APPENDICES AVAILABLE ON THE HEI WEBSITE

Special Report 23

Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

Chapter 9: Traffic-Related Air Pollution and Respiratory Outcomes

These Appendices were reviewed solely for spelling, grammar, and cross-references to the main text. They have not been formatted or fully edited by HEI. This document was part of the HEI Panel's review process.

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Chapter 9: Traffic-Related Air Pollution and Respiratory Outcomes

Appendix A

Appendix 9A Wheeze Outcomes in Children and Adults

9A.1 Prevalence of wheeze ever and asthma-like symptoms in children

9A.1.1 Study selection and description

Eight studies explored associations between TRAP and prevalence of wheeze ever in children, and nine explored associations with indirect measures of traffic exposures (i.e., distance to roads or density of traffic on nearby roads). Combined, these studies presented 29 different effect estimates. Appendix Table 9A-1 presents details, including the effect estimates, for the eight studies that considered exposures to the pollutants. Four of these eight studies were based in Europe, two in Canada, and two in Asia. Although some of the studies analyzed cohorts, all measured outcomes as prevalence, and none were analyzed as longitudinal study designs. Most of the studies included a few hundred to a few thousand participants, but one study (Hasunuma et al. 2016) was notably larger than all others with nearly 58,000 participants. All but two studies (Pikhart et al. 1997; Zhang et al. 2002) were published after 2008 (the end of the search date for the review of the HEI 2010 Traffic report). Across these eight studies that considered exposures to pollutants, five reported effect estimates for exposures to NO_2, three for NO_x, and one for each of $PM_{2.5}$ and EC.

Appendix Table 9A-1. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Wheeze Ever in Children – Pollutants.

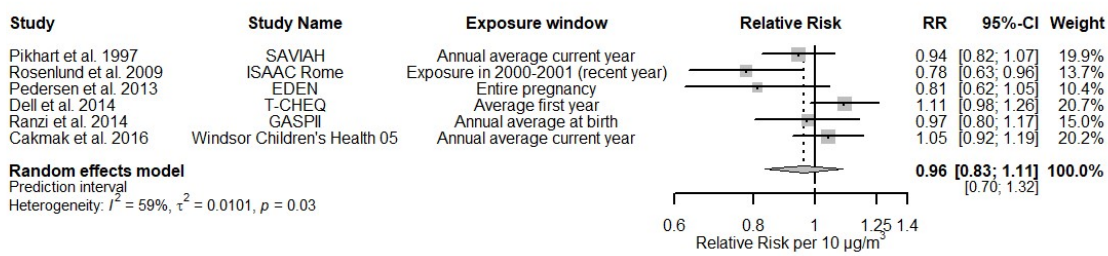
Reference	Study Name	Study Design	Location	Study period	Sample size[a]	Exposure Assessment	Pollutant	Mean or median exposure[b]	Exposure Window	Effect Estimate (95% CI)[c]	Increment
Cakmak 2016	Windsor Children's Health 05	Cross sectional	Windsor, Ontario, Canada	2005-2005	1,570	LUR	NO_2	11.6	Annual average current year	**0.99 (0.90, 1.10)** (income > $80,000)[d]	2.27 ppb
										1.03 (0.95, 1.10) (income $35,000-80,000)[d]	
										1.05 (0.90, 1.23) (income < $35,000)[d]	
Dell 2014	T-CHEQ	Case-control	Toronto, Canada	2006-2006	1,441	LUR	NO_2	18.3-28.3	Average first year	**1.12 (0.98, 1.28)**	5.7 ppb
									Annual average current year	1.10 (0.96, 1.26)	5.3 ppb
									Cumulative average	1.01 (0.89, 1.14)	3.3 ppb
Hasunuma 2016	SORA	Cohort	Multiple cities, Japan	2006-2010	57,682	Personal exposure	NO_x	37.7	Cumulative average	1.00 (1.00, 1.01)	1 ppb
							EC	2.85		1.01 (1.00, 1.01)	0.1 μg/m^3
Nordling 2008	BAMSE	Cohort	Stockholm County, Sweden	1994-2000	3,515	Dispersion / CTM	NO_x	23.1	Average first year	0.82 (0.48, 1.40)	44 μg/m^3
							traffic PM_{10}	3.9		0.90 (0.45, 1.81)	6 μg/m^3
Pedersen 2013	EDEN	Cohort	Nancy and Poitiers, France	2003-2007	926	Dispersion / CTM	NO_2	18.8	Entire pregnancy	**0.81 (0.62, 1.05)**	10 μg/m^3
							PM_{10} mass	20.3		0.60 (0.29, 1.25)	10 μg/m^3

Pikhart 1997	SAVIAH	Cross sectional	Prague, Czech Republic	1993-1994	3,334	LUR	NO_2	31.2	Annual average current year	**0.94 (0.82, 1.07)**	10 μg/m[3]
Ranzi 2014	GASPII	Cohort	Rome, Italy	2003-2011	672	LUR	NO_2	37.88	Annual average at birth	**0.97 (0.80, 1.17)**	10 μg/m[3]
									Cumulative average	1.07 (0.90, 1.28)	
Rosenlund 2009	ISAAC Rome	Cross sectional	Rome, Italy	2000-2001	1,760	LUR	NO_2	45	Exposure in 2000-2001 (recent year)	**0.7 (0.5, 0.9)**	14.16 μg/m[3]
Zhang 2002	Chinese 4-City School Survey	Cross sectional	Multiple cities, China	1993-1996	7,392	Surface monitoring	NO_x	90	At baseline	0.82 (0.53, 1.28)	64 μg/m[3]

[a] All studies included male and female participants.
[b] Units are in the increment column.
[c] The effect estimate in all studies was odds ratio. **Bold** indicates the effect estimate was included in the meta-analysis.
[d] Estimates were combined by a fixed effect meta-analysis before entering the random-effects model.

9A.1.2 Primary meta-analysis

Meta-analyses were not conducted for pollutants with fewer than three estimates of association or for distance or traffic density metrics. Additionally, studies were not included in meta-analyses when indoor pollutant levels or exposures related to time-activity patterns were modeled (i.e., Hasunuma et al. 2016). As such, meta-analysis was conducted only for six studies that considered NO_2 (Appendix Figure 9A-1). Here, three of these studies suggested inverse associations between exposure and odds of wheeze in the past 12 months, and two suggested small increased risks. Only one of these (i.e., Rosenlund et al. 2009) presented a statistically significant association (i.e., 0.78; 95% CI: 0.63–0.96). The random-effects summary estimate was 0.96 (95% CI: 0.83–1.11) per 10 μg/m^3. The six studies had approximately equal weighting on the summary estimate, and the heterogeneity of the associations was moderate (I^2 = 59%).

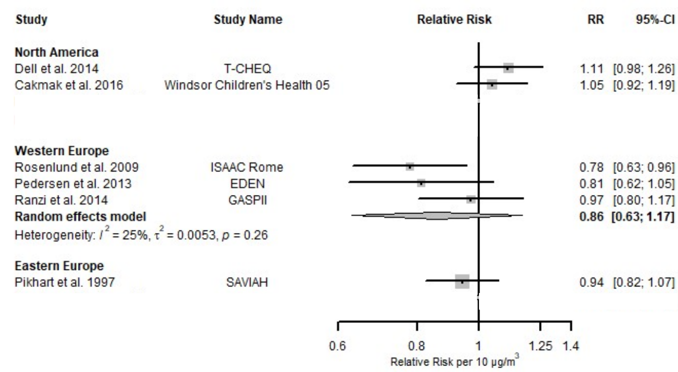


Appendix Figure 9A-1. Meta-analysis of associations between NO_2 and prevalence of wheeze ever in children.

9A.1.3 Additional meta-analyses

The two studies that suggested positive associations between exposure to NO_2 and prevalence of wheeze ever among children were based in North America (in fact, both were based in Southwestern Ontario, Canada). Appendix Figure 9A 2 illustrates that the heterogeneity of estimates of association with NO_2 was notably lower when stratified by region (i.e., I^2 = 25% for the European studies).

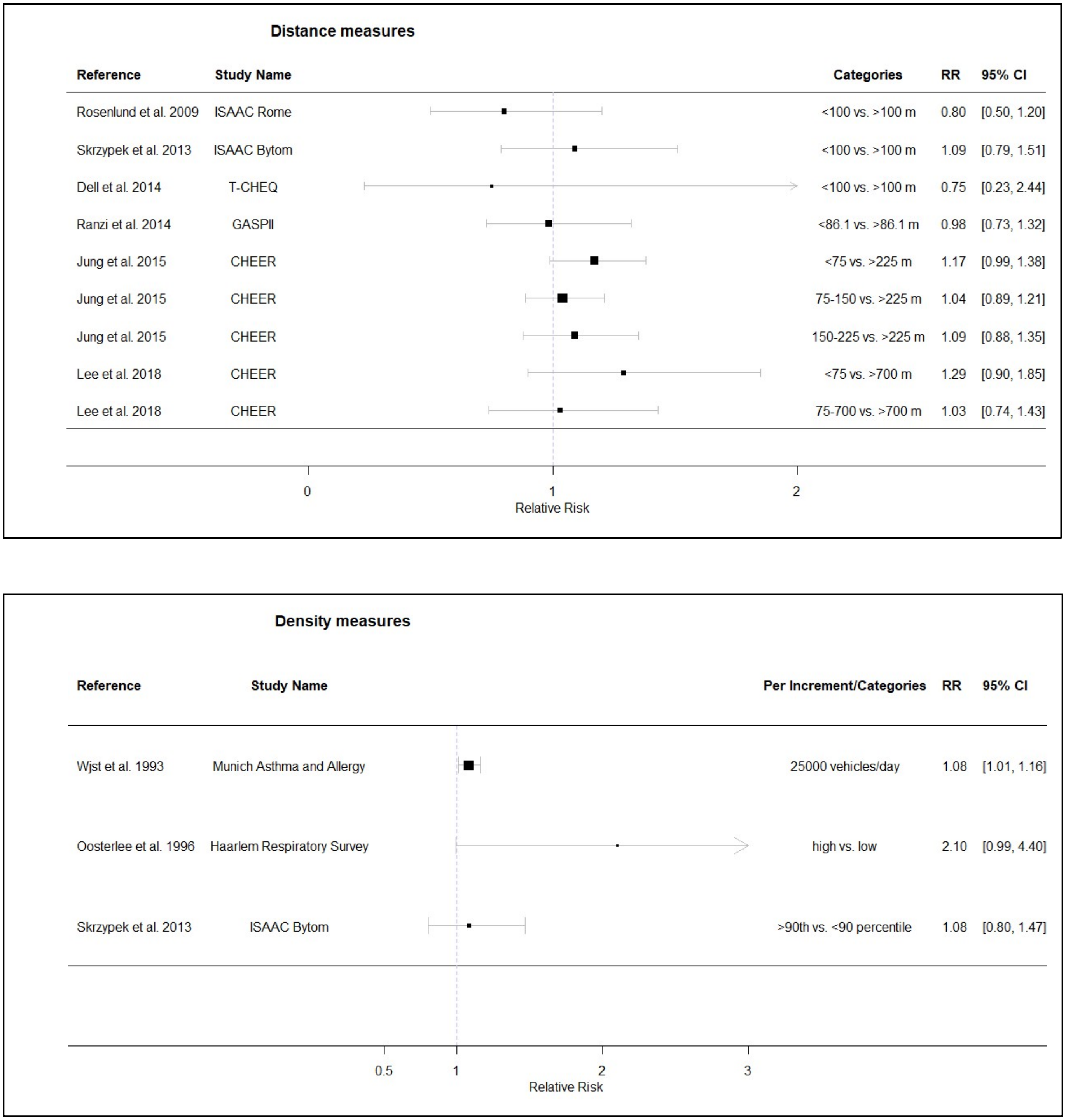
These differences in estimates of association between geographic regions may be due to differing pollution concentrations or mixtures, or to differing study designs and statistical adjustments, among other issues. There were no other notable differences in size or direction of effect estimates, nor any obvious patterns of or explanations for heterogeneity, in meta-analyses for NO_2 stratified according to potential risk of bias, year of publication, adjustment for smoking, or study design.



Appendix Figure 9A-2. Association between NO_2 and prevalence of wheeze ever in children: meta-analysis by region.

9A.2.4 Associations with indirect traffic measures

Studies on indirect traffic measures (i.e., distance and traffic density measures) provide additional information to assess the evidence of associations between TRAP exposure and wheeze onset in children (Appendix Figure 9A-3). In the case of distance measures, although six of the nine studies suggested positive associations between living near major roads and this outcome, confidence intervals all included unity. Three studies reported estimates of association with traffic density measures, only one (Wjst et al. 1993, based in Munich Germany), reported a statistically significant association with prevalence of wheeze ever in children (i.e., RR 1.08, 95% CI: 1.01-1.16 associated with 25,000 vehicles per day around the home compared to no traffic around the home). The study by Oosterlee et al. (1996), set in the Netherlands, also reported increased odds of this outcome (i.e., RR 2.10, 95% CI: 0.99-4.40) associated with relatively high vs. relatively low densities of traffic around the home.



Appendix Figure 9A-3. Association of distance to major roads and traffic density with prevalence of wheeze ever in children.

9A.1.5 Narrative assessment

In summary, the evidence linking TRAP and wheeze ever in children is low: the overall body of evidence is relatively small, and few studies considered associations with pollutants other than NO_2. As noted above, in the single case where meta-analysis was possible (i.e., for NO_2), moderate heterogeneity was evident, and the confidence intervals for the summary estimate included unity. Additionally, none of the studies not included in the meta-analysis (i.e., those that considered exposures to NO_x, PM_{10}, or EC) reported statistically significant associations, either.

Moreover, the studies on indirect traffic measures did not provide any substantial additional support for an association between TRAP and this outcome, as confidence intervals for 13 of the 14 reported RRs that also included unity. In conclusion, the evidence for the presence of an association between TRAP and prevalence of wheeze ever is low.

9A.1.6 Risk of bias assessment

Appendix Table 9A-2 presents an overview of the results of the risk of bias assessment for exposure-outcome pairs of studies on wheeze ever among children that were meta-analyzed; Appendix Table 9A-3 presents the assessment for each individual study. The purpose of the risk of bias assessment is to consider potential risk of bias, and does not provide a determination of actual risk. The risk of bias assessment also does not inform on the direction of any bias. Most of the estimates of association were rated low or moderate risk of bias for all the domains in this case. Only two studies were found to be at high risk of bias for any domain; both Pikhart et al. (1997) and Cakmak et al. (2016) were rated high for lack of adjustment for important potential confounders. Pikhart did not include a correction for smoking, whereas Cakmak did not correct for sex.

Appendix Table 9A-2. Summary of risk of bias rating for studies on prevalence of wheeze ever in children.

		Per study			Per pollutant-study pair		
Domain	**Subdomain**	**Low-risk**	**Moderate -risk**	**High-risk**	**Low-risk**	**Moderate -risk**	**High-risk**
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	4	0	2	4	0	2
	Validity of measuring of confounding factors	6	0	0	6	0	0
	Control in analysis	5	1	0	5	1	0
	Overall	4	0	2	4	0	2
2. Selection Bias	Selection of participants into the study	5	1	0	5	1	0
3. Exposure assessment	Methods used for exposure assessment	6	0	0	6	0	0
	Exposure measurement methods comparable across the range of exposure	6	0	0	6	0	0
	Change in exposure status	6	0	0	6	0	0
	Overall	6	0	0	6	0	0
4. Outcome measurements	Blinding of outcome measurements	0	6	0	0	6	0
	Validity of outcome measurements	4	2	0	4	2	0
	Outcome measurements	4	2	0	4	2	0
	Overall	0	6	0	0	6	0
5. Missing data	Missing data on outcome measures	4	2	0	4	2	0
	Missing data on exposures	5	1	0	5	1	0
	Overall	3	3	0	3	3	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	6	0	0	6	0	0

Appendix Table 9A-3. Risk of bias assessment for individual studies on prevalence of wheeze ever in children.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Cakmak 2016	Windsor Children's Health 05	High	Mod	Low	Mod	Mod	Low
Dell 2014	T-CHEQ	Low	Low	Low	Mod	Low	Low
Pedersen 2013	EDEN	Low	Low	Low	Mod	Mod	Low
Pikhart 1997	SAVIAH	High	Low	Low	Mod	Low	Low
Ranzi 2014	GASPII	Low	Low	Low	Mod	Mod	Low
Rosenlund 2009	ISAAC Rome	Low	Low	Low	Mod	Low	Low

Mod=moderate.

9A.1.7 Confidence assessment of the body of evidence

Appendix Table 9A-4 provides the assessment of the evidence for the exposures for which meta-analyses were conducted. The table, therefore, does not include the pollutants with fewer than three studies or the traffic indicators for which a meta-analysis was not possible.

The initial rating for the body of evidence for associations with NO_2 was set at low because, as explained above, longitudinal assessments (for which it is possible to ascertain if the exposure preceded the outcome) were not conducted here.

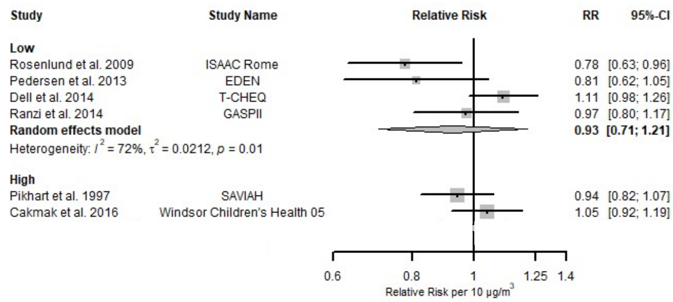
9A.1.7.1 Factors that decrease confidence

No downgrade was applied for *Risk of Bias*. Subgroup analyses with respect to risk of bias showed that excluding the two estimates rated at high risk of bias due to confounding, as well as specifically not adjusting for tobacco smoke, had minimal influence on the meta-analytic estimate (Appendix Figures 9A-4 and 9A-5).

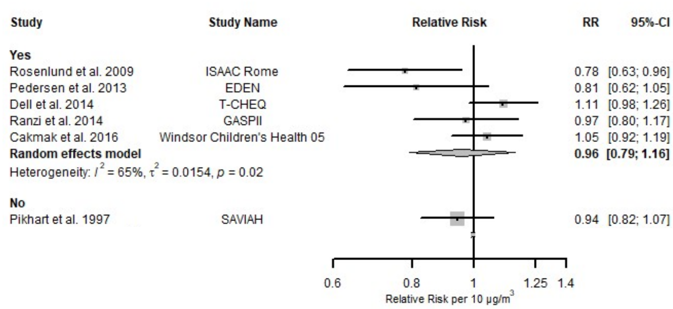
Heterogeneity was moderate (I^2 = 59%), but there were inconsistencies in the direction of association between NO_2 exposures and wheeze ever in children (i.e., both positive and negative estimates of association; Appendix Figure 9A 7). Confidence intervals around most estimates, however, included unity, which suggests minimal substantial heterogeneity overall. Across the six studies, there were some inconsistencies in study designs, and mean exposures, ranging from 11.6 (Cakmak et al. 2016) to 45 µg/m^3 (Rosenlund et al. 2009). For these reasons, no downgrade was necessary for *unexplained inconsistency*.

Regarding *imprecision*, the confidence interval of the meta-analytic effect estimate included unity, and both a positive and a negative association cannot be excluded, and as such, a downgrade was applied.

Due to the small number of studies here it was not possible to assess *publication bias* for studies on associations with NO_2. For this, the Panel decided not to downgrade, per protocol.



Appendix Figure 9A-4. Association between NO_2 and prevalence of wheeze ever in children: meta-analysis by risk of bias confounding.



Appendix Figure 9A-5. Association between NO_2 and prevalence of wheeze ever in children: meta-analysis by smoking.

9A.1.7.2 Factors that increase confidence

No study provided evidence of a *plausible monotonic exposure-response function* and hence an upgrade was not applied. In the current body of evidence, the Panel found no clear indication that *residual confounding or other factors* are likely to lead to an underestimation of the associations. An upgrade was thus not considered appropriate. The Panel found positive associations between exposure to NO_2 and this outcome among the two studies based in Canada, but inverse associations among the remaining three studies, each of which was based in Europe, although all but one these five effect estimates included unity. All but one study was published after 2008, hence the Panel could not adequately assess *consistency* across time periods. Because of the general variability of the estimates, the Panel did not upgrade the evidence for NO_2.

9A.1.7.3 Evaluation of confidence for combined measures of TRAP

The Panel assessed the confidence in the quality of the body of evidence only for NO_2 and judged it to be very low. The Panel did not see any reason to upgrade because of traffic-specificity or studies not entering a meta-analysis.

9A.1.8 Overall assessment

Since the level of confidence in the evidence was considered low in the narrative assessment and the confidence in the body of evidence was very low, the overall confidence assessment of TRAP and prevalence of wheeze ever in children was very low to low.

Appendix Table 9A-4. Confidence rating in the quality of the body of evidence for traffic-related air pollutants and wheeze ever in children[a].

