ in the strata of published year ($P > 0.05$) (Table 2).

Results of stratified analyses and meta-regressions for current asthma, lifetime asthma, current wheeze and lifetime wheeze are also presented in Tables 2 and 3.

The funnel plots (Supplementary Figure 1, available as Supplementary data at *IJE* online) and P-values from Begg's ($P_{asthma} = 0.971$, $P_{wheeze} = 0.975$) and Egger's ($P_{asthma} = 0.890$, $P_{wheeze} = 0.644$) tests provided no evidence of publication bias.

Discussion

Our meta-analyses suggest that children living in a home with gas cooking have a 42% increased risk of having current asthma, a 24% increased risk of lifetime asthma and an overall 32% increased risk of

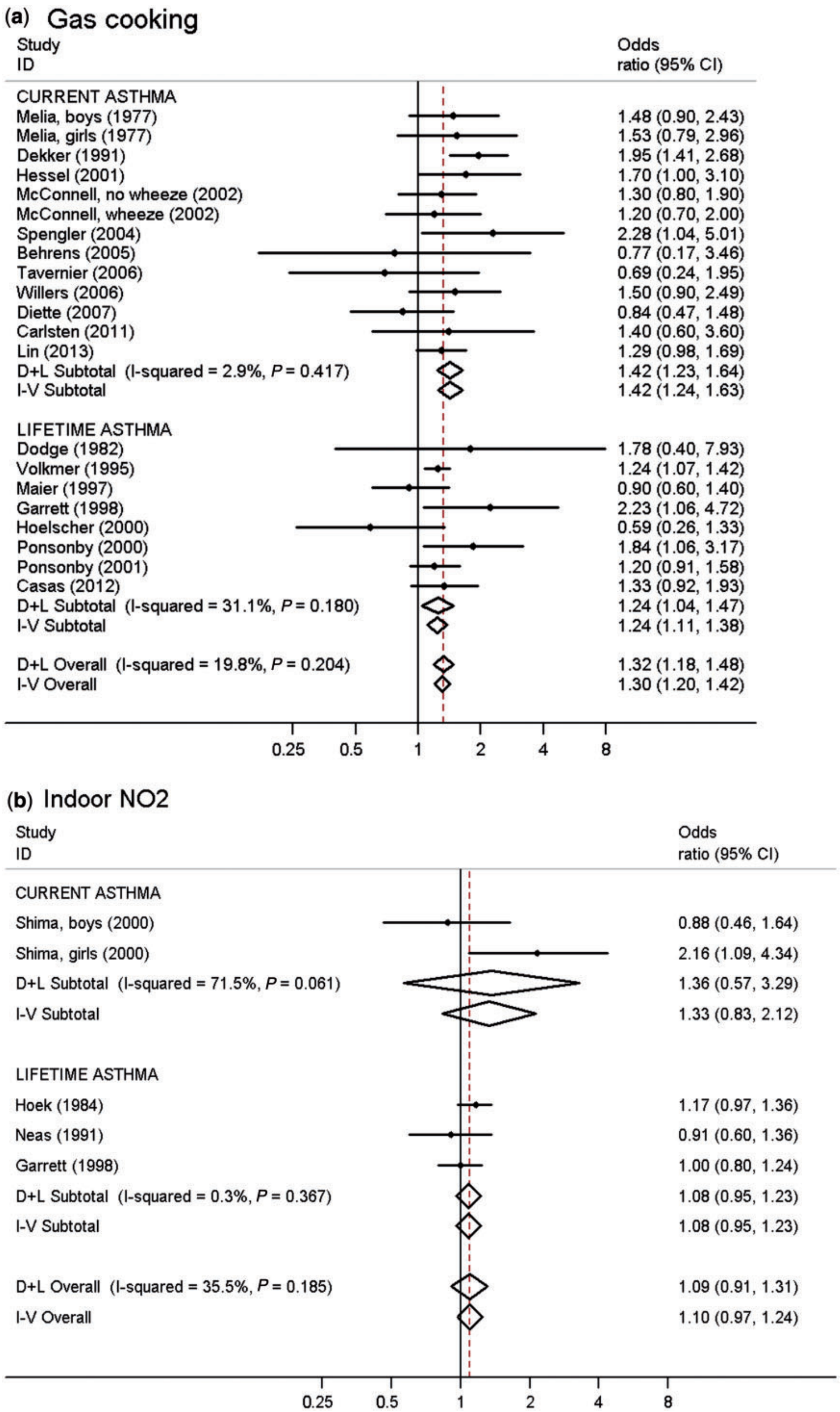

Figure 2 Meta-analysis of studies assessing association between asthma (current/lifetime) and gas cooking (a) or indoor NO_2, (b) in children. The odds ratio for each study is indicated by a black dot, and the horizontal line shows the corresponding 95% CI. The combined estimate is indicated by the diamond-shaped box. D + L Subtotal/Overall = random effect meta-analysis; I-V Subtotal/Overall = fixed effects meta-analysis