	High ++++ **Moderate +++** **Low ++** **Very low +**		**Factors decreasing confidence "0" if no concern; "-" if serious concern to downgrade confidence**				**Factors increasing confidence "0" if not present; "+" if sufficient to upgrade confidence**			
Pollutant	**Study design**	**Initial confidence rating (# studies)**	Risk of Bias	Unexplained inconsistency	Imprecision	Publication bias	Monotonic exposure-response	Consideration of residual confounding	Consistency across populations	**Final confidence rating**
NO_2	Cross-sectional	++ (N = 6)	0	0	-	0	0	0	0	+ (Very low)
	Rationale	Studies were cross-sectional	Two studies rated high RoB, but no evidence of difference in effect estimates between these.	Moderate heterogeneity (I^2 = 59%). Plausible reasons to explain inconsistency.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

[a] The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

9A.2 Prevalence of active wheeze and asthma-like symptoms in children

9A.2.1 Study selection and description

Forty studies reported associations between traffic-related air pollution and the prevalence of wheeze in the past 12 months (active wheeze) among children under the age of 18 (Appendix Table 9A-5). The vast majority of these studies were based in various locations across Europe, with a handful based in the United States or China. Study sample sizes varied from a few hundred to 20+ thousand participants, and covered periods from the early 1990s through to the early 2010s. Although approximately half of the studies were based on cohorts (as opposed to cross-sectional designs), nearly none were longitudinal by design and used logistic regression to report measures of prevalence. Several birth cohorts reported prevalence at various ages (e.g., Esplugues et al. 2011; Gruzieva et al. 2013; Lindgren et al. 2013). Combined, these 40 studies presented 100 effect estimates, including 45 for associations with NO_2, 30 for particulate matter generally, 12 for NO_x, and a few for each of EC, benzene, CO. Estimates of exposure from surface monitoring networks, LUR models, and dispersion models were used to estimate pollutant concentrations assigned to study participants. Twenty-five of these studies were published after 2008 (the end of the search date for the review of the HEI 2010 Traffic review).

Appendix Table 9A-5. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Wheeze in Children – Pollutants.

Reference	Study Name	Study Design	Location	Study period	Sample size	Sex	Exposure Assessment	Pollutant	Mean or median exposure[a]	Exposure Window	Effect measure	Effect Estimate (95% CI)[b]	Increment
Abidin 2014	ISAAC Malaysia	Cross sectional	Kuala Lumpur, Malaysia	2009-2009	1,893	Both	Surface monitoring	NO_2	15.8-43.9	Annual average current year	OR	**1.90 (1.02, 3.52)**	10 μg/m³
Aguilera 2013	INMA	Cohort	Multiple cities, Spain	2003-2010	2,199	Both	LUR	NO_2	17-38	Average first year	RR	1.04 (0.98, 1.12)	10 μg/m³
										Entire pregnancy		1.03 (0.96, 1.10)	
								Benzene	0.8-1.9	Average first year		0.97 (0.90, 1.05)	1 μg/m³
										Entire pregnancy		1.01 (0.94, 1.09)	
Altuğ 2013	ISAAC Eskisehir	Cross sectional	Eskişehir, Turkey	2008-2009	1,667	Male	Surface monitoring	NO_2	7.3-43.4	Annual average current year	OR	**0.66 (0.35, 1.23)** (summer)[d]	10 μg/m³
						Female						**0.92 (0.53, 1.60)** (summer)[d]	
						Male						**0.88 (0.70, 1.09)** (winter)[d]	
						Female						**1.02 (0.81, 1.28)** (winter)[d]	
Brauer 2002	PIAMA	Cohort	The Netherlands	1996-1999	2,029	Both	LUR	NO_2	25.6	Annual average	OR	1.08 (0.86, 1.34)	10.3 μg/m³
								$PM_{2.5\ abs}$	1.72			0.99 (0.79, 1.25)	0.54 $1{\times}10^{-5}$/m
								$PM_{2.5}$ mass	16.9			1.00 (0.74, 1.36)	3.2 μg/m³

Chiu 2014	ACCESS	Cohort	Boston, Massachusetts, United States	2002-2011	708	Both	LUR	BC	0.38	Entire pregnancy	OR	1.84 (1.08, 3.12)	<0.38 vs. >0.38 μg/m³
								$PM_{2.5}$ mass	11.22			2.02 (1.20, 3.40)	<11.22 vs. >11.22 μg/m³
Clifford 2018	Brisbane Respiratory	Cross sectional	Brisbane Metropolitan Area, Australia	2010-2012	468	Both	Personal exposure	PNC > 5 nm	15,000	Annual average current year	OR	1.06 (0.91, 1.25)	1,000 particles/cm³
Dell 2014	T-CHEQ	Case-control	Toronto, Canada	2006-2006	1,441	Both	LUR	NO_2	18.3-28.3	Average first year	OR	**0.98 (0.82, 1.17)**	5.7 ppb
										Annual average current year		1.05 (0.89, 1.23)	5.3 ppb
										Cumulative average		0.88 (0.74, 1.04)	3.3 ppb
Deng 2016	CCHH Changsha	Cross sectional	Changsha, China	2011-2012	2,598	Both	Surface monitoring	NO_2	46	Entire pregnancy	OR	**0.95 (0.77, 1.19)**	16 μg/m³
										Cumulative average		0.95 (0.78, 1.16)	12 μg/m³
Ebisu 2011	Yale Childhood Asthma Study	Cohort	Connecticut, United States	1996-1999	680	Both	LUR	NO_2	27-46	Average first year	OR	**1.22 (0.98, 1.52)**	9.21 ppb
Emenius 2003	BAMSE	Case-control	Stockholm, Sweden	1994-1996	500	Both	Surface monitoring	NO_2	21.8	Average first year	OR	1.60 (0.78, 3.26)	>28.4 vs. <14.8 μg/m³
												0.80 (0.43, 1.47)	21.4-28.4 vs. <14.8 μg/m³
												0.76 (0.42, 1.36)	14.8-21.4 vs. <14.8 μg/m³
Esplugues 2011	INMA Valencia	Cohort	Valencia, Spain	2003-2006	706	Both	LUR	NO_2	36.8	Entire pregnancy	OR	1.21 (0.92, 1.59)	10 μg/m³
					352		Surface monitoring			Average first year		1.04 (0.85, 1.27)	10 μg/m³
Gauderman 2005	CHS	Cohort	Multiple cities, United States	1993-2000	208	Both	Dispersion / CTM	NO_2 (freeways)	about 40	Annual average recent year	OR	1.70 (1.12, 2.58)[c]	0.64 ppb

Gehring 2010	PIAMA	Cohort	The Netherlands	1996-2006	3,184	Both	LUR	NO_2	25.4	Annual average at birth	OR	**1.01 (0.86, 1.17)**	10.4 μg/m³
								$PM_{2.5\ abs}$	1.72			**1.03 (0.88, 1.20)**	0.57 1×10^{-5}/m
								$PM_{2.5}$ mass	16.9			**1.04 (0.85, 1.28)**	3.2 μg/m³
Gruzieva 2013	BAMSE	Cohort	Stockholm County, Sweden	1994-2008	3,633	Both	Dispersion / CTM	NO_x	7.8-21.4	Average first year	OR	**1.12 (0.84, 1.49)**	46.8 μg/m³
										Cumulative average		1.07 (0.82, 1.39)	46.8 μg/m³
								PM_{10} mass	3.5-4.6	Average first year		**1.15 (0.81, 1.63)**	7.2 μg/m³
										Cumulative average		1.03 (0.81, 1.30)	7.2 μg/m³
Hirsch 1999	ISAAC Dresden	Cross sectional	Dresden, Germany	1995-1996	4,518	Both	Surface monitoring	NO_2	33.8	Annual mean	OR	**1.13 (0.93, 1.37)**	10 μg/m³
								CO	0.69			1.05 (0.93, 1.18)	0.2 mg/m³
								Benzene	4.0			1.05 (0.93, 1.18)	1 μg/m³
Janssen 2003	ISAAC Southwestern Netherlands	Cross sectional	Multiple cities, The Netherlands	1997-1998	2,071	Both	Surface monitoring	NO_2	34.8	Annual average current year	OR	**1.74 (0.99, 3.05)**	17.6 μg/m³
								BS	10.3			**1.43 (0.66, 3.07)**	9.3 μg/m³
Knibbs 2018	ACHAPS	Cross sectional	Multiple cities, Australia	2007-2008	2,601	Both	LUR	NO_2	8.8	Previous year annual average	OR	**1.25 (0.99, 1.57)**	4.03 ppb
Krämer 2000	Düsseldorf School Survey	Cross sectional	Düsseldorf, Germany	1996-1996	317	Both	Surface monitoring	NO_2	44.4-61.7	Annual average current year	OR	**1.70 (0.90, 3.19)**	10 μg/m³
Krämer 2009	GINI, LISA: Wesel	Cohort	Multiple cities, Germany	1995-2005	1,808	Both	LUR	NO_2	24.0	Cumulative average	RR	**0.64 (0.40, 1.03)**	9 μg/m³
								$PM_{2.5\ abs}$	1.6			**0.75 (0.49, 1.14)**	0.5 1×10^{-5}/m

Lindgren 2013	Scania Birth Cohort 05/11	Cohort	Scania including Malmö, Sweden	2005-2011	6,005	Both	Dispersion / CTM	NO_x	22	Annual average at birth	HR	0.7 (0.6, 0.9)	>25 vs. <15 μg/m^3
												0.8 (0.7, 1.0)	15-25 vs. <15 μg/m^3
										Cumulative average		0.8 (0.6, 1.1)	>25 vs. <15 μg/m^3
												0.8 (0.7, 0.9)	15-25 vs. <15 μg/m^3
Liu 2013	SNEC Kindergarten	Cross sectional	Liaoning Province, China	2009-2009	6,730	Both	Surface monitoring	NO_2	36.7	Three-year average at baseline	OR	**0.96 (0.82, 1.12)**	10 μg/m^3
Liu 2014	SNEC	Cross sectional	Liaoning Province, China	2009-2009	23,326	Both	Surface monitoring	NO_2	36.7	Three-year average at baseline	OR	**0.92 (0.84, 1.01)**	10 μg/m^3
Madsen 2017	MoBa	Cohort	Multiple cities, Norway	1999-2011	11,387	Both	LUR	NO_2	13.6	Entire pregnancy	RR	**1.02 (0.97, 1.07)**	10 μg/m^3
McConnell 2006	CHS	Cross sectional	California, United States	2003-2003	4,762	Both	Dispersion / CTM	NO_x	25.9	Early life exposure	OR	**1.14 (0.98, 1.32)**	28.7 ppb
Mölter 2014	MAAS	Cohort	Manchester, United Kingdom	1995-2008	373	Both	Personal exposure	NO_2	20.3-31.9	Cumulative average	OR	0.97 (0.85, 1.10)	1 μg/m^3
								PM_{10} mass	15.1-20			1.00 (0.78, 1.27)	1 μg/m^3

Mölter 2015	ESCAPE	Cohort	Multiple cities, Multiple countries	1994-2010	10,379	Both	LUR	NO_2	11.9-23.7	Cumulative average	OR	1.07 (0.84, 1.35) (age 4-5)	10 μg/m^3
									11.9-23.7			**1.00 (0.85, 1.18) (age 8-10)**	
								NO_x	21.1-39.6			1.07 (0.86, 1.33) (age 4-5)	20 μg/m^3
									21.1-39.6			**1.01 (0.87, 1.17) (age 8-10)**	
								$PM_{2.5\ abs}$	0.6-1.65			1.21 (0.88, 1.65) (age 4-5)	1 1×10^{-5}/m
									0.6-1.65			**1.19 (0.82, 1.73) (age 8-10)**	
								PM_{10} mass	15.3-25.5			0.93 (0.73, 1.19) (age 4-5)	10 μg/m^3
									15.3-25.5			**1.11 (0.70, 1.75) (age 8-10)**	
								$PM_{2.5}$ mass	7.4-17.4			1.21 (0.85, 1.71) (age 4-5)	5 μg/m^3
									7.4-17.4			**0.96 (0.62, 1.49) (age 8-10)**	
								PM_{coarse} mass	6.3-8.5			0.98 (0.83, 1.15) (age 4-5)	5 μg/m^3
									6.3-8.5			1.03 (0.74, 1.44) (age 8-10)	

Morgenstern 2007	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995-2001	2,882	Both	LUR	NO_2	35.3	Annual average at birth	OR	1.09 (0.88, 1.35) (age 1)	5.7 μg/m³
												1.09 (0.90, 1.31) (age 2)	
								$PM_{2.5\ abs}$	1.7			0.97 (0.77, 1.23) (age 1)	0.22 1×10^{-5}/m
												1.09 (0.90, 1.33) (age 2)	
								$PM_{2.5}$ mass	12.8			1.01 (0.87, 1.18) (age 1)	1.04 μg/m³
												1.10 (0.96, 1.25) (age 2)	
Morgenstern 2008	GINI, LISA: Munich	Cohort	Multiple cities, Germany	1995-2005	2,496	Both	LUR	NO_2	34.6	Annual average at current address	OR	1.03 (0.90, 1.17)	6.4 μg/m³
								$PM_{2.5\ abs}$	1.7			0.96 (0.83, 1.11)	0.2 1×10^{-5}/m
								$PM_{2.5}$ mass	11.1			**0.97 (0.91, 1.02)**	1 μg/m³
Nicolai 2003	ISAAC Munich	Cross sectional	Munich, Germany	1995-1996	about 3,000	Both	LUR	NO_2	about 45	Annual average current year	OR	1.58 (1.00, 2.48)	>57.44 vs. <57.44 μg/m³
								EC	about 9			1.41 (0.88, 2.25)	>10.73 vs. <10.73 μg/m³
								Benzene	about 5			1.65 (1.06, 2.55)	>7.27 vs. <7.27 μg/m³
Nordling 2008	BAMSE	Cohort	Stockholm County, Sweden	1994-2000	3,515	Both	Dispersion / CTM	NO_x	23.1	Average first year	OR	1.60 (1.09, 2.36)	44 μg/m³
								traffic PM_{10}	3.9			1.64 (0.90, 3.00)	6 μg/m³
Oftedal 2009	Oslo Birth Cohort	Cohort	Oslo, Norway	1992-2002	2,205	Both	Dispersion / CTM	NO_2	39.3	Annual average at birth	OR	**1.01 (0.83, 1.23)**	17.9 μg/m³

Pan 2010	Liaoning Survey 2002	Cross sectional	Liaoning Province, China	2002-2002	11,860	Both	Surface monitoring	NO_2	53	Four-year average at baseline	OR	**0.87 (0.76, 1.00)**	30 $\mu g/m^3$
Pénard-Morand 2010	French Six Cities	Cross sectional	Multiple cities, France	1999-2000	4,907	Both	Dispersion / CTM	NO_2	30.5-56.6	Annual average current year	OR	**1.37 (0.85, 2.13)**	18.5 $\mu g/m^3$
								NO_x	51.6-108.6			**1.32 (1.00, 1.89)**	52.1 $\mu g/m^3$
								CO	381.4-637.5			1.45 (1.02, 2.04)	199 $\mu g/m^3$
								PM_{10} mass	19.7-33.3			**1.31 (0.92, 1.95)**	10.5 $\mu g/m^3$
								Benzene	1.5-3.3			1.36 (1.00, 1.96)	1.1 $\mu g/m^3$
Pierse 2006	Leicestershire Respiratory Survey	Cohort	Leicestershire, United Kingdom	1998-2001	1,319	Both	Dispersion / CTM	traffic PM_{10}	1.33-1.47	Annual average current year	OR	1.42 (1.02, 1.97)	1 $\mu g/m^3$
					2,175				1.47			0.99 (0.88, 1.12) (age 1-5)	1 $\mu g/m^3$
					1,774				1.33			1.28 (1.04, 1.58) (age 4-8)	1 $\mu g/m^3$
Pikhart 1997	SAVIAH	Cross sectional	Prague, Czech Republic	1993-1994	3,334	Both	LUR	NO_2	31.2	Annual average current year	OR	**0.98 (0.82, 1.18)**	10 $\mu g/m^3$
Pikhart 2000	SAVIAH	Cross sectional	Prague, Czech Republic	1993-1994	3,045	Both	LUR	NO_2	35.8	Annual average current year	OR	1.08 (0.86, 1.36)	10 $\mu g/m^3$
Rosenlund 2009	ISAAC Rome	Cross sectional	Rome, Italy	2000-2001	1,760	Both	LUR	NO_2	45	Exposure in 2000-2001 (recent year)	OR	**1.0 (0.5, 1.7)**	14.16 $\mu g/m^3$
Ryan 2009	CCAAPS	Cohort	Cincinnati, Ohio, United States	2001-2003	624	Both	LUR	EC	0.39	Average birth to age 3	OR	1.59 (0.88, 2.87)	>0.41 vs. <0.41 $\mu g/m^3$

Sucharew 2010	CCAAPS	Cohort	Cincinnati, Ohio, United States	2001-2006	550	Both	LUR	EC	about 0.4	Exposure at child's address at birth	OR	1.29 (1.01, 1.64)	>0.375 vs. <0.375 µg/m^3
Svendsen 2012	El Paso Children's Health	Cross sectional	El Paso and Texas, United States	2001-2001	4,231	Both	LUR	NO_2	20-27	Average recent	OR	**1.45 (0.97, 2.19)** (Upland schools)[d]	10 ppb
												0.51 (0.33, 0.79) (Valley schools)[d]	
Wood 2015	ISAAC East London	Cross sectional	London, United Kingdom	2008-2011	995	Both	Dispersion / CTM	NO_2	43.5	Annual average current year	OR	**1.01 (0.97, 1.04)**	1 µg/m^3
								NO_x	75.7			**1.00 (0.99, 1.02)**	1 µg/m^3
								PM_{10} mass	23.4			**1.06 (0.91, 1.22)**	1 µg/m^3
								$PM_{2.5}$ mass	13.7			**1.16 (0.82, 1.65)**	1 µg/m^3

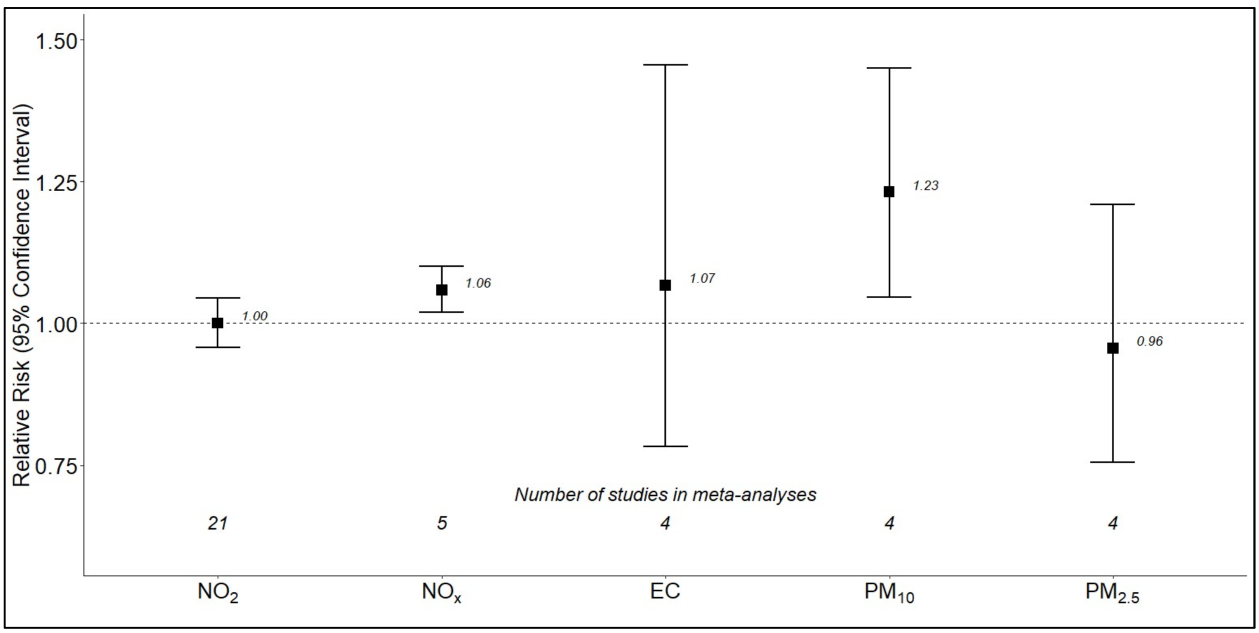
[a] Units are in the increment column.
[b] **Bold** indicates the effect estimate was included in the meta-analysis.
[c] Estimate was log transformed.
[d] Estimates were combined by a fixed effect meta-analysis before entering the random-effects model.

9A.2.2 Primary meta-analysis

Appendix Figure 9A-6 presents the effect estimates across individual pollutants for wheeze prevalence in the past 12 months among children based upon meta-analyses. In these studies, wheeze prevalence is diagnosed through parental or self-reported responses to interviewer-led questionnaires at selected ages or at selected points during study follow-up. No meta-analyses were conducted for pollutants with fewer than three estimates of association. The number of studies included in Appendix Figure 9A-6 is also fewer than the total number of selected studies (Appendix Table 9A-5) because studies were also excluded from the meta-analyses when pollutant levels were logged or categorized or when indoor pollutant levels, or exposures related to time-activity patterns were modeled.