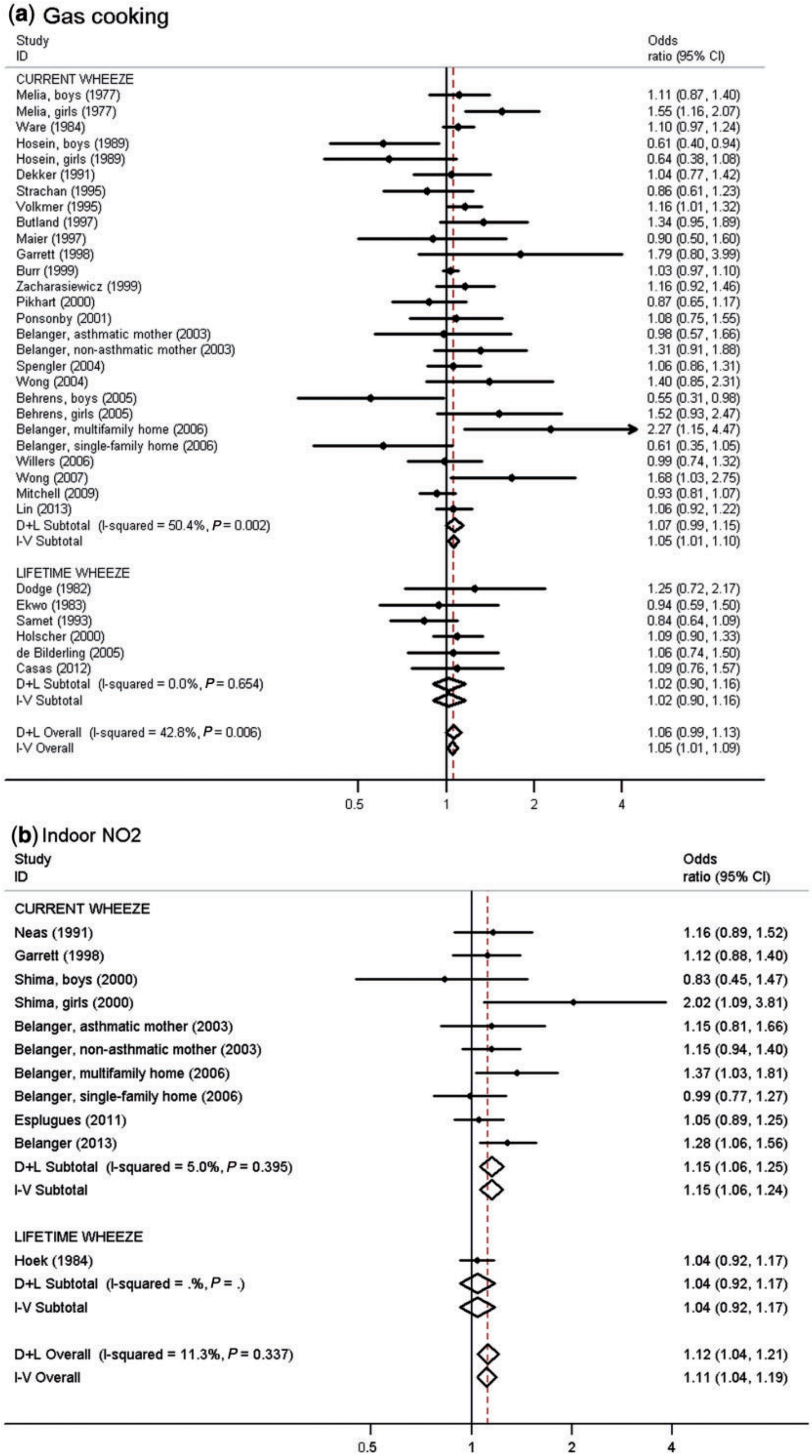

Figure 3 Meta-analysis of studies assessing association between wheeze (current/lifetime) and gas cooking (a) or indoor NO_2, (b) in children. The odds ratio for each study is indicated by a black dot, and the horizontal line shows the corresponding 95% CI. The combined estimate is indicated by the diamond-shaped box. D + L Subtotal/Overall = random effects meta-analysis; I-V Subtotal/Overall = fixed effects meta-analysis

Table 1 Meta-analysis results of studies restricted to unselected children and of studies with confounder adjustment

Variable	Number of studies included	Summary odds ratio (95% CI)	I^2 (heterogeneity P-value)
Unselected children[a]			
Gas cooking			
Current wheeze	21	1.06 (1.01–1.10)	45.1% (0.008)
All wheeze[b]	27	1.05 (1.01–1.09)	36.5% (0.024)
Indoor NO_2[a]			
Current wheeze	5	1.12 (1.01–1.23)	0.0% (0.530)
All wheeze[b]	6	1.09 (1.01–1.17)	0.0% (0.547)
Studies with confounder adjustment			
Asthma			
Gas cooking			
Current asthma	8	1.49 (1.28–1.73)	0.0% (0.548)
Lifetime asthma	7	1.29 (1.09–1.52)	23.6% (0.249)
All asthma [b]	15	1.37 (1.22–1.53)	14.4% (0.288)
Indoor NO_2			
Current asthma	1	1.36 (0.57–3.29)	–
Lifetime asthma	3	1.08 (0.95–1.23)	0.0% (0.367)
All asthma [b]	4	1.09 (0.91–1.31)	35.5% (0.185)
Wheeze			
Gas cooking			
Current wheeze	19	1.05 (1.01–1.10)	40.6% (0.026)
Lifetime wheeze	6	1.02 (0.90–1.16)	0.0% (0.654)
All wheeze[b]	25	1.05 (1.01–1.09)	30.5% (0.065)
Indoor NO_2			
Current wheeze	7	1.15 (1.06–1.24)	5.0% (0.395)
Lifetime wheeze	1	1.04 (0.92–1.17)	–
All wheeze[b]	8	1.11 (1.04–1.19)	11.3% (0.337)

[a]Without two studies performed in asthmatics only [Belanger *et al.* 2006 (gas cooking) and Belanger *et al.* 2013 (NO_2)]. The health outcome in these two studies was 'current wheeze'. Results for 'lifetime wheeze' are the same as in Figure 3, as all studies were performed in unselected children and are therefore not presented here.
[b]Current + lifetime.
[c]Per 15-ppb increase in NO_2.

having current and lifetime asthma; per 15 ppb increase in indoor NO_2 level, children have a 15% increased risk of having current wheeze. The meta-analyses found no increase in the risk of asthma in relation to indoor NO_2 exposure and no increase in the risk of wheeze in relation to gas cooking exposure. The risk estimates for asthma were somewhat higher in studies which had <30% of participants using gas cooking compared with those ⩾30%. The results did not vary much between age groups (⩽6 years, 6–10 years and >10 years) or among regions (Europe, Asian-Pacific region and North America). There was no indication of publication bias when considering all the evidence.