NO_2 was by far the most studied pollutant with 21 estimates of association, while there were five or fewer estimates for each of the other four pollutants for which meta-analyses were performed. In the case of NO_2, the random-effects summary estimate describes a null association, with an RR of 1.00.

These meta-analyses show significant, positive associations between wheeze and exposure to NO_x and PM_{10}, but no significant associations with either EC or $PM_{2.5}$. Note that estimates of association summarized here as EC are based on several related but distinct metrics (i.e., BC and $PM_{2.5}$ absorbance), which the Panel combined in the analysis.



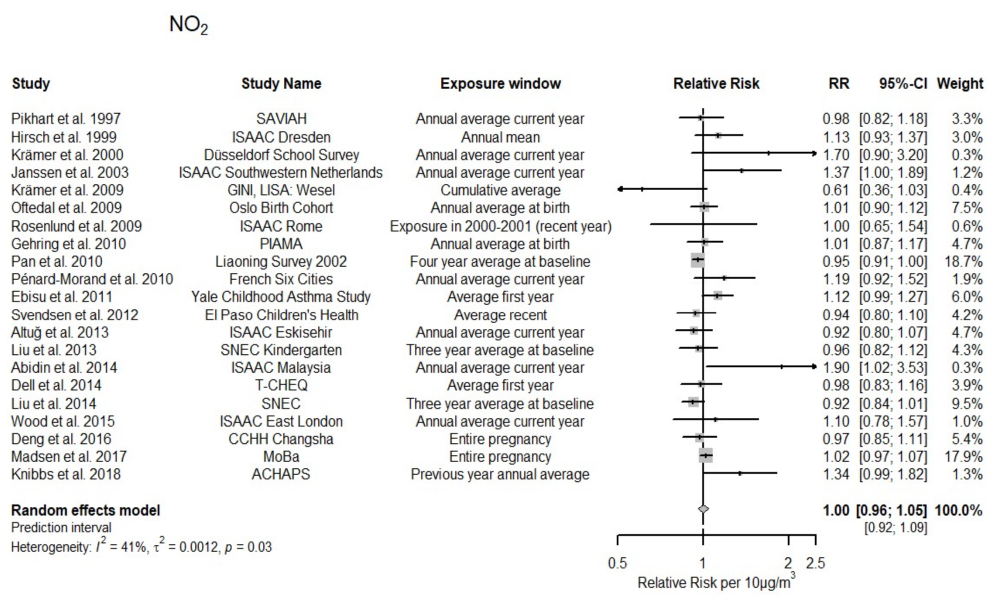
Appendix Figure 9A-6. Meta-analysis of associations between TRAP and prevalence of active wheeze in children. The following increments were used: 10 µg/m^3 for NO_2, 20 µg/m^3 for NO_x, 1 µg/m^3 for EC, 10 µg/m^3 for PM_{10} and 5 µg/m^3 for $PM_{2.5}$. Effect estimates cannot be directly compared across the different traffic-related pollutants because the selected increments do not necessarily represent the same contrast in exposure.

Appendix Figure 9A-7 presents forest plots of individual studies for selected pollutants (i.e., NO_2, NO_x, $PM_{2.5}$) for which at least three estimates of association were available (when considering the criteria described above).

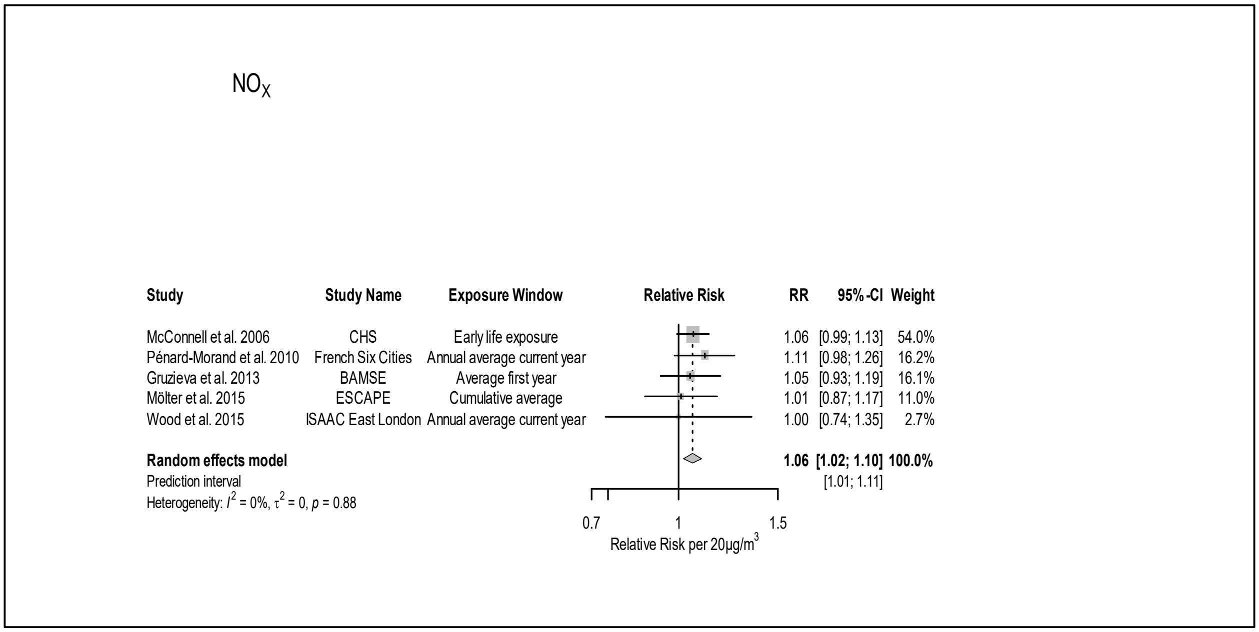
As noted above, the summary effect estimate for NO_2 was null (i.e., 1.00; 95% CI: 0.96–1.05 per increment in exposure of 10 μg/m^3). Although effect estimates from individual studies ranged from a low of 0.61 to a high of 1.90, most were in the range from ~0.95 to ~1.05 and there was evidence of only low heterogeneity (I^2 = 41%). The overall summary estimate was not influenced highly by any single study as nearly all had weights below 10% and none had a weight greater than 18.7%. Only a single study (Abidin et al. 2014) had confidence intervals that did not include unity.

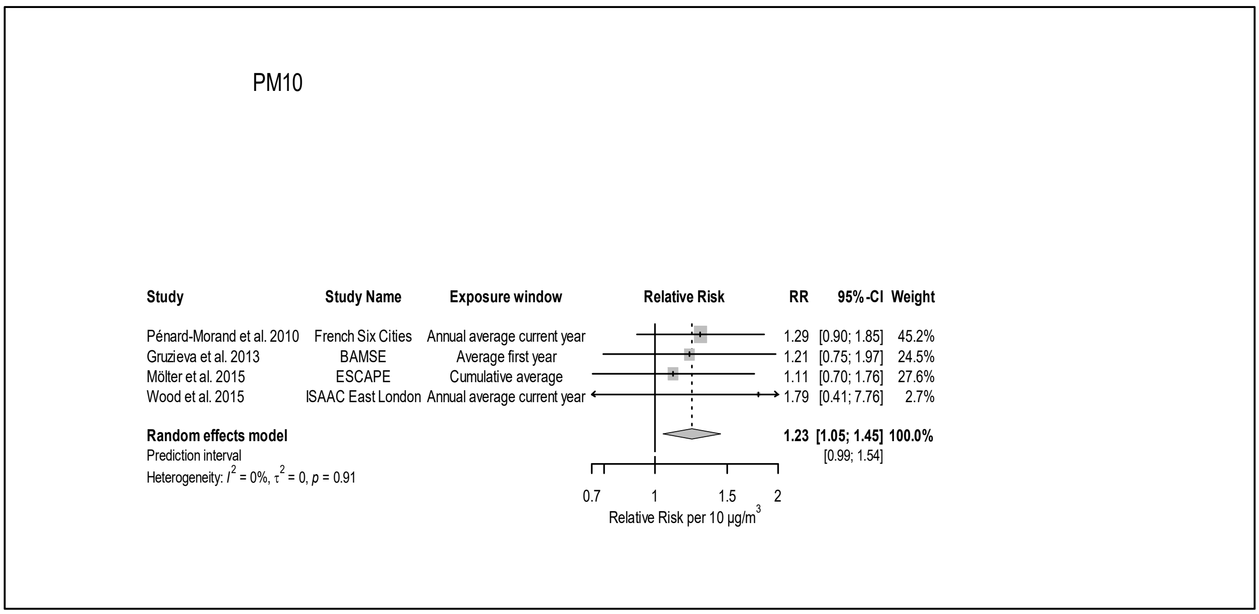
Five studies provided estimates for meta-analysis with NO_x and four provided estimates with PM_{10}. Estimates of associations between both of these pollutants and prevalence of wheeze in the past 12 months among children were all positive, but their confidence intervals all included unity. The measured heterogeneity of the associations in both cases was low (I^2 = 0%). The summary estimate was 1.06 (95% CI: 1.02–1.10) per 20 μg/m^3 increase in NO_x levels, and 1.23 (95% CI: 1.05–1.45) per 10 μg/m^3 increase in PM_{10} levels. The combined estimate for studies on associations with NO_x was influenced heavily by the estimate from the study by McConnell et al. 2006 (weight of 54%), and that for PM_{10} was influenced by that from Penard-Morand et al. 2010 (weight of 45%).

Additionally, findings from two European studies (Hirsch et al. 1999; Penard-Morand et al. 2010) suggested positive associations with exposures to CO, and those from three other European studies (Hirsch et al. 1999; Nicolai et al. 2003; Penard-Morand et al. 2010) suggested positive associations with benzene.



Appendix Figure 9A-7. Association between NO_2, NO_x, and PM_{10} and prevalence of active wheeze in children: primary meta-analysis. *Figure continues next page.*



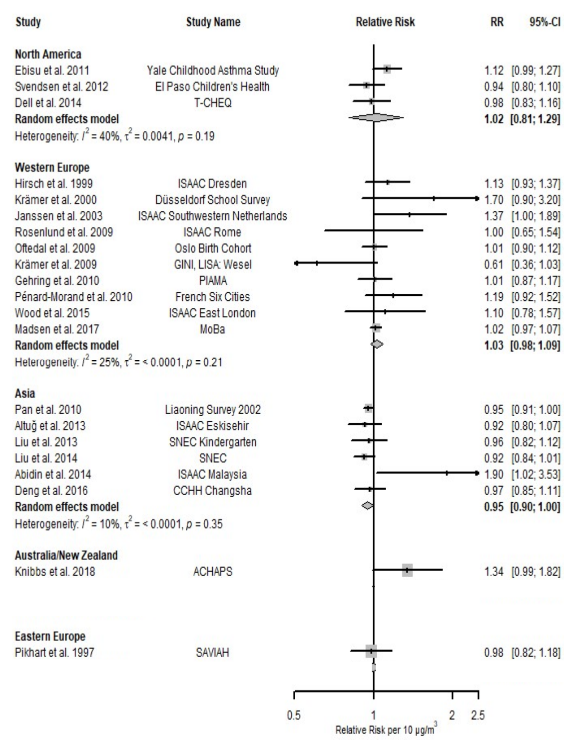


Appendix Figure 9A-7. *(Continued).*

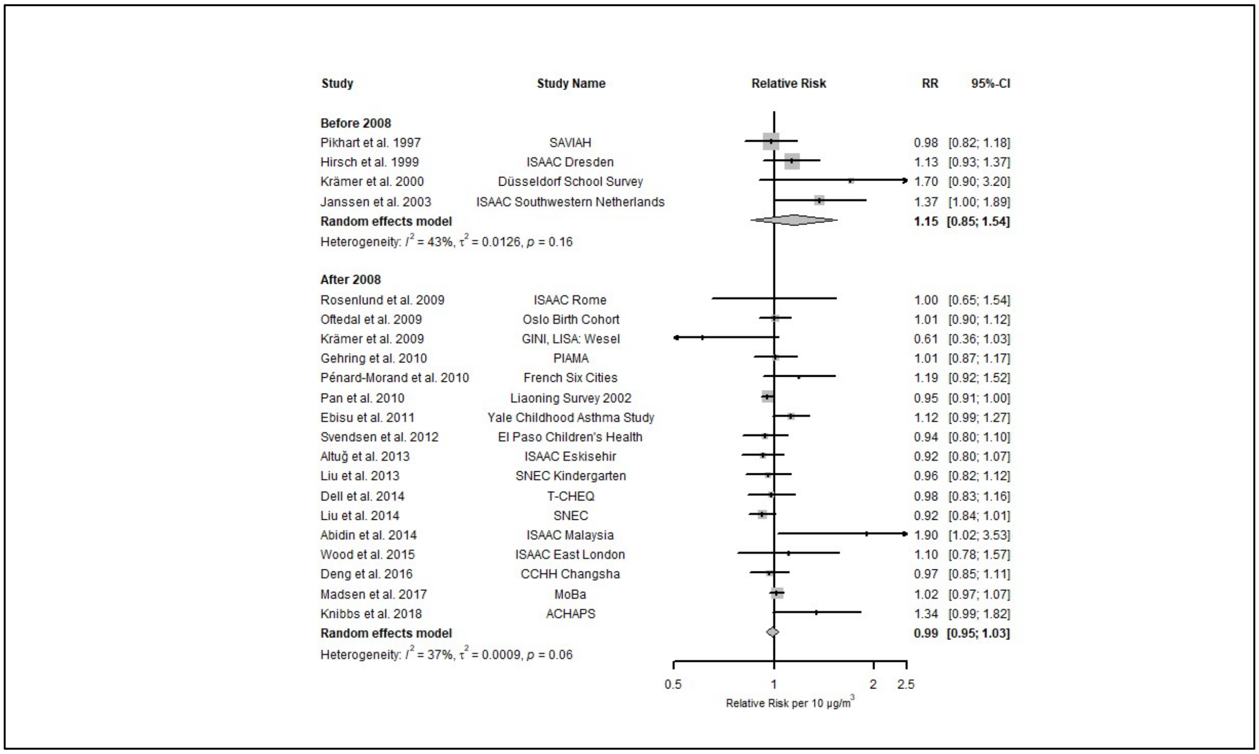
9A.2.3 Additional meta-analyses

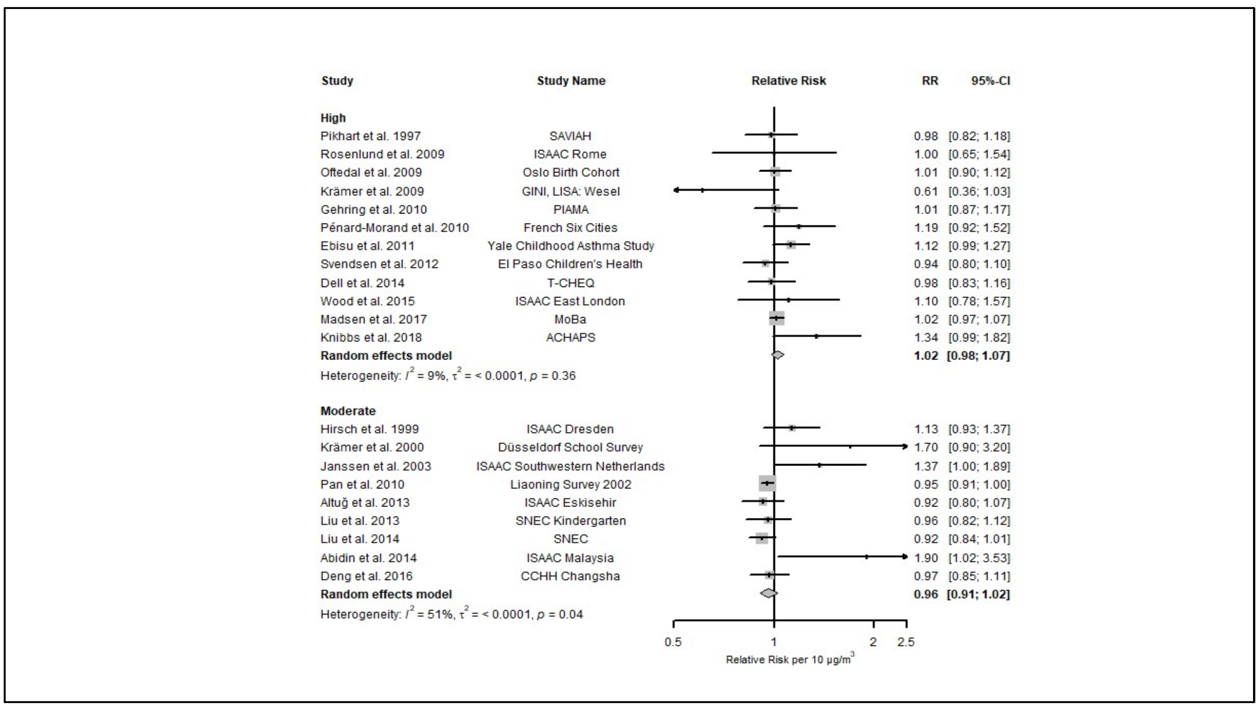
Appendix Figure 9A-8 illustrates that the heterogeneity of estimates of association with NO_2 and wheeze prevalence in the past 12 months among children were somewhat low across the three studies based in North America (I^2 = 40%), as compared to among those studies based in Western Europe (I^2 = 25%) or Asia (I^2 = 10%). In no region, however, was there evidence of statistically significant summary estimates between NO_2 and this outcome. There was an approximately equal amount of heterogeneity among those studies with NO_2 published before 2008 (I^2 = 43%) and after (I^2 = 37%). In the case of traffic specificity, there was very low heterogeneity across those studies with high specificity (I^2 = 9%), but notably higher heterogeneity among those with only moderate specificity (I^2 = 51%). Similar to all previous analyses mentioned above, however, in both cases here, confidence intervals for the random-effects summary estimates included unity. The Panel also examined stratification by study design (i.e., case-control, cohort, cross-sectional) for estimates of association with NO_2. Here, the summary estimates were all within 2% of unity, and confidence intervals all included unity. This general consistency of results across study designs suggests that the quality of outcome assessment and exposure assessment available through longitudinal vs. cross-sectional designs had no important bearings on results of these studies. Typically, one would expect that exposure and outcome assessment in a cross-sectional analysis of data from a longitudinal cohort would be of better quality than that of a similar analysis not nested in a cohort.

There were generally too few studies to consider meaningful differences in heterogeneity according to geographic region, traffic specificity, accounting for smoking, year of publication, or study design across the other pollutants.