The present study extends the previous meta-analysis of indoor NO_2 by Hasselblad *et al.*[2] which reported that indoor NO_2 increased lower respiratory tract illnesses (LRI) by 18% (OR = 1.18, 95% CI, 1.11–1.25) in children for each 15-ppb increase in indoor NO_2. The LRI definitions used in the reviewed studies in the Hasselblad meta-analysis[2] often included relatively minor symptoms probably related to transient respiratory tract infections. The results of this and our study are therefore not directly comparable. Our meta-analysis did not focus on LRI but on asthma and wheeze (without colds), included data from only those studies with gas cooking without other combustion sources as exposure variable, and indoor NO_2 only when dominated by indoor sources. The definitions of 'asthma' and 'wheeze' differed in various studies; we categorized them into current and lifetime symptoms to standardize the

Table 2 Random effects meta-analysis and univariate meta-regression of studies on gas cooking and asthma stratified by age, study region, proportion of gas cooking and year of publication

	Number of studies	Summary odds ratio (95% CI)	I^2 (heterogeneity *P*-value)	Ratio of odds ratios (95% CI)[a]
Current asthma				
Age of participants				
⩽6years	3	1.22 (0.95–1.56)	0.0% (0.504)	1.00 (ref)
6–10 years	4	1.51 (1.12–2.02)	33.5% (0.211)	1.25 (0.82–1.90)
>10 years	4	1.54 (1.16–2.06)	0.0% (0.500)	1.27 (0.80–2.03)
Study region				
Europe	7	1.34 (1.13–1.60)	0.0% (0.666)	1.00 (ref)
North America	3	1.36 (0.76–2.43)	68.7% (0.041)	1.13 (0.74–1.71)
Asia-Pacific	1	1.50 (1.01–2.23)	0.0% (0.937)	1.11 (0.65–1.89)
Proportion of gas cooking[b]				
<30%	4	1.79 (1.38–2.33)	0.0% (0.615)	1.00 (ref)
⩾30%	6	1.32 (1.12–1.56)	0.0% (0.655)	0.74 (0.52–1.05)
Publication year				
Before 2000	2	1.76 (1.37–2.25)	0.0% (0.597)	1.00 (ref)
2000 or later	9	1.30 (1.10–1.53)	0.0% (0.601)	0.74 (0.53–1.03)
Lifetime asthma				
Age of participants				
⩽6years	2	1.38 (0.98–1.94)	0.0% (0.506)	1.00 (ref)
6–10 years	3	1.16 (0.95–1.41)	0.0% (0.375)	0.83 (0.41–1.67)
>10 years	3	1.28 (0.50–3.29)	65.3% (0.056)	0.92 (0.33–2.53)
Study region				
Europe	1	1.33 (0.92–1.93)	–	1.00 (ref)
North America	3	0.86 (0.60–1.24)	0.0% (0.412)	0.65 (0.31–1.37)
Asia-Pacific	4	1.32 (1.10–1.59)	28.7% (0.240)	0.96 (0.55–1.68)
Proportion of gas cooking[b]				
<30%	3	1.27 (0.87–1.84)	53.8% (0.115)	1.00 (ref)
⩾30%	3	1.07 (0.65–1.76)	10.4% (0.188)	0.98 (0.62–1.53)
Year of publication				
Before 2000	4	1.24 (0.93–1.65)	37.2% (0.189)	1.00 (ref)
2000 or later	3	1.25 (0.93–1.68)	44.0% (0.148)	1.02 (0.68–1.54)
All asthma[c]				
Age of participants				
⩽6 years	5	1.26 (1.12–1.42)	0.0% (0.506)	1.00 (ref)
6–10 years	7	1.31 (1.08–1.59)	38.8% (0.133)	1.03 (0.79–1.35)
>10 years	7	1.45 (1.07–1.97)	26.6% (0.217)	1.27 (1.05–1.54)
Study region				
Europe	8	1.34 (1.15–1.57)	0.0% (0.763)	1.00 (ref)
North America	6	1.12 (0.73–1.73)	66.7% (0.010)	0.92 (0.69–1.23)
Asian–Pacific	5	1.29 (1.15–1.45)	0.0% (0.442)	1.01 (0.76–1.35)
Proportion of gas cooking[b]				
<30%	7	1.45 (1.12–1.87)	40.1% (0.124)	1.00 (ref)
⩾30%	10	1.25 (1.13–1.38)	0.0% (0.617)	0.86 (0.68–1.06)
Publication year				
Before 2000	6	1.42 (1.13–1.80)	50.0% (0.062)	1.00 (ref)
2000 or later	13	1.28 (1.13–1.45)	0.0% (0.467)	0.93 (0.75–1.16)