Appendix Figure 9A-8. Association between NO_2 and prevalence of active wheeze in children: meta-analysis by region, period and by traffic specificity. *Figure continues next page.*



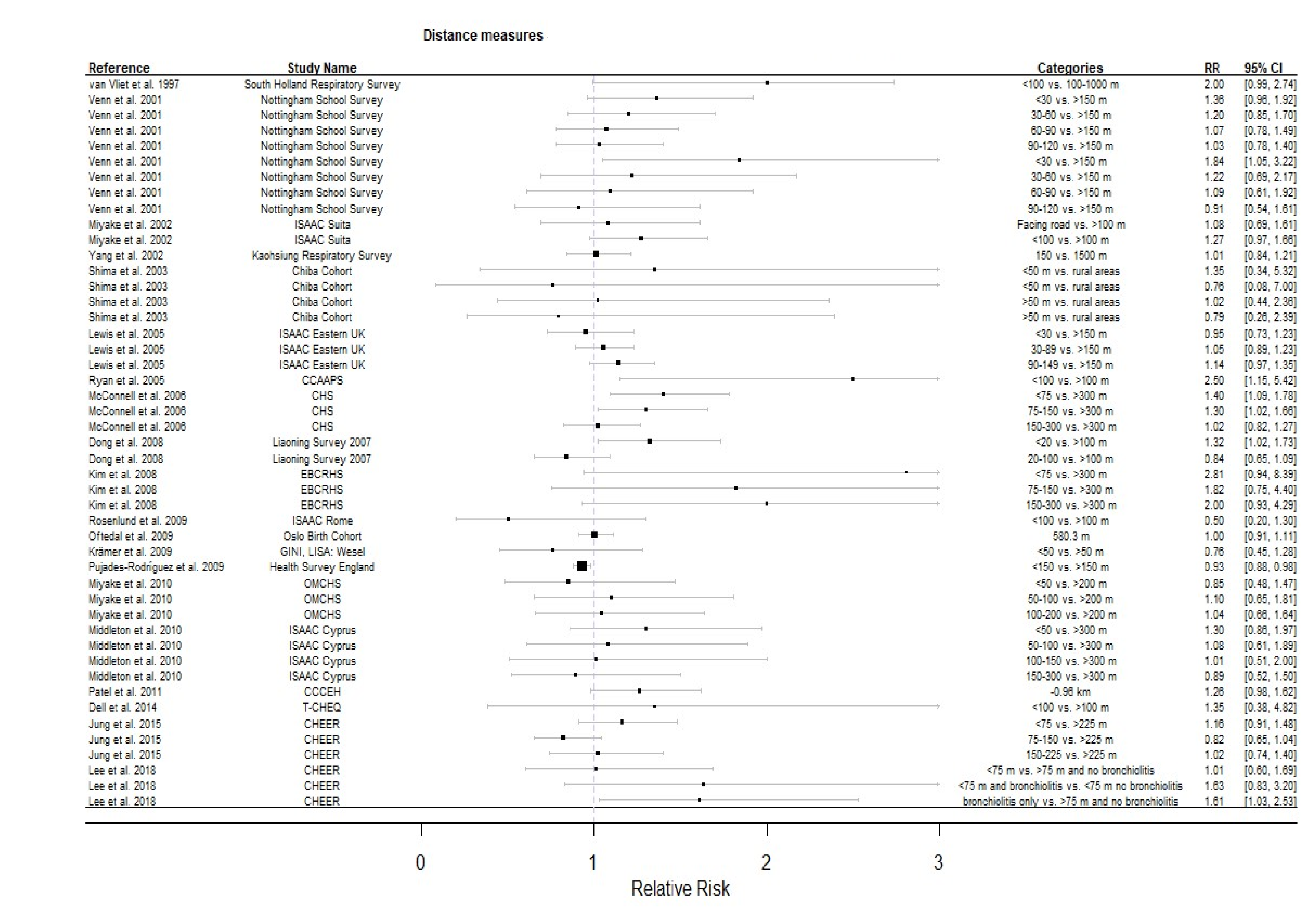


Appendix Figure 9A-8. *(Continued).*

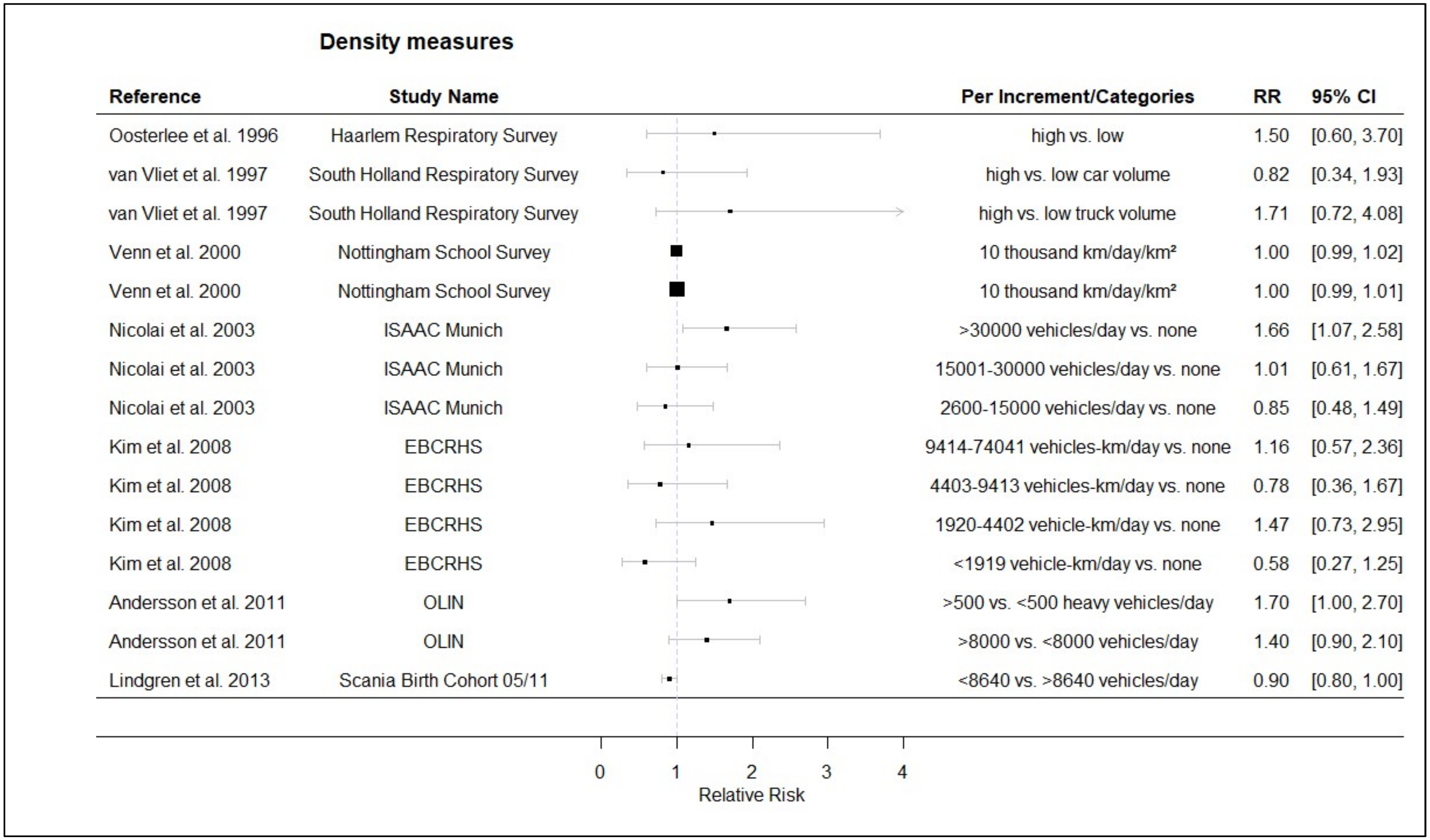
9A.2.4 Associations with indirect traffic measures

Studies on indirect traffic measures (i.e., distance and traffic density measures) were too heterogeneous in their definitions to allow meta-analysis and provided limited additional evidence of associations between TRAP exposure and the prevalence of wheeze in the past 12 months among children. Estimates of association with measures of distance to major roads were highly variable and many had large confidence intervals (Appendix Figure 9A-9). Although many studies suggested positive associations between living near roads and prevalence of active wheeze, only six of the 47 effect estimates from this body of literature reported positive associations that did not include unity. On the other hand, 11 other analyses suggested inverse associations between living near major roads and this outcome. Similarly, patterns from some studies suggested decreasing odds of this outcome associated with incremental increases in distances from major roads (e.g., Lewis et al. 2005; Miyake et al. 2002), whereas others reported the opposite (e.g., McConnell et al. 2006; Venn et al. 2001). The confidence intervals for only one of these (Pujades-Rodríguez et al. 2009a), however, did not include unity, namely RR 0.93 (95%CI: 0.88-0.98) for prevalence of wheeze within 12 months associated with living within 150m of a major road as compared to living beyond that.

In the case of density measures, only a single study (Nicolai et al. 2003) reported an effect estimate that did not include unity. These authors reported an increased RR (1.66; 95% CI: 1.07–2.58) of wheeze in the past 12 months among children with annual average counts of greater than 30,000 vehicles on streets within 50m of their home compared to those with no vehicles on streets within 50m of the home, in Munich, Germany. In their study based in Lulea, Sweden, Andersson et al. (2011) also reported increased RR (1.70; 95% CI: 1.00–2.70) of wheeze prevalence among those with volumes of heavy vehicles exceeding 500/day around the home as compared to those reporting volumes below that.



Appendix Figure 9A-9. Association of distance to major roads and traffic density with prevalence of active wheeze in children. *(Continues)*



Appendix Figure 9A-9. *(Continued).*

9A.2.5 Narrative assessment

In summary, the evidence for an association between TRAP and wheeze prevalence in the past 12 months among children is low. Overall, most studies from this moderately-sized body of literature (N~40 studies; including those that considered both exposures to pollutants and indirect exposures to TRAP) suggested null associations. Two reasons why it may be more difficult to see an association between wheeze and TRAP include: because it is a symptom for more than one disease and because of errors in reporting the symptoms. Several studies with NO_X, PM_{10}, benzene, and CO, however, did report positive associations between exposure and this outcome. It is beyond the scope of this review to speculate on why associations may have been reported with some pollutants but not with others.

It is also important to note that many studies from this body of evidence were not included in the meta-analyses for various reasons and were therefore excluded from most of the Panel's modified OHAT assessments. Specifically, of the 100 effect estimates presented in Appendix Table 9A-5, 61 were ultimately excluded from all meta-analyses. These studies still contribute insight, however, into the (lack of) associations between exposure to TRAP and risk of active wheeze among children. A large Swedish cohort study of >5,000 children (Lindgren et al. 2013) that was excluded from meta-analyses also reported null associations with active wheeze and exposure in categories to NO_x measured both cumulatively and at birth. In the case of studies with NO_2, the pollutant that was assessed the most frequently, only two of the 23 studies excluded from meta-analysis reported any associations with active wheeze among children, and one these (Gauderman et al. 2005) was based on only 208 participants. In summary, findings from such studies should not be discounted simply because they did not meet the Panel's meta-analysis inclusion criteria.

As noted above, some heterogeneity was evident across the many studies that considered NO_2, in terms of direction of association. It is unlikely, however, that potential biases would have attenuated all effect estimates towards the null given the overall number of studies and the fact that they represent diverse populations from different regions of the world.

As discussed above, studies that considered NO_x (N = 5) and PM_{10} (N = 4) suggested positive associations with this outcome, whereas studies with the three other meta-analyzed pollutants suggested no evidence of an association. Additionally, the many studies on indirect traffic measures did not provide evidence of an association between TRAP broadly and this outcome, as confidence intervals for the effect estimates for all but a handful of these studies included unity. As noted above, however, a few other studies considered associations with other pollutants (for which no meta-analysis was possible), which tended to suggest that exposures were associated with increased risk of this outcome. Therefore, based on the Panel's assessment, the evidence for the presence of an association between TRAP and prevalence of wheeze in the past 12 months among children is low.

9A.2.6 Risk of bias assessment

Appendix Table 9A-6 shows an overview of the results of the risk of bias assessment for the 39 exposure-outcome pairs that were meta-analyzed for studies on wheeze prevalence in the past 12 months in children; Appendix Table 9A-7 presents the assessment for each individual study. The purpose of the risk of bias assessment is to consider a potential risk of bias; it is not a determination of actual risk and it does not inform on the direction or magnitude of any potential bias. Most estimates of association were rated low risk of bias across all categories of assessment other than that for blinding of outcome measurement. Typically, prevalence of wheeze among children is self-reported (either by the child or by the child's parent or guardian), and the Panel rated such instances as moderate or high risk of bias. This rating reflects the fact that outcome measurements that are self-reported may be influenced by knowledge of exposures, often leading to potential over-reporting of outcomes (e.g., among those who live near major roads and who are aware of potential health risks associated with this exposure). Thirteen of the 39 exposure-outcome pairs were also rated as either moderate or high risk of bias due to potential selection bias, which relate to cases where for various reasons, participants in all exposure levels did not have equal opportunity to be included in the study.

Appendix Table 9A 6. Summary of risk of bias rating for studies on prevalence of active wheeze in children.

		Per study			Per pollutant-study pair		
Domain	**Subdomain**	**Low-risk**	**Moderate-risk**	**High-risk**	**Low-risk**	**Moderate-risk**	**High-risk**
1. Confounding	Were all important potential confounders adjusted for in the design or analysis?	20	2	3	33	2	4
	Validity of measuring of confounding factors	25	0	0	39	0	0
	Control in analysis	23	2	0	37	2	0
	Overall	18	4	3	31	4	4
2. Selection Bias	Selection of participants into the study	17	6	2	26	8	5
3. Exposure assessment	Methods used for exposure assessment	25	0	0	39	0	0
	Exposure measurement methods comparable across the range of exposure	25	0	0	39	0	0
	Change in exposure status	24	1	0	33	6	0
	Overall	24	1	0	33	6	0
4. Outcome measurements	Blinding of outcome measurements	1	23	1	1	34	4
	Validity of outcome measurements	24	1	0	38	1	0
	Outcome measurements	24	1	0	38	1	0
	Overall	1	23	1	1	34	4
5. Missing data	Missing data on outcome measures	23	2	0	36	3	0
	Missing data on exposures	23	2	0	36	3	0
	Overall	22	3	0	35	4	0
6. Selective reporting	Authors reported a priori primary and secondary study aims	25	0	0	39	0	0

Appendix Table 9A 7. Risk of bias assessment for individual studies: prevalence of active wheeze in children.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measure ment	Missing Data	Selective Reporting
Abidin 2014	ISAAC Malaysia	Low	Mod	Low	Mod	Low	Low
Altuğ 2013	ISAAC Eskisehir	Low	Low	Low	Mod	Low	Low
Dell 2014	T-CHEQ	Low	Low	Low	Mod	Low	Low
Deng 2016	CCHH Changsha	High	High	Low	Mod	Low	Low
Ebisu 2011	Yale Childhood Asthma Study	Low	Low	Low	Low	Mod	Low
Gehring 2010	PIAMA	Low	Low	Low	Mod	Low	Low
Gruzieva 2013	BAMSE (NO_x)	High	Low	Low	Mod	Low	Low
Gruzieva 2013	BAMSE (PM_{10})	High	Low	Mod	Mod	Low	Low
Hirsch 1999	ISAAC Dresden	Low	Low	Low	Mod	Low	Low
Janssen 2003	ISAAC Southwestern Netherlands	Low	Low	Low	Mod	Low	Low
Knibbs 2018	ACHAPS	Low	Mod	Low	Mod	Low	Low
Krämer 2000	Düsseldorf School Survey	Mod	Mod	Low	Mod	Low	Low
Krämer 2009	GINI, LISA: Wesel	Low	Low	Low	Mod	Mod	Low
Liu 2013	SNEC Kindergarten	Mod	Low	Low	Mod	Low	Low
Liu 2014	SNEC	Mod	Low	Low	Mod	Low	Low
Madsen 2017	MoBa	Low	Low	Low	Mod	Mod	Low
McConnell, 2006	CHS	Mod	Low	Low	Mod	Low	Low
Mölter 2015	ESCAPE	Low	Low	Mod	Mod	Low	Low
Morgenstern 2008	GINI, LISA: Munich	Low	Low	Low	Mod	Low	Low
Oftedal 2009	Oslo Birth Cohort	Low	Mod	Low	Mod	Low	Low
Pan 2010	Liaoning Survey 2002	Low	Low	Low	Mod	Low	Low
Pénard-Morand 2010	French Six Cities	Low	Mod	Low	Mod	Low	Low
Pikhart 1997	SAVIAH	High	Low	Low	Mod	Low	Low
Rosenlund 2009b	ISAAC Rome	Low	Low	Low	Mod	Low	Low
Svendsen 2012	El Paso Children's Health	Low	Mod	Low	Mod	Low	Low
Wood 2015	ISAAC East London	Low	High	Low	High	Low	Low

Mod = Moderate

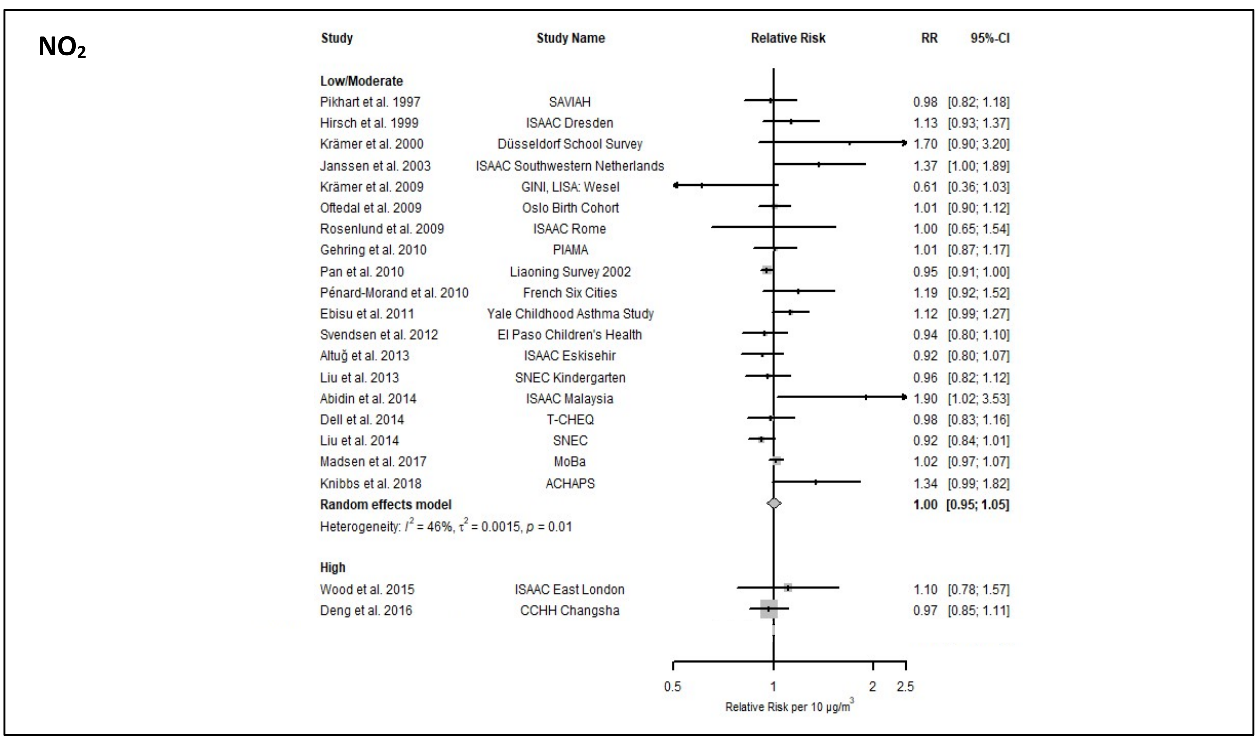
9A.2.7 Confidence assessment of the body of evidence

Appendix Table 9A-8 provides the modified OHAT assessment of the evidence for pollutants for which a meta-analysis was conducted.

The initial rating for this body of evidence was set at low, as nearly all studies considered prevalence of this outcome in cross-sectional studies. A few studies did, however, consider disease incidence based on longitudinal designs, namely cohort studies (Chiu et al. 2014; Lindgren et al. 2013; Pierse et al. 2006) and case-control studies (Emenius et al. 2003). For the downgrade factor indirectness, all studies addressed the research question directly, and therefore no downgrade was applied. Next, factors that may increase confidence (upgrades) are discussed. The Panel decided a priori not to consider the upgrading factor large magnitude of the effect.

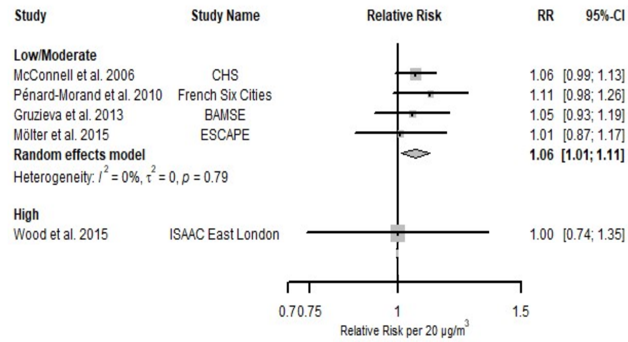
9A.2.7.1 Factors that decrease confidence

The overview of the *risk of bias* ratings for each exposure-outcome pair that was meta-analyzed was presented in Appendix Table 9A-6. Appendix Figure 9A-10 presents the results of meta-analysis stratified by low/moderate and potential high risk of bias for selection bias among studies that considered exposures to NO_2, NO_x, and PM_{10}. Here the Panel found essentially null associations in all but one case (i.e., low/moderate risk of bias studies that considered NO_x), suggesting that neither the potential presence nor absence of selection bias had a major impact on the reported patterns. Overall, the risk of bias assessment does not suggest a need to downgrade the confidence in the evidence for the pollutants included in the meta-analysis.