[a]Ratios of odds ratios are the odds ratio from studies with the characteristic divided by the odds ratios from studies of the reference category and were calculated from coefficients of meta-regression b as exp(b). Ratios above 1.0 indicate a larger odds ratio for studies with the characteristic.

[b]Information of proportion of gas cooking was not available in two studies (Garrett *et al.* 1998; Tavernier *et al*. 2005). Belanger *et al.* (2006) was counted twice in this analysis as results were presented for multi-family and single-family homes separately, and proportions for gas cooking were ⩾30% for multi-family homes and <30% for single-family homes, respectively.

[c]Current + lifetime.

Table 3 Random effects meta-analysis and univariate meta-regression of studies on gas cooking and wheeze stratified by age, study region, proportion of gas cooking and year of publication

	Number of studies	Summary odds ratio (95% CI)	I^2 (heterogeneity *P*-value)	Ratio of odds ratios (95% CI)[a]
Current wheeze				
Age of participants				
⩽6 years	4	1.16 (1.03–1.30)	3.7% (0.386)	1.00 (ref)
6–10 years	11	1.05 (0.96–1.15)	32.6% (0.129)	0.90 (0.70–1.17)
>10 years	7	1.02 (0.86–1.21)	68.5% (0.001)	0.88 (0.67–1.16)
Study region				
Europe	9	1.07 (0.97–1.18)	48.7% (0.035)	1.00 (ref)
North America	6	0.96 (0.78–1.19)	61.3% (0.008)	0.92 (0.72–1.18)
Asia-Pacific	7	1.14 (0.99–1.31)	47.9% (0.074)	1.08 (0.85–1.37)
Proportion of gas cooking				
<30%	4	0.91 (0.73–1.14)	49.4% (0.079)	1.00 (ref)
⩾30%	15	1.09 (1.01–1.18)	49.2% (0.008)	1.16 (0.95–1.42)
Publication year				
Before 2000	11	1.08 (0.98–1.19)	52.5% (0.014)	1.00 (ref)
2000 or later	11	1.06 (0.93–1.20)	50.7% (0.015)	0.96 (0.81–1.14)
Lifetime wheeze				
Age of participants				
⩽6 years	1	0.84 (0.64–1.10)	–	1.00 (ref)
6–10 years	1	1.09 (0.76–1.67)	–	1.30 (0.62–2.69)
>10 years	4	1.08 (0.92–1.26)	0.0% (0.890)	1.28 (0.78–2.12)
Study region				
Europe	3	1.08 (0.93–1.27)	0.0% (0.990)	1.00 (ref)
North America	3	0.91 (0.74–1.13)	0.0% (0.441)	0.84 (0.58–1.22)
Asia-Pacific	0	-	-	-
Proportion of gas cooking[b]				
<30%	1	1.09 (0.76–1.57)	-	1.00 (ref)
⩾30%	4	1.08 (0.92–1.26)	0.0% (0.890)	0.99 (0.52–1.88)
Publication year				
Before 2000	3	0.91 (0.74–1.13)	0.0% (0.441)	1.00 (ref)
2000 or later	3	1.08 (0.93–1.27)	0.0% (0.990)	1.19 (0.82–1.73)
All wheeze[c]				
Age of participants				
⩽6 years	5	1.10 (0.93–1.29)	44.3% (0.110)	1.00 (ref)
6–10 years	12	1.05 (0.97–1.15)	26.7% (0.175)	0.96 (0.78–1.18)
>10 years	11	1.04 (0.92–1.17)	55.8% (0.006)	0.95 (0.77–1.18)
Study region				
Europe	12	1.07 (0.99–1.15)	34.0% (0.103)	1.00 (ref)
North America	9	0.97 (0.82–1.13)	53.2% (0.015)	0.92 (0.77–1.10)
Asia-Pacific	7	1.14 (0.99–1.31)	47.9% (0.074)	1.06 (0.88–1.27)
Proportion of gas cooking[b]				
<30%	6	0.94 (0.78–1.14)	43.0% (0.104)	1.00 (ref)
⩾30%	20	1.09 (1.01–1.16)	39.1% (0.030)	1.14 (0.96–1.34)
Publication year				
Before 2000	14	1.06 (0.97–1.16)	48.1% (0.017)	1.00 (ref)
2000 or later	14	1.06 (0.96–1.17)	40.3% (0.044)	0.98 (0.86–1.13)