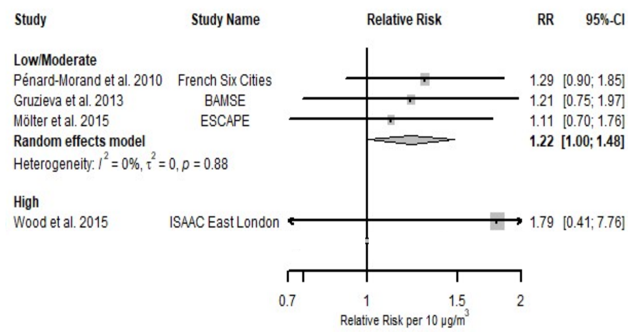


Appendix Figure 9A-10. Association between NO_2, NO_x, and PM_{10} and prevalence of active wheeze in children: meta-analysis by risk of bias selection bias. *Figure continues next page.*

NO_x



PM_{10}



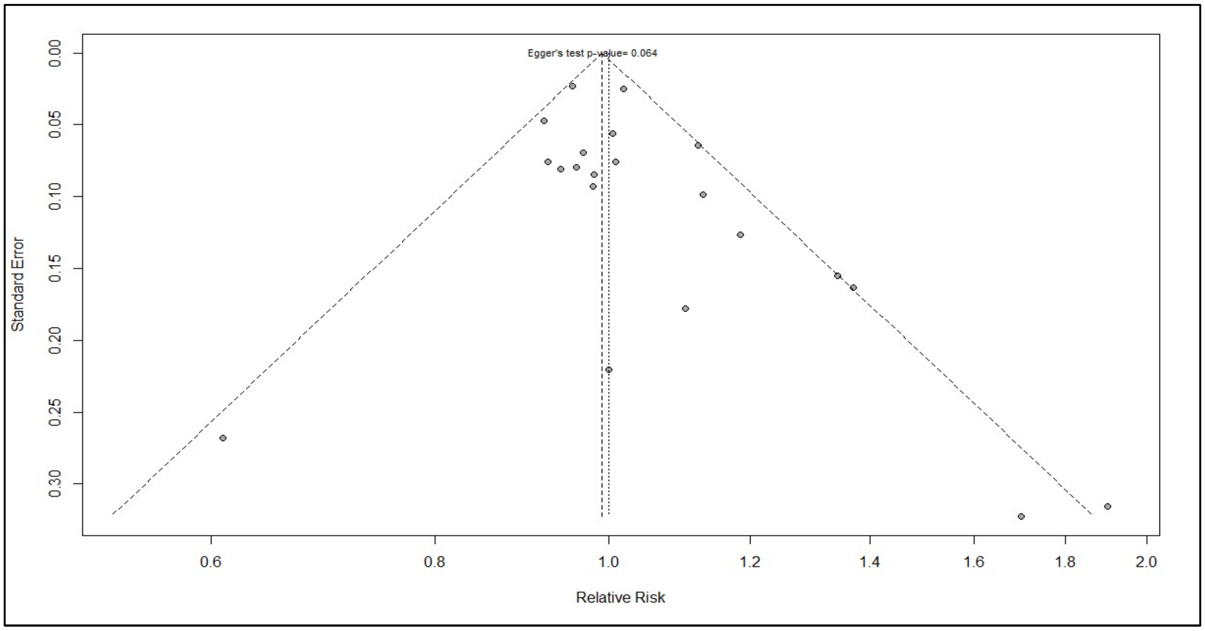
Appendix Figure 9A-10. *(Continued).*

As there appeared to be no real patterns of *inconsistency*, no downgrade was applied. The Panel found generally only low to moderate levels of heterogeneity among effect estimates across each of the pollutants that were meta-analyzed for prevalence of wheeze in the past 12 months among children. Although both positive and negative estimates of association were reported here, confidence intervals of most estimates included unity, and the magnitude of effect sizes were for the most part relatively low.

Regarding the downgrading factor *imprecision*, only for NO_2 was the overall sample size (number of people) larger than the minimum sample size specified in the protocol. The confidence intervals for EC and $PM_{2.5}$ were wide, and clearly included unity. The evidence for those two pollutants was therefore downgraded. The Panel did not downgrade the other pollutants for various reasons. NO_2 was not downgraded because the confidence interval was considered narrow according to the protocol, although it included unity. In addition, the NO_x and PM_{10} confidence interval did not included unity.

About *publication bias*, there were more than 10 studies and hence a funnel plot and Egger test were produced for NO_2. The funnel plot and the Egger test did not suggest asymmetry (Appendix Figure 9A 11) although the Egger test was almost significant (p-value = 0.064). Most effect estimates were clustered together, but the funnel plot did include one highly negative association (Kramer et al. 2010) and two highly positive associations (Abidin et al. 2014; Kramer et al. 2000).

Also, additional analyses on the number of studies reporting positive, negative, and no effect over time suggest no bias (Additional Materials to Chapter 14). Due to the small number of studies, it was not possible to assess publication bias for studies on associations with the other pollutants meta-analyzed. As there was no evidence of publication bias, the Panel chose to not downgrade the evidence for any pollutants.



Appendix Figure 9A-11. Funnel Plot for NO_2 and prevalence of active wheeze in children. The vertical lines in the funnel plots represent the pooled fixed and random effect estimates. The vertical dashed line in the middle of the funnel shows the fixed effect estimate. As the Panel applied a random-effects model, the funnel plot also presents the random-effects estimate with the dotted line.

9A.2.7.2 Factors that increase confidence

Only one study (Knibbs et al. 2018) provided evidence of a plausible *monotonic exposure-response function* and hence an upgrade was not applied. The Panel found no clear indication that *residual confounding or other factors* are likely to lead to an underestimation of the associations, thus an upgrade was not considered appropriate. Regarding *consistency*, the Panel found generally consistent null associations between this outcome and exposure to NO_2 overall and across geographic regions. There was suggestion, however, of a positive association among the pooled studies conducted before 2008, but the summary estimate was not statistically significant (i.e., RR = 1.15; 95% CI: 0.85–1.54). Given the absence of any evidence of associations here, the Panel decided not to upgrade the evidence for NO_2. There were too few studies on NO_x, EC, PM_{10}, or $PM_{2.5}$ for the Panel to assess consistency adequately across regions of period of publication.

9A.2.7.3 Evaluation of confidence for combined measures of TRAP

Confidence assessments were low (NO_2, NO_X, PM_{10}) or very low (EC, $PM_{2.5}$). Since the highest rating was low, the Panel's assessment of confidence in the quality of the body of evidence of TRAP and prevalence of active wheeze among children is low. The Panel did not see any reason to downgrade or upgrade because of traffic specificity or studies not entering a meta-analysis.

9A.2.8 Overall assessment

Since the level of confidence in the evidence was considered low in the narrative assessment and the confidence in the body of evidence was low, the overall confidence assessment of TRAP and prevalence of active wheeze among children is low.

Appendix Table 9A-8. Confidence rating in the quality of the body of evidence for traffic-related air pollutants and prevalence of active wheeze in children[a].

	High ++++ **Moderate +++** **Low ++** **Very low +**		**Factors decreasing confidence "0" if no concern; "-" if serious concern to downgrade confidence**				**Factors increasing confidence "0" if not present; "+" if sufficient to upgrade confidence**			
Pollutant	**Study design**	**Initial confidence rating** (# studies)	Risk of Bias	Unexplained inconsistency	Imprecision	Publication bias	Monotonic exposure-response	Consideration of residual confounding	Consistency across populations	**Final confidence rating**
NO_2	Cross-sectional	++ (N = 21)	0	0	0	0	0	0	0	+ (Low)
	Rationale	Nearly all studies were cross-sectional, and only a few were longitudinal.	Only 4 studies with high RoB.	Low heterogeneity (I^2 = 41%). No clear patterns of inconsistency.	Sample size met and confidence interval includes unity, but confidence interval precise.	No evidence found in plot and test.	Very limited evidence of plausible shape of ERF (Knibbs 2018).	Confounding in both directions possible.	No evidence of associations in any region.	
NO_X	Cross-sectional	++ (N = 5)	0	0	0	0	0	0	0	++ (Low)
	Rationale	Nearly all studies were cross-sectional, and only a few were longitudinal.	Only 2/5 studies with high RoB.	No heterogeneity (I^2 = 0%). No clear patterns of inconsistency.	Sample size not met, but confidence interval does not include unity.	No formal evaluation possible, no clear evidence.	No evidence of plausible shape of ERF	Confounding in both directions possible.	Too few studies to assess consistency.	
EC	Cross-sectional	++ (N = 4)	0	0	-	0	0	0	0	+ (Very low)
	Rationale	Nearly all studies were cross-sectional, and only a few were longitudinal.	No studies with high RoB	Low heterogeneity (I^2 = 4%). No clear patterns of inconsistency.	Sample size not met and confidence interval wide and clearly includes unity.	No formal evaluation possible, no clear evidence.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

PM_{10}	Cross-sectional	++ (N = 4)	0	0	0	0	0	0	0	++ (Low)
	Rationale	Nearly all studies were cross-sectional, and only a few were longitudinal	2/4 studies with high RoB, but no evidence of difference in effect estimates between these.	No heterogeneity (I^2 = 0%). No clear patterns of inconsistency.	Sample size not met, but confidence interval does not include unity.	No formal evaluation possible, no clear evidence.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	
$PM_{2.5}$	Cross-sectional	++ (N = 4)	0	0	-	0	0	0	0	+ (Very low)
	Rationale	Only one was longitudinal	Only 1 study with high RoB.	No heterogeneity (I^2 = 0%). No clear patterns of inconsistency.	Sample size not met and confidence interval wide and clearly includes unity.	No formal evaluation possible, no clear evidence.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	Too few studies to assess consistency.	

[a] The downgrading factor indirectness and the upgrading factor large magnitude of effect were not considered further.

9A.3 Prevalence of wheeze ever and asthma-like symptoms in adults

9A.3.1 Study selection and description

Only two studies reported associations between TRAP and prevalence of wheeze ever in adults whereas one additional study used traffic density as an indirect traffic measure. Appendix Table 9A-9 shows all the identified studies including effect estimates. Of the two studies assessing air pollutants, one was conducted in Estonia (Pindus et al. 2016) and the other in the Netherlands (Doiron et al. 2017). The study on traffic density was conducted in the Netherlands (Oosterlee et al. 1996), and it was the only one conducted before 2008.

The studies were based on a cross-sectional design with a limited sample size for both the study in Estonia (Pindus et al. 2016) and the traffic study in the Netherlands (Oosterlee et al. 1996), whereas the investigation of the Lifelines project included several cities in the Netherlands for a total of more than 50,000 individuals (Doiron et al. 2017). Pollutant exposure assessment was based on LUR or dispersion models. Cases were identified using a self-administered questionnaire. Note that the large study in the Netherlands (Doiron et al. 2017) included another cohort (UK Biobank), but the latter cohort did not meet the exposure framework, hence only the Lifelines estimate was included. The study was able to correct for several individual confounding factors.

For wheeze ever and all the individual pollutants, only a few effect estimates were available, and no meta-analysis was conducted. In fact, only two studies were available for PM_{10} exposure as a continuous variable and lifetime wheeze (Doiron et al. 2017; Pindus et al. 2016) indicating, the first one, an increased RR with large confidence intervals, and the second one a strong effect with a narrower confidence interval (RR 1.20, 95% CI 1.02–1.41). Doiron et al. (2017) provided also results for NO_2, $PM_{2.5}$, and PM_{coarse} with statistically significant increased effect estimates for all but PM_{coarse}.

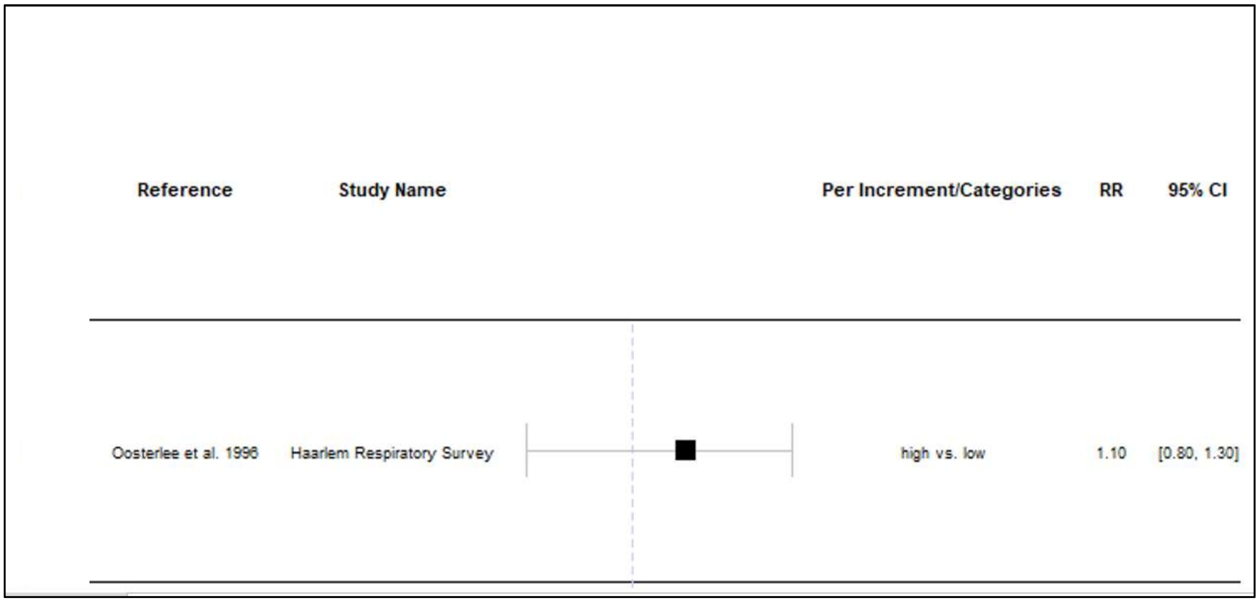
Appendix Table 9A-9. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Wheeze Ever in Adults – Pollutants.

Reference	Study Name	Location	Study period	Sample size	Sex	Exposure Assessment	Pollutant	Mean or median exposure[a]	Effect Estimate (95% CI)[b]	Increment
Doiron 2017	Lifelines	Northern part, The Netherlands	2006-2013	52,062	Both	LUR	NO_2	16.48	1.11 (1.05, 1.18)	10 μg/m^3
							PM_{10} mass	24.23	1.20 (1.02, 1.41)	5 μg/m^3
							PM_{coarse} mass	8.68	1.15 (0.90, 1.46)	5 μg/m^3
							$PM_{2.5}$ mass	15.55	1.51 (1.12, 2.03)	5 μg/m^3
Pindus 2016	RHINE Tartu	Tartu, Estonia	2011-2012	905	Both	Dispersion / CTM	traffic PM_{10}	3.3	1.06 (0.79, 1.45)	2.2 μg/m^3

[a] Units are in the increment column.
[b] The effect estimate in all studies was odds ratio.

9A.3.2 Associations with indirect traffic measures

There was only one study (Oosterlee et al. 1996) that addressed traffic density from busy roads and prevalence of lifetime wheeze. Appendix Figure 9A-12 reports the results, and no evidence of an association was found.



Appendix Figure 9A-12. Association of traffic density with prevalence of wheeze ever in adults.

9A.3.3 Narrative and overall assessment

The evidence on TRAP and wheeze ever in adults is low, as the main results refer only to a few observations. There was, however, a strong association in the large study in the Netherlands (Doiron et al. 2017) for both NO_2 and PM_{10}, as already seen for prevalence of asthma ever. Ultimately, the evidence is still weak. No modified OHAT assessment was undertaken because of the lack of studies; therefore, the overall assessment was also low.

9A.4 Prevalence of active wheeze and asthma-like symptoms in adults

9A.4.1 Study selection and description

A total of seven studies, all conducted in Europe but one in Australia (Lazarevic et al. 2015), investigated the occurrence of active wheeze (wheeze in the last 12 months) in relation to traffic-related air pollutants, all studies were conducted after 2008. There were four cross-sectional studies assessing prevalence, one case-control study (Lindgren et al. 2010) based on prevalent cases, one cohort — the multicenter ECHRS study in Europe (Jacquemin et al. 2009) — evaluating incidence of wheeze in the last 12 months, and the SAPALDIA study in Switzerland (Schindler et al. 2009) evaluating prevalence of current wheeze in relation to changes of air pollution exposure during the 11 years of follow-up (Appendix Table 9A-10). All the studies included several thousand participants (minimum around 1700 participants for the study in Estonia (Orru et al. 2009), maximum 27,000 participants — all females — for the study in Australia (Lazarevic et al. 2015). Both dispersion models and LUR were used for exposure assessment.

Few results with a continuous exposure were available for active wheeze in adults. For NO_2, an increased risk of wheeze incidence (1.28, 95% CI 1.0–1.62 per 10 μg/m^3) was seen in the ECHRS study (Jacquemin et al. 2009). An increased prevalence was detected in the Australian investigation (Lazarevic et al. 2015) in relation to NO_2, which did not reach statistical significance. No association with NO_2 was reported in a study from UK (Pujades-Rodríguez et al. 2009b) when the exposure was categorized. Similarly, no clear gradient was detected in two Swedish reports with the analyses based on categories of NO_x (Lindgren et al. 2009, 2010). The association with PM_{10} was also weak in two investigations in Estonia and Switzerland (Orru et al. 2009; Schindler et al. 2009) as they reported increased risk but imprecise effect estimates.

9A.4.2 Associations with indirect traffic measures

Appendix Table 9A-11 lists the studies with indirect traffic measures for prevalence of active wheeze. The indirect traffic measures were too heterogeneous in their definitions and did not provide estimates useful for meta-analysis. Estimates of association with distance measures provided limited information for the overall evidence assessment, as positive and null associations were reported. For example, the two largest studies (Bayer-Oglesby et al. 2006; Lazarevic et al. 2015) provide no evidence of an association with distance from busy roads. Note that Lazarevic et al. 2015 presented only log transformed results.

9A.4.3 Narrative and overall assessment

The evidence on TRAP and active wheeze in adults is low as only some evidence exists for current wheeze in relation to NO_2 for studies in Europe (Jacquemin et al. 2009) and in Australia (Lazarevic et al. 2015) but such evidence is still weak. No modified OHAT assessment was undertaken because of the lack of studies; therefore, the overall confidence assessment was also low.

Appendix Table 9A-10. Key Study Characteristics of Articles in the Systematic Review for Prevalence of Active Wheeze in Adults – Pollutants.

Reference	Study Name	Study Design	Location	Study period	Sample size	Sex	Exposure Assessment	Pollutant	Mean or median exposure[a]	Effect Estimate (95% CI)[b]	Increment
Jacquemin 2009	ECRHS	Cohort	Multiple cities, Multiple countries	1991-2001	4,185	Both	LUR	NO_2	27.7	1.28 (1.00, 1.62)	10 μg/m³
Lazarevic 2015	ALSWH	Cross sectional	Australia	2006-2011	26,991	Female	LUR	NO_2	5	1.05 (0.96, 1.15)	3.4 ppb
Lindgren 2009	Scania Respiratory Survey 2000	Cross sectional	Scania including Malmö, Sweden	2000-2000	9,316	Both	Dispersion / CTM	NOx	13.5	1.21 (0.99, 1.46)	>19 vs. <8 μg/m³
										0.90 (0.74, 1.11)	14-19 vs. <8 μg/m³
										0.94 (0.77, 1.15)	11-14 vs. <8 μg/m³
										0.97 (0.80, 1.19)	8-11 vs. <8 μg/m³
Lindgren 2010	Scania Health Survey 2004	Case-control	Scania, Sweden	2004-2005	2,858	Both	Dispersion / CTM	NOx	12	1.1 (0.60, 1.9)	>19 vs. <8 μg/m³
										0.99 (0.60, 1.6)	14-19 vs. <8 μg/m³
										0.97 (0.68, 1.39)	11-14 vs. <8 μg/m³
										1 (0.74, 1.49)	8-11 vs. <8 μg/m³
Orru 2009	RHINE Tartu	Cross sectional	Tartu, Estonia	2000-2001	1,684	Both	Dispersion / CTM	traffic PM_{10}	0.10	1.99 (0.36, 11.83)	1 μg/m³
Pujades-Rodríguez 2009b	Nottingham Cohort	Cross sectional	Nottingham, United Kingdom	1991-1991	2,599	Both	Dispersion / CTM	NO_2	34.5	0.88 (0.66, 1.19)	>36.79 μg/m³
										0.84 (0.63, 1.14)	34.73 – 36.79 μg/m³
										0.86 (0.63, 1.16)	34.23 – 34.73 μg/m³
										1.03 (0.76, 1.39)	33.92 – 34.23 μg/m³

Schindler 2009	SAPALDIA	Cohort	Multiple cities, Switzerland	1991-2002	7,019	Both	Dispersion / CTM	PM_{10} mass	11-45	1.01 (0.74, 1.39) (new)	-10 μg/m³
										0.50 (0.32, 0.80) (persistent)	-10 μg/m³

[a] Units are in the increment column.

[b] The effect estimate in all studies was odds ratio.

Appendix Table 9A-11. Key Study Characteristics of Articles Included in the Systematic Review for Prevalence of Active Wheeze in Adults – Indirect Traffic Measures.