[a]Ratios of odds ratios are ratios of the odds ratio from studies with the characteristic divided by the odds ratio from studies of the reference category and were calculated from coefficients of meta-regression b as exp(b). Ratios above 1.0 indicate a larger odds ratio for studies with the characteristic.

[b]Information on proportion of gas cooking was unavailable in three studies (Garrett *et al.* 1998; Samet *et al.* 1993; Zacharasiewicz *et al.* 1999).

[c]All (current + lifetime).

health effects and thus to reduce the heterogeneity between studies.

Although asthma and wheeze are associated, they present distinct entities. In a Dutch birth cohort study, for example, it was found that only 11% of children with symptoms suggestive of asthma, including wheeze, at preschool age had asthma at age 7–8 years.[76] Moreover, one-time wheeze was sufficient to characterize a child as having wheezed in many of the studies included in the meta-analysis and typically no distinction was made between wheeze with and without respiratory infections. This may explain why our meta-analysis revealed stronger associations with gas cooking for asthma compared with wheeze.

Gas cooking produces NO_2 and other pollutants such as ultrafine particles. Our finding of an association between gas cooking and asthma in the absence of an association between measured NO_2 and asthma suggests that gas cooking may act as a surrogate for causal variables other than air pollutants produced by gas combustion. This is supported by an Australian study, where the association between gas cooking and respiratory symptoms remained significant after adjustment for measured NO_2.[29] Residual confounding by (unmeasured) factors that are associated with gas cooking might be another explanation for our finding of an association between asthma and gas cooking, but not with indoor NO_2. However, this is not very likely as we used effect estimates from the included studies which were almost always adjusted for known determinants of childhood asthma. It is also possible that no relationship between indoor NO_2 and asthma was found because there were fewer studies that had direct NO_2 measurements, and study populations were usually smaller in these studies. Point estimates for the association of NO_2 and gas cooking with current asthma were actually very similar to those for gas cooking and asthma, but confidence intervals were wider for NO_2. As gas cooking is a strong determinant of indoor NO_2, it has been argued that one is actually more likely to find associations with gas cooking than with NO_2 because much larger studies can be (and have been) conducted using the surrogate exposure variable.[77]