Reference	Study Name	Study Design	Location	Study period	Sample size	Age	Sex	Traffic measure	Effect Estimate (95% CI)[a]	Increment
Bayer-Oglesby 2006	SAPALDIA	Cross sectional	Multiple cities, Switzerland	1991-2002	12,999	Adults (18-64)	Both	Distance	0.94 (0.78, 1.12)	<20 vs. >20 m
Bowatte 2017a	TAHS	Cohort	Tasmania, Australia	2005-2012	709	Adults (18-64)	Both	Distance	1.61 (1.19, 2.19)	<200 vs. >200 m
Bowatte 2017b		Cross-sectional		2005-2005	1,367				1.38 (1.06, 1.80)	<200 vs. >200 m
Garshick 2003	ATS US Veterans	Cross sectional	Massachusetts, United States	1988-1992	2,243	Adults (18+)	Male	Distance	1.31 (1.00, 1.71)	<50 vs. >50 m
Hazenkamp-von Arx 2011	MfMU	Cross sectional	Multiple cities, Switzerland	2005-2005	1,581	Adults (18+)	Both	Distance	3.10 (1.27, 7.55)	<200 vs. >200 m
Lazarevic 2015	ALSWH	Cross sectional	Australia	2006-2011	26,991	Adults (18+)	Female	Distance	1.00 (0.98, 1.03)[b]	1 km
Lindgren 2010	Scania Health Survey 2004	Case-control	Scania, Sweden	2004-2005	2,856	Adults (18-64)	Both	Density	2.7 (1.3, 5.5)	>10 vs. 0 vehicles/minute
									0.81 (0.38, 1.7)	6-10 vs. 0 vehicles/minute
									1.1 (0.8, 1.7)	2-5 vs. 0 vehicles/minute
									1.2 (0.92, 1.7)	<2 vs. 0 vehicles/minute
Nitta 1993	Tokyo Respiratory Survey	Cross sectional	Tokyo, Japan	1979	1,517	Adults (18-64)	Female	Distance	2.75 (1.65, 4.73)	<20 vs. 20-150 m
				1982	2,413				1.52 (0.91, 2.55)	<20 vs. 50-150 m
									1.17 (0.69, 2.00)	20-50 vs. 50-150 m
				1983	2,389				0.94 (0.61, 1.42)	<20 vs. 20-150 m

Nuvolone 2011	Tuscany Health Survey	Cross sectional	Pisa, Tuscany, Italy	1991-1993	2,062	Children (<18) and Adults (18+)	Female	Distance	1.32 (0.76, 2.28)	<100 vs. 250-800 m
							Male		1.76 (1.08, 2.87)	<100 vs. 250-800 m
							Female		0.77 (0.42, 1.42)	100-250 vs. 250-800 m
							Male		1.54 (0.94, 2.53)	100-250 vs. 250-800 m
Oosterlee 1996	Haarlem Respiratory Survey	Cross sectional	Haarlem, The Netherlands	1991-1991	1,108	Adults (18-64)	Both	Density	1.1 (0.6, 1.8)	high vs. low
Pujades-Rodríguez 2009a	Nottingham Cohort	Cross sectional	Nottingham, United Kingdom	1991-1991	2,599	Adults (18+)	Both	Distance	1.60 (0.96, 2.68)	<50 vs. >100-150 m
									1.0 (0.61, 1.66)	50-100 vs. 100-150 m
Venn 2005	Jimma Respiratory Survey	Cohort	Jimma, Ethiopia	1996-1996	7,609	Adults (18-64)	Both	Distance	1.83 (0.78, 4.23)	<30 vs. 120-150 m
									1.59 (0.65, 3.90)	30-60 vs. >120-150 m
									1.65 (0.65, 4.10)	60-90 vs. >120-150 m
									0.96 (0.30, 2.96)	90-120 vs. >120-150 m

[a] The effect estimate in all studies was odds ratio.
[b] Estimate was log transformed.

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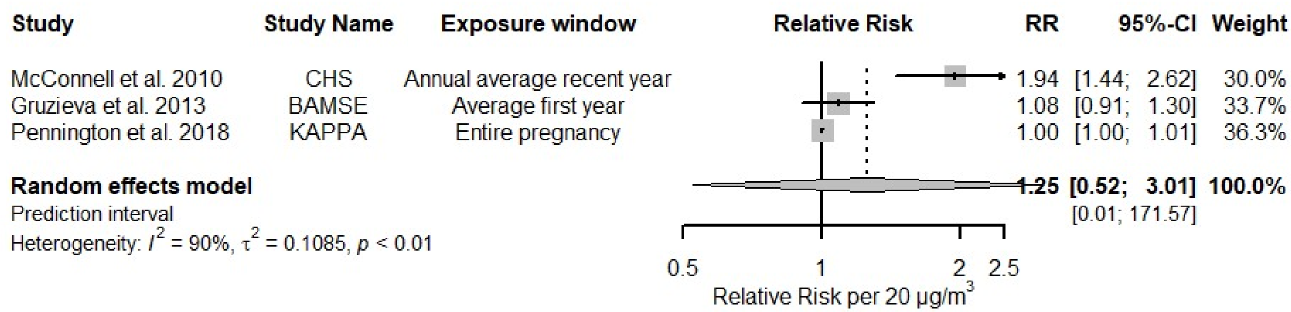
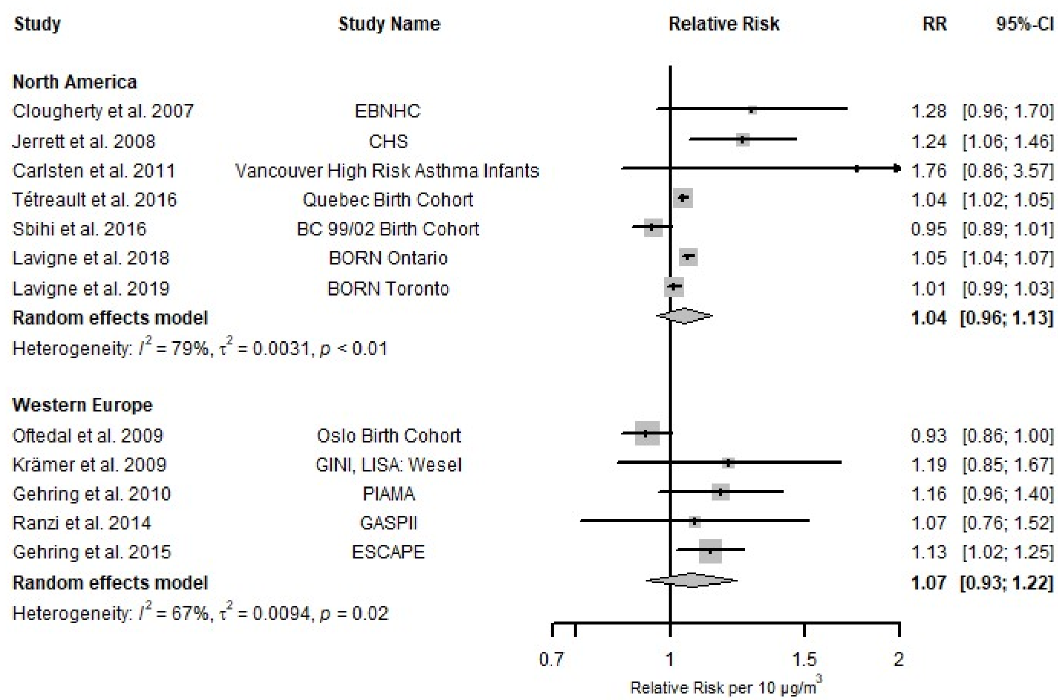
Chapter 9: Traffic-Related Air Pollution and Respiratory Outcomes

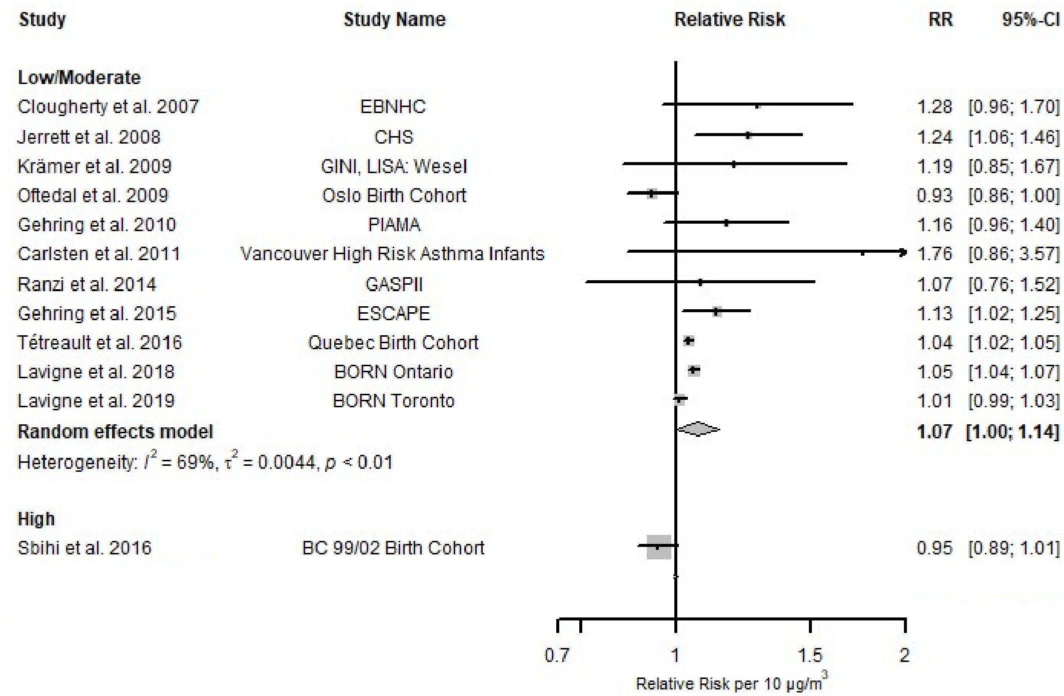
Appendices B and C



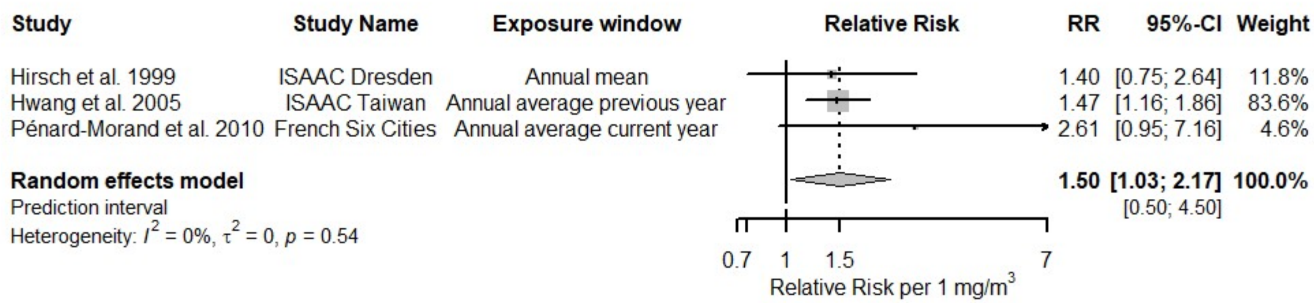
Appendix Figure 9B-1. Association between NO_x and asthma onset in children: meta-analysis.



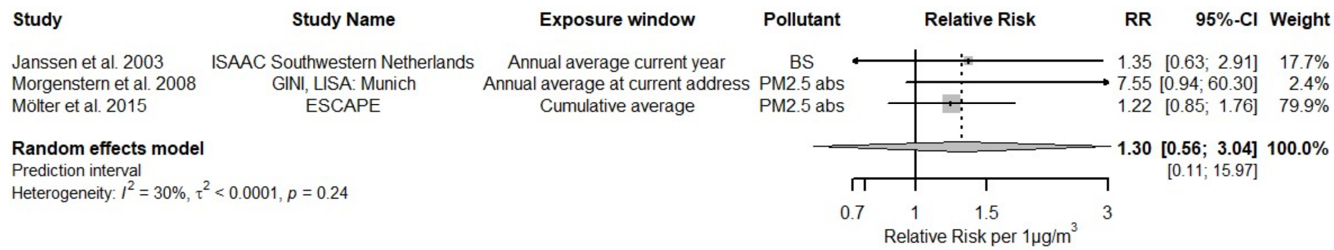
Appendix Figure 9B-2. Association between NO_2 and asthma onset in children: meta-analysis by region.



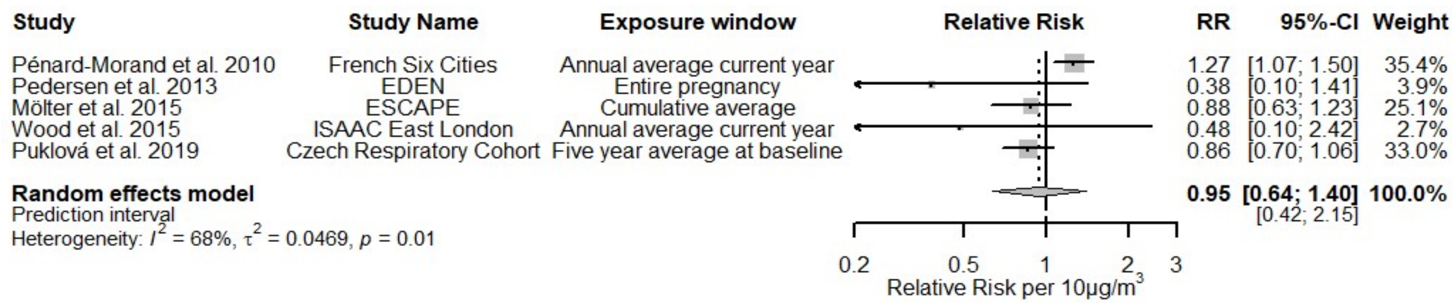
Appendix Figure 9B-3. Association between NO_2 and asthma onset in children: meta-analysis by risk of bias confounding.



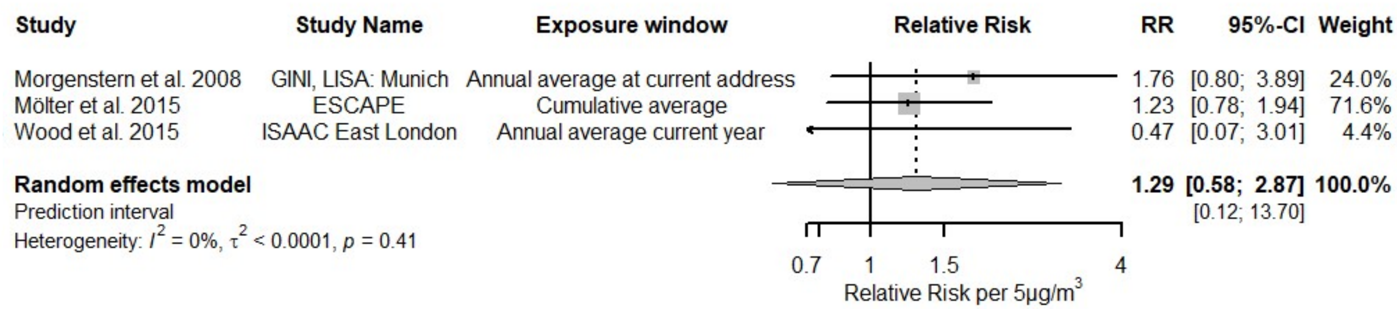
Appendix Figure 9B-4. Association between CO and prevalence of asthma ever in children: meta-analysis.



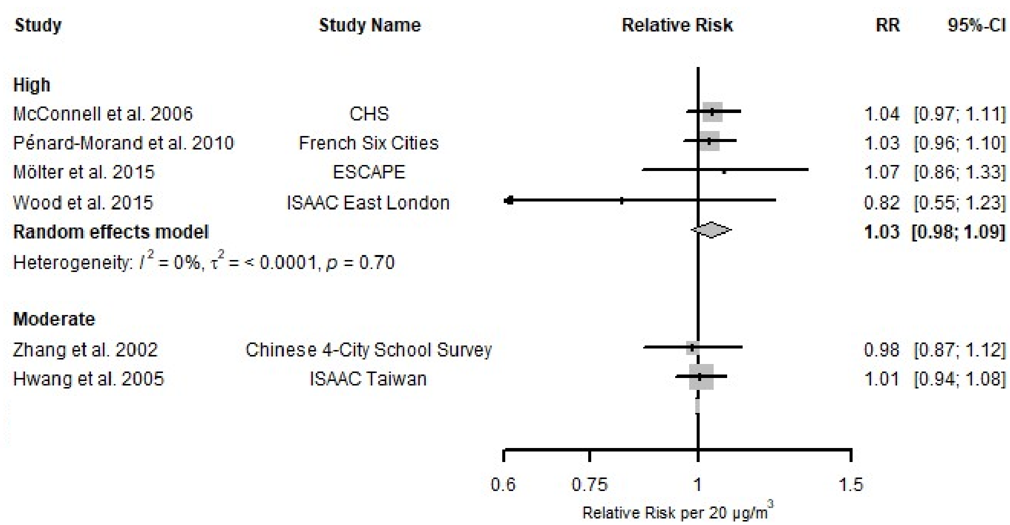
Appendix Figure 9B-5. Association between EC and prevalence of asthma ever in children: meta-analysis.



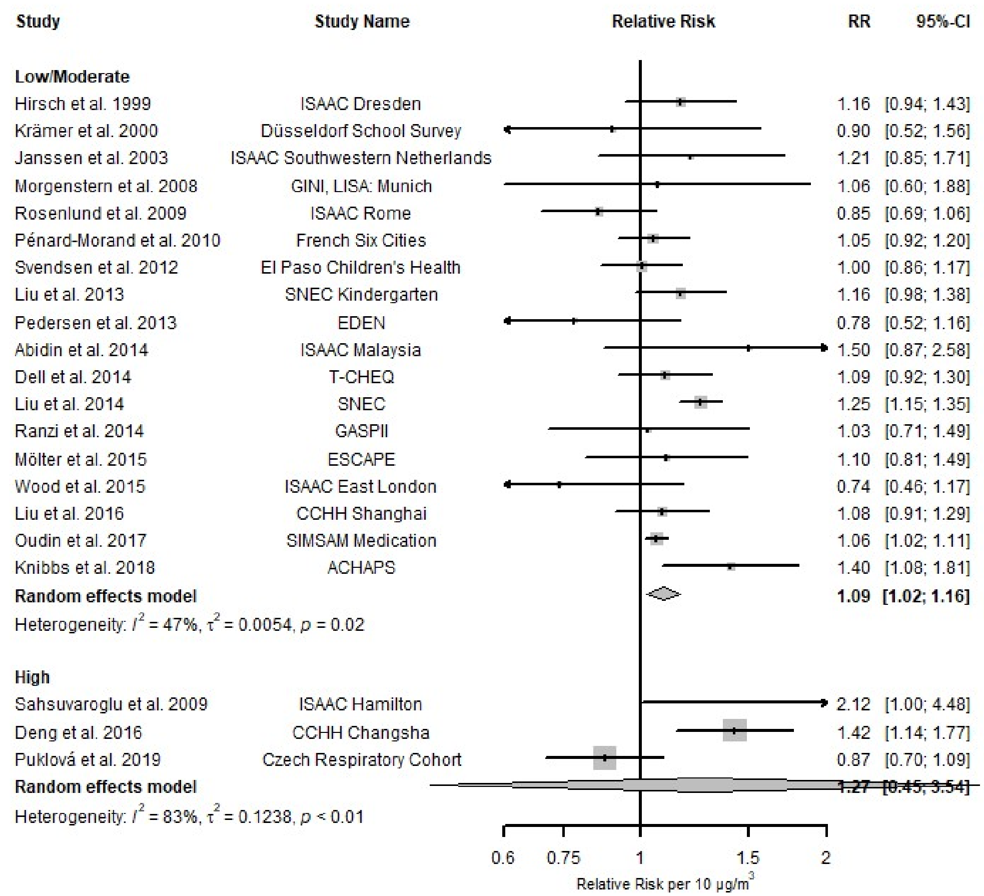
Appendix Figure 9B-6. Association between PM_{10} and prevalence of asthma ever in children: meta-analysis.



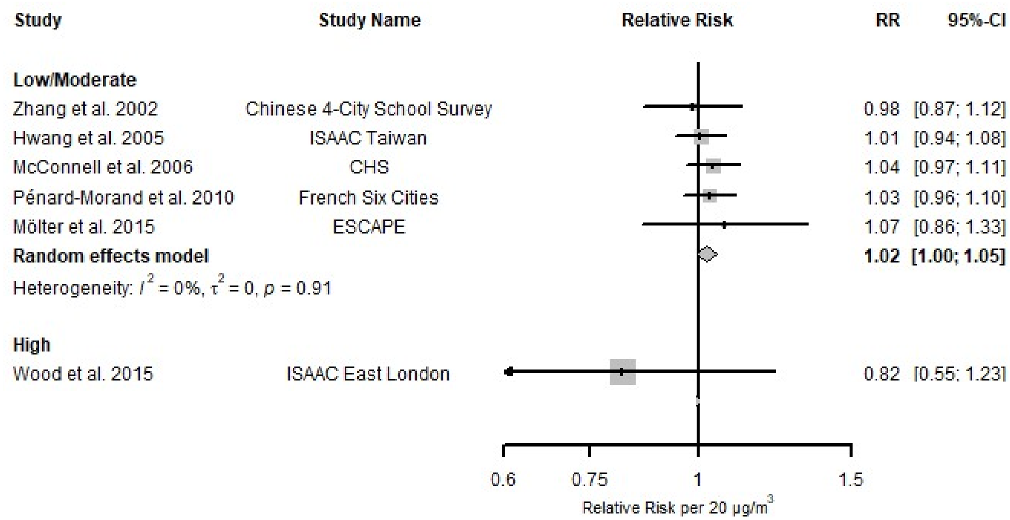
Appendix Figure 9B-7. Association between $PM_{2.5}$ and prevalence of asthma ever in children: meta-analysis.



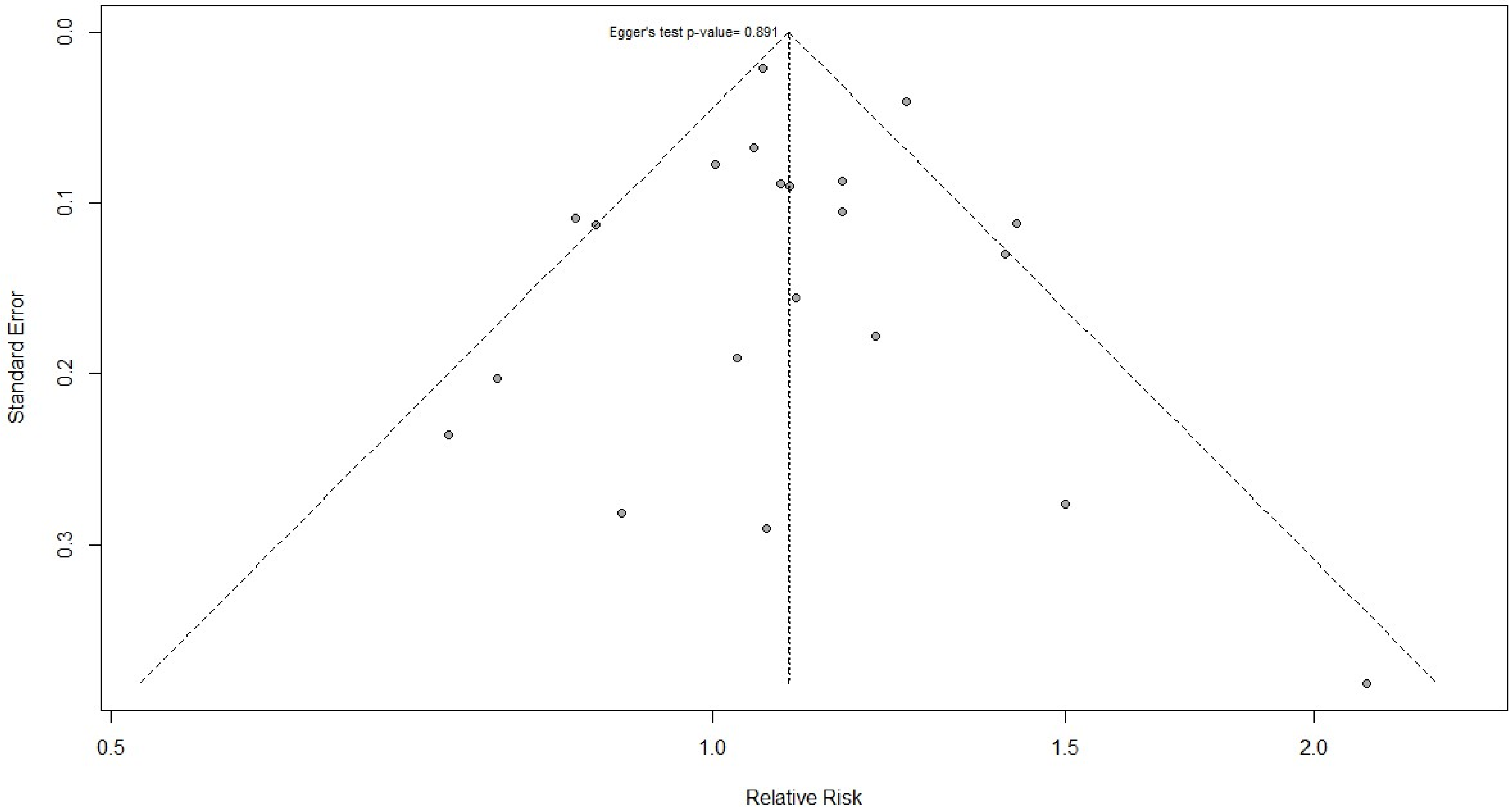
Appendix Figure 9B-8. Association between NO_x and prevalence of asthma ever in children: meta-analysis by traffic specificity.



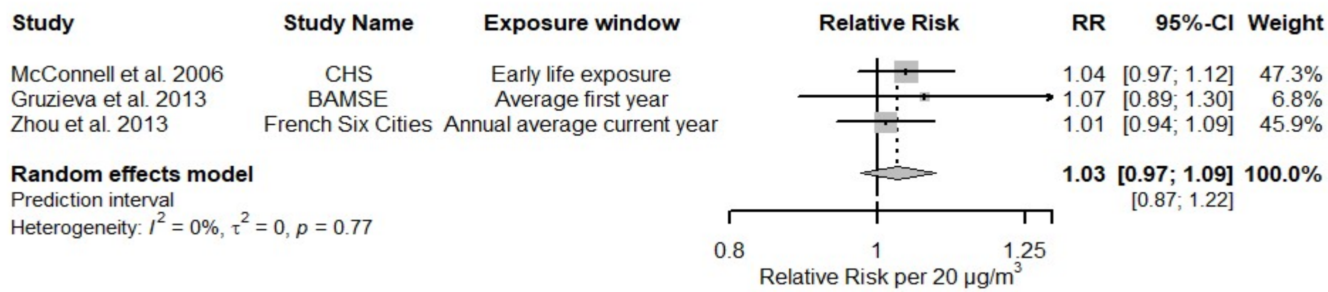
Appendix Figure 9B-9. Association between NO_2 and prevalence of asthma ever in children: meta-analysis by risk of bias confounding.



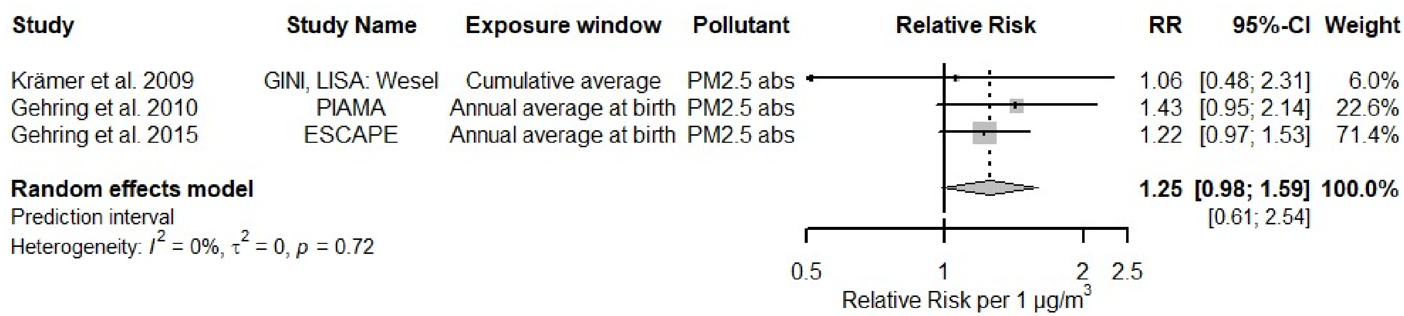
Appendix Figure 9B-10. Association between NO_x and prevalence of asthma ever in children: meta-analysis by risk of bias selection bias.



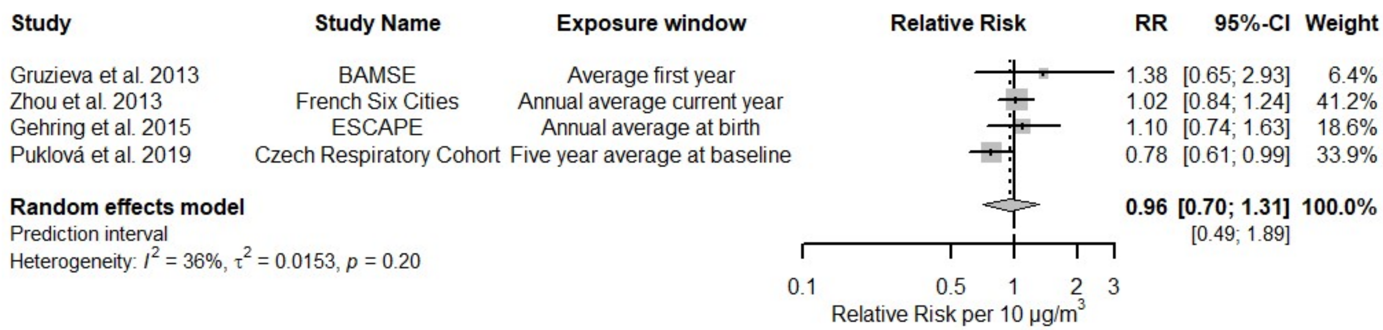
Appendix Figure 9B-11. Funnel plot for NO_2 and prevalence of asthma ever in children. The vertical lines in the funnel plots represent the pooled fixed and random effect estimates. The vertical dashed line in the middle of the funnel shows the fixed effect estimate. As the Panel applied a random-effects model, the funnel plot also presents the random-effects estimate with the dotted line.



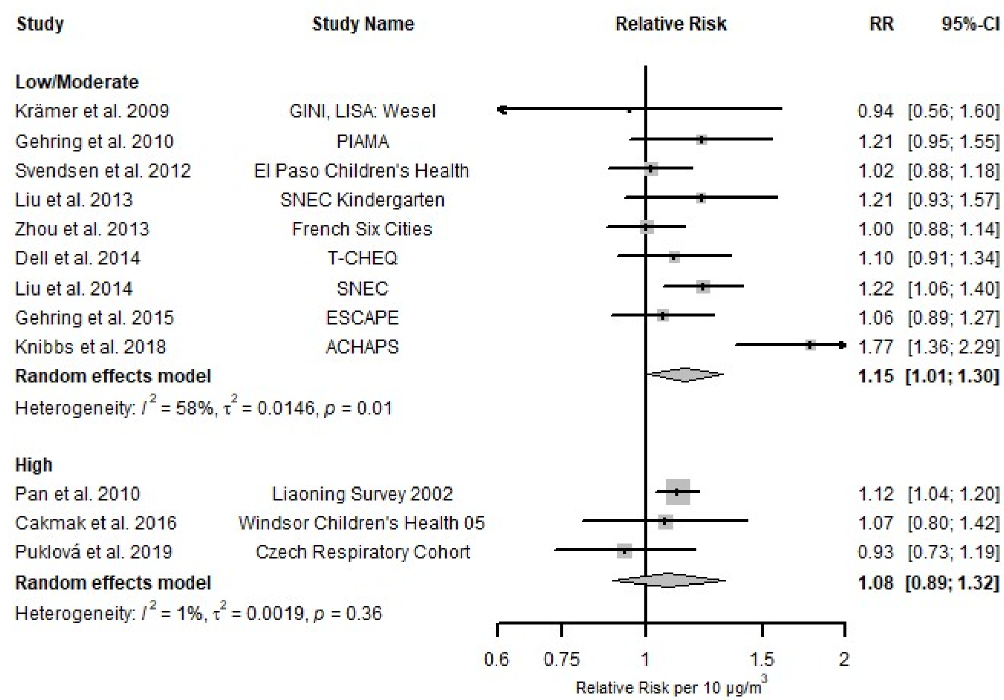
Appendix Figure 9B-12. Association between NO_x and prevalence of active asthma in children: meta-analysis.



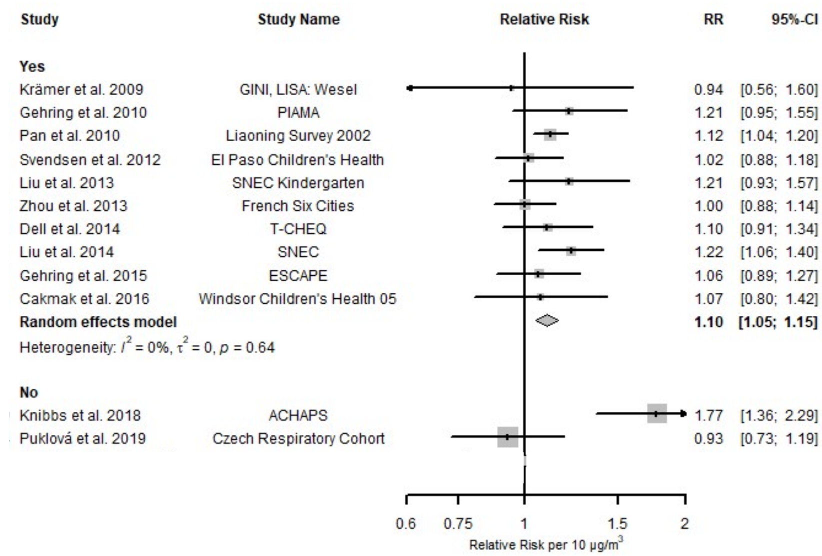
Appendix Figure 9B-13. Association between EC and prevalence of active asthma in children: meta-analysis.



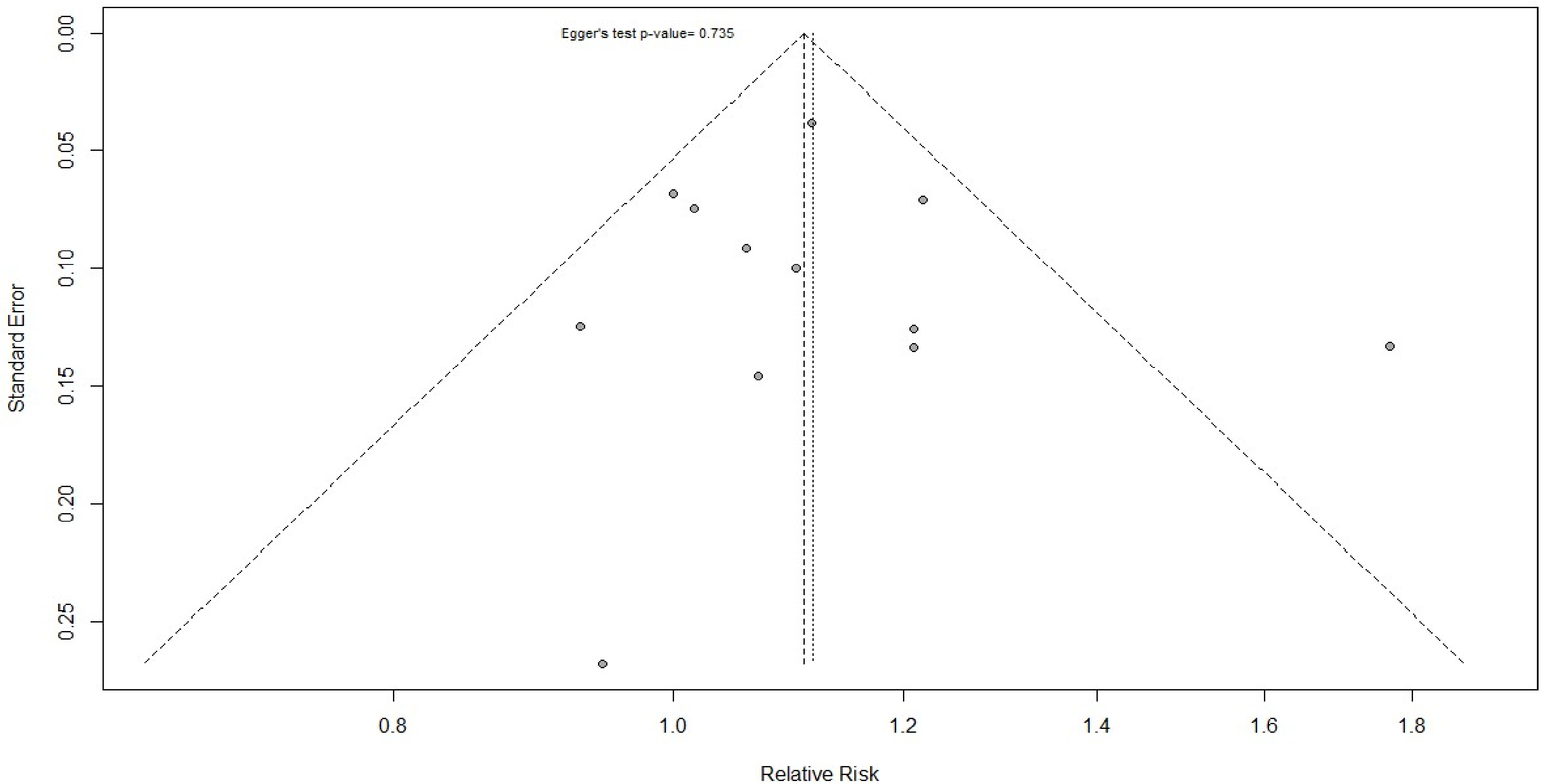
Appendix Figure 9B-14. Association between PM_{10} and prevalence of active asthma in children: meta-analysis.



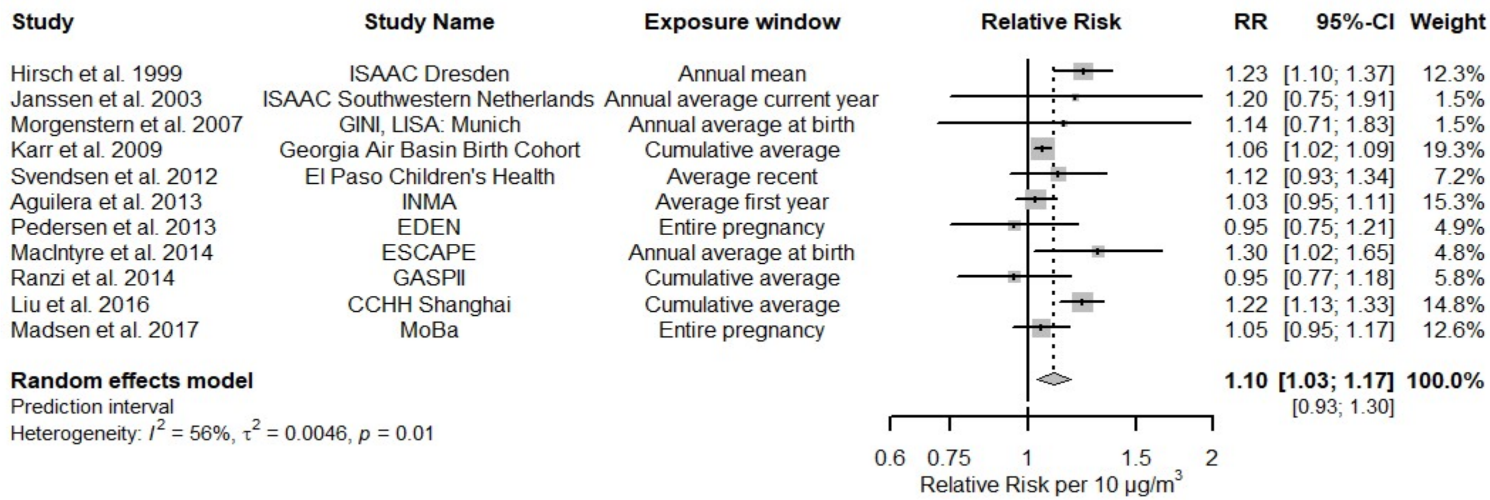
Appendix Figure 9B-15. Association between NO_2 and prevalence of active asthma in children: meta-analysis by risk of bias confounding.