Heterogeneity among reviewed studies existed in various factors such as stove type, age of population, size of population exposed to gas cooking, susceptibility of study population, study region, study design, sampling season, other indoor factors and diagnosis of asthma and wheeze. We therefore conducted meta-regression to explore whether the heterogeneity could be explained by age, study region, study design or size of the population exposed to gas cooking. None of these factors appeared to be associated with the magnitude of the effect estimates extracted from the study papers. We did note that the association between gas cooking and asthma was somewhat stronger in studies published before the year 2000 than in later studies. Possibly, gas cooking in newer studies is associated with lower indoor pollution levels because of the introduction of microwaves displacing some of the meal preparation, changes in stove performance or kitchen ventilation etc.[53,72] Exposure assessment (questionnaire reports of gas cookers and passive measurements of NO_2) and statistical analysis (mostly logistic regression) were mostly rather straightforward and, therefore, they do not seem a likely source of heterogeneity between the reviewed studies.

The findings of our meta-analysis on asthma were also not different when we excluded studies where less than 30% of the population used gas for cooking, by restricting the study population to general population of children, and by excluding studies without adjustment for potential confounders. The exclusion of single studies from the analysis did not change the pooled estimates. Also, *P*-values from the Egger's and Begg's tests, as well as the absence of funnel plot asymmetry, suggested that no publication bias exists in our results.

Our analysis was based on observational studies and we cannot exclude that associations between gas cooking and asthma are in part due to information bias, e.g. because parents may suspect risks are associated with gas cooking. However, with studies coming from so many different settings, we do not think this is a likely explanation for the observed associations.

Although the effects of gas cooking and indoor NO_2 on asthma and wheeze were found to be relatively small (all random-effects meta-odds ratios were less than 1.5) the public health impact may still be considerable because gas cooking is widespread. A recent large population study found that 60–70% of European children lived in gas-cooking homes.[78] It is not clear to what extent the observed associations with gas cooking are attributable to NO_2 alone or also to other pollutants associated with the use of gas for cooking. In outdoor air pollution studies, NO_2 often is used as a marker of a complex, traffic-related air pollution mixture, which makes extrapolation of our results to outdoor air pollution difficult. Indoors, gas cookers can be replaced by electric cookers, and gas cooking fumes can be removed by using ventilation hoods.

Conclusion

In summary, this meta-analysis provides quantitative evidence that gas cooking increases the risk of asthma in children, and indoor NO_2 increases the risk of current wheeze in children.

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All authors had full access to all the data and take responsibility for the integrity of the data, the accuracy of the data analysis and the accuracy and completeness of references. W.L., U.G. and B.B. conducted the literature search independently and decided on inclusion of studies. Discrepancies among the authors were discussed and adjudicated. W.L. and U.G. extracted the data. W.L. did the statistical analyses and wrote the manuscript. U.G. and B.B. critically reviewed the manuscript and provided important intellectual content.

Conflict of interest: None declared.

KEY MESSAGES

- The last meta-analysis of the respiratory health effects of indoor NO_2 exposure was published almost 20 years ago. The current paper provides an up-to-date review of the literature with childhood respiratory health data that used either indoor NO_2 or the use of gas for cooking as the exposure metric.
- Household gas cooking is associated with increased odds of current asthma and lifetime asthma in children. The risk of overall asthma in children with gas cooking exposure was 1.32 (95% confidence interval, 1.18–1.48).
- The risk of childhood current wheeze increases by 15% per 15-ppb increase in indoor NO_2 levels.

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Commentary: Gas cooking and child respiratory health—time to identify the culprits?

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In this issue of the *IJE*, Lin and colleagues[1] report the results of a meta-analysis of the effect of indoor nitrogen dioxide (NO_2) and gas cooking on asthma and wheeze in children. Effect estimates summarizing 19 studies show that the risk of asthma increases by 32% when a gas cooker is present in the home, and 7 studies combined show that the risk of wheeze increases by 15% for a 15 ppb increase in NO_2. The presence of gas cookers inside the home is common in developed countries (around 50–70%) and has long been established as a main source of indoor air pollution, in particular NO_2.[2] Young children are among