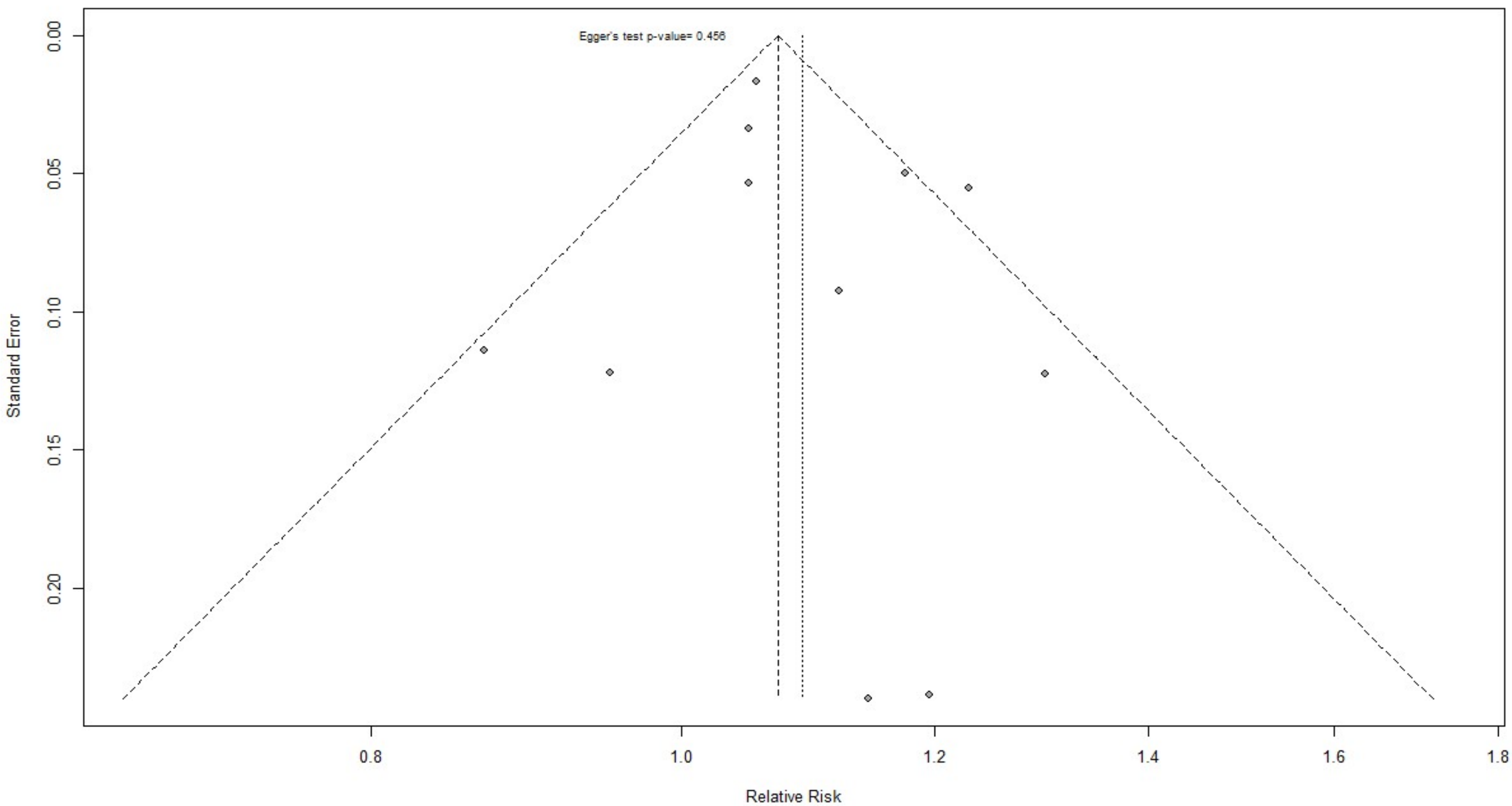
Appendix Figure 9B-16. Association between NO_2 and prevalence of active asthma in children: meta-analysis by smoking adjustment.



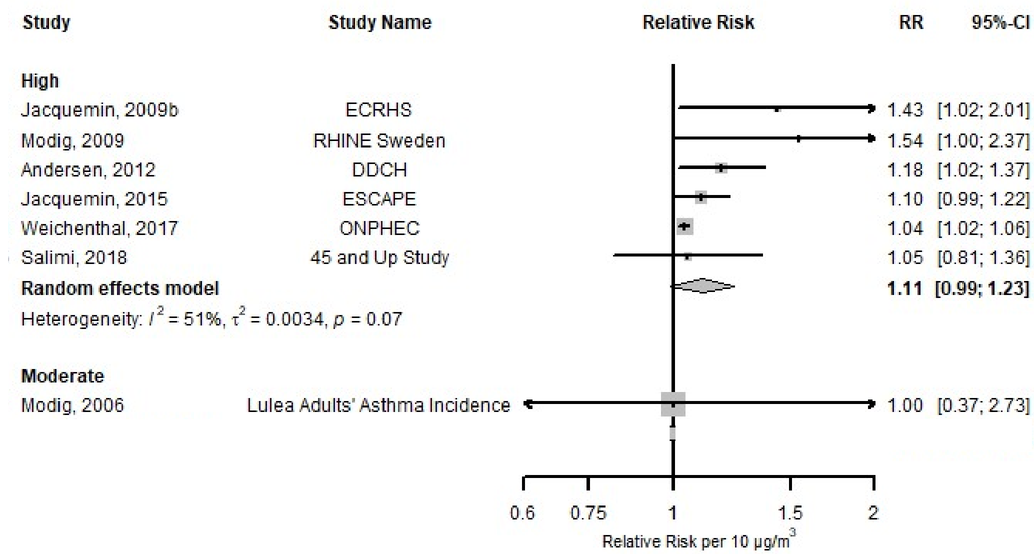
Appendix Figure 9B-17. Funnel plot for NO_2 and prevalence of active asthma in children. The vertical lines in the funnel plots represent the pooled fixed and random effect estimates. The vertical dashed line in the middle of the funnel shows the fixed effect estimate. As the Panel applied a random-effects model, the funnel plot also presents the random-effects estimate with the dotted line.



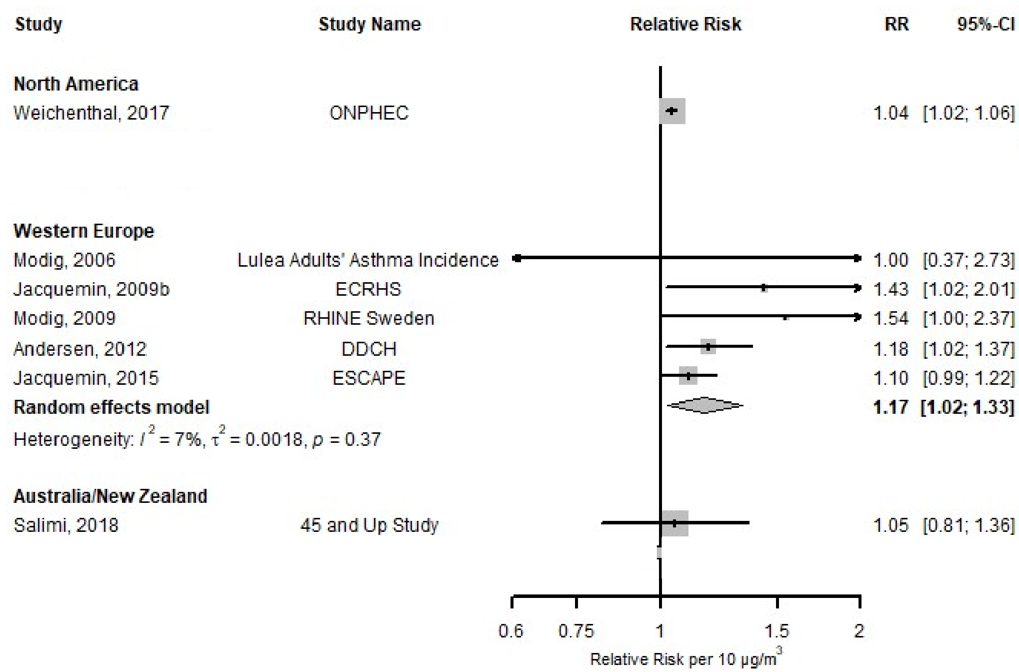
Appendix Figure 9B-18. Association between NO_2 and acute lower respiratory infections in children: meta-analysis giving priority to postnatal exposures.



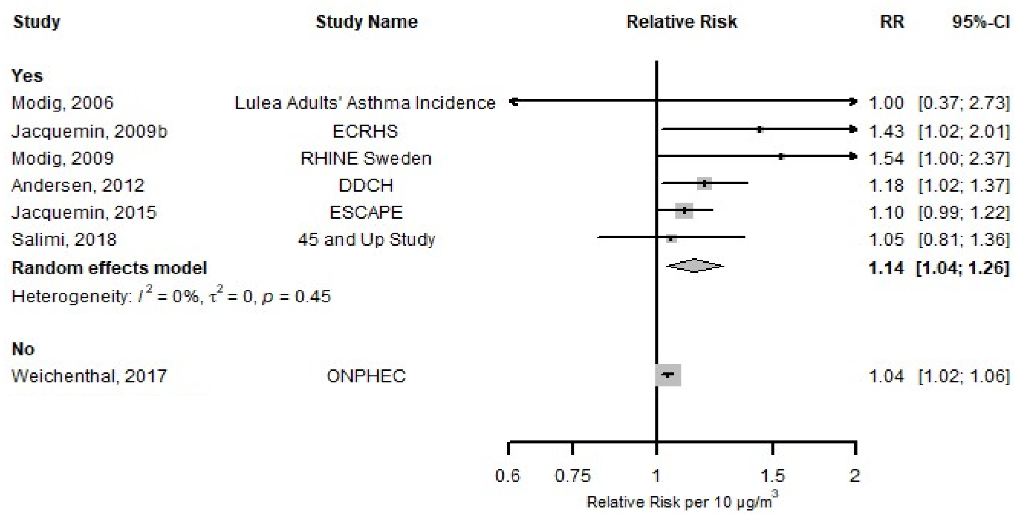
Appendix Figure 9B-19. Funnel plot for NO_2 and acute lower respiratory infections in children. The vertical lines in the funnel plots represent the pooled fixed and random effect estimates. The vertical dashed line in the middle of the funnel shows the fixed effect estimate. As the Panel applied a random-effects model, the funnel plot also presents the random-effects estimate with the dotted line.



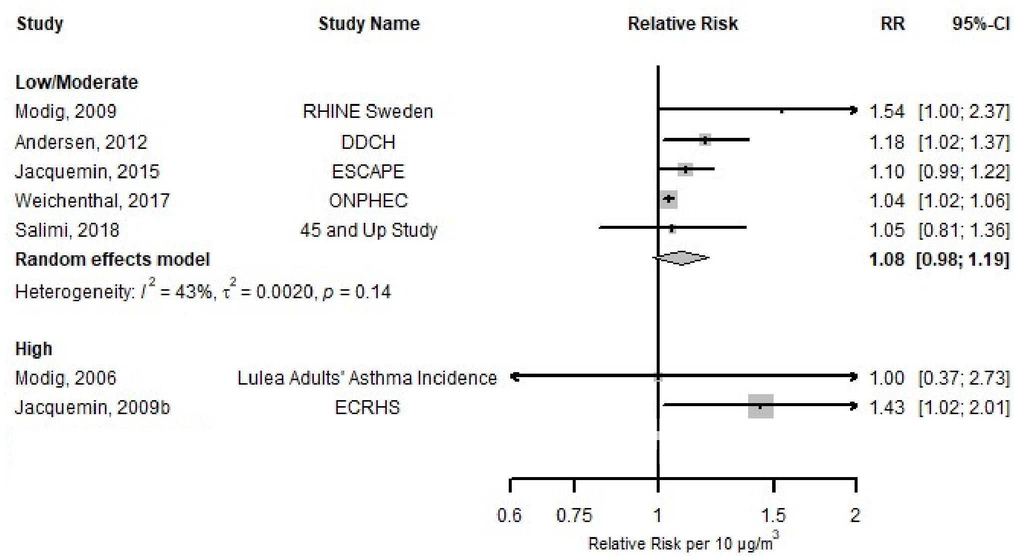
Appendix Figure 9B-20. Association between NO_2 and asthma onset in adults: meta-analysis by traffic specificity.



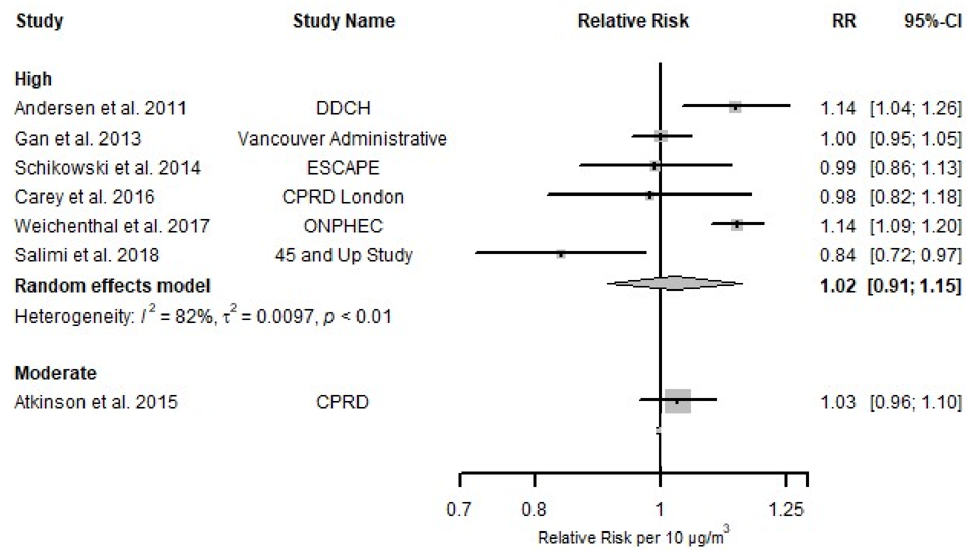
Appendix Figure 9B-21. Association between NO_2 and asthma onset in adults: meta-analysis by region.



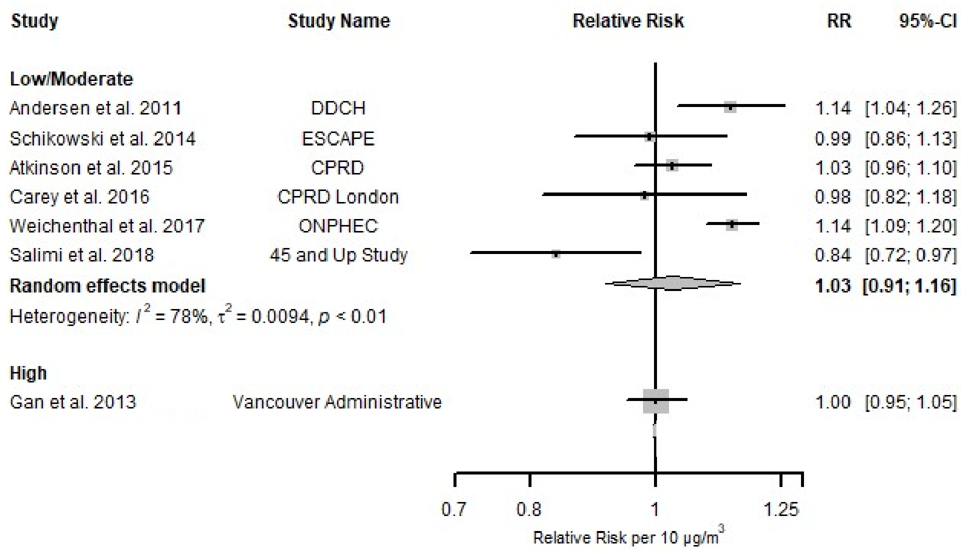
Appendix Figure 9B-22. Association between NO_2 and asthma onset in adults: meta-analysis by smoking adjustment.



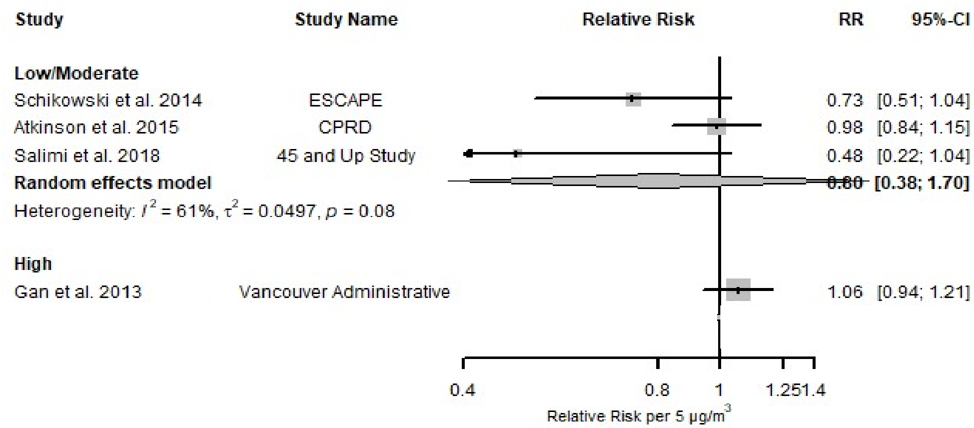
Appendix Figure 9B-23. Association between NO_2 and asthma onset in adults: meta-analysis by risk of bias missing data.



Appendix Figure 9B-24. Association between NO_2 and chronic obstructive pulmonary disease incidence in adults: meta-analysis by traffic specificity.



Appendix Figure 9B-25. Association between NO_2 and chronic obstructive pulmonary disease incidence in adults: meta-analysis by risk of bias confounding.



Appendix Figure 9B-26. Association between $PM_{2.5}$ and chronic obstructive pulmonary disease incidence in adults: meta-analysis by risk of bias confounding.

Appendix Table 9B-1. Risk of bias assessment for individual studies: asthma onset in children.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Carlsten 2011	Vancouver High Risk Asthma Infants	Low	Low	Low	Low	Mod	Low
Clougherty 2007	EBNHC	Low	Low	Low	Mod	Mod	Low
Gehring 2010	PIAMA	Low	Low	Low	Mod	Low	Low
Gehring 2015	ESCAPE	Low	Low	Mod	Mod	Mod	Low
Gruzieva 2013 (NO_x)	BAMSE	High	Low	Low	Mod	Low	Low
Jerrett 2008	CHS	Mod	Low	Mod	Mod	Low	Low
Krämer 2009	GINI, LISA: Wesel	Low	Low	Low	Mod	Mod	Low
Lavigne 2018	BORN Ontario	Mod	Low	Low	Low	High	Low
Lavigne 2019	BORN Toronto	Mod	Low	Low	Low	Mod	Low
Lee 2018	ACCESS	High	Low	Low	Mod	High	Low
McConnell 2010	CHS	Mod	Low	Low	Mod	Low	Low
Oftedal 2009	Oslo Birth Cohort	Low	Mod	Low	Mod	Low	Low
Pennington 2018	KAPPA	High	Low	Low	Mod	High	Low
Ranzi 2014	GASPII	Low	Low	Low	Mod	Mod	Low
Sbihi 2016	BC 99/02 Birth Cohort	High	Low	Low	Low	Low	Low
Tétreault 2016	Quebec Birth Cohort	Mod	Low	Mod	Mod	Low	Low

Mod = moderate.

Appendix Table 9B-2. Risk of bias assessment for individual studies: prevalence of asthma ever in children.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Abidin 2014	ISAAC Malaysia	Low	Mod	Low	Mod	Low	Low
Dell 2014	T-CHEQ	Low	Low	Low	Mod	Low	Low
Deng 2016	CCHH Changsha	High	High	Low	Mod	Low	Low
Hirsch 1999	ISAAC Dresden	Low	Low	Low	Mod	Low	Low
Hwang 2005	ISAAC Taiwan	Low	Low	Mod	Mod	Low	Low
Janssen 2003	ISAAC Southwestern Netherlands	Low	Low	Low	Mod	Low	Low
Knibbs 2018	ACHAPS	Low	Mod	Low	Mod	Low	Low
Krämer 2000	Düsseldorf School Survey	Mod	Mod	Low	Mod	Low	Low
Liu 2013	SNEC Kindergarten	Mod	Low	Low	Mod	Low	Low
Liu 2014	SNEC	Mod	Low	Low	Mod	Low	Low
Liu 2016	CCHH Shanghai	Low	Low	Low	Mod	Low	Low
McConnell 2006	CHS	Low	Low	Low	Mod	Low	Low
Mölter 2015	ESCAPE	Low	Low	Mod	Mod	Low	Low
Morgenstern 2008	GINI, LISA: Munich	Low	Low	Low	Mod	Low	Low
Oudin 2017	SIMSAM Medication	Mod	Low	Mod	Low	Low	Low
Pedersen 2013	EDEN	Low	Low	Low	Mod	Mod	Low
Pénard-Morand 2010	French Six Cities	Low	Mod	Low	Mod	Low	Low
Puklová 2019	Czech Respiratory Cohort	High	Low	Low	Low	Low	Low
Ranzi 2014	GASPII	Low	Low	Low	Mod	Mod	Low
Rosenlund 2009	ISAAC Rome	Low	Low	Low	Mod	Low	Low
Sahsuvaroglu 2009	ISAAC Hamilton	High	Low	Low	Mod	Low	Mod
Svendsen 2012	El Paso Children's Health	Low	Mod	Low	Mod	Low	Low
Wood 2015	ISAAC East London	Low	High	Low	High	Low	Low
Zhang 2002	Chinese 4-City School Survey	Low	Low	Low	Mod	Low	Low

Mod = moderate.

Appendix Table 9B-3. Risk of bias assessment for individual studies: prevalence of active asthma in children.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Cakmak 2016	Windsor Children's Health 05	High	Mod	Low	Mod	Mod	Low
Dell 2014	T-CHEQ	Low	Low	Low	Mod	Low	Low
Gehring 2010	PIAMA	Low	Low	Low	Mod	Low	Low
Gehring 2015	ESCAPE	Low	Low	Mod	Mod	Mod	Low
Gruzieva 2013	BAMSE (NO_x)	High	Low	Low	Mod	Low	Low
Gruzieva 2013	BAMSE (PM_{10})	High	Low	Mod	Mod	Low	Low
Knibbs 2018	ACHAPS	Low	Mod	Low	Mod	Low	Low
Krämer 2009	GINI, LISA: Wesel	Low	Low	Low	Mod	Mod	Low
Liu 2013	SNEC Kindergarten	Mod	Low	Low	Mod	Low	Low
Liu 2014	SNEC	Mod	Low	Low	Mod	Low	Low
McConnell 2006	CHS	Low	Low	Low	Mod	Low	Low
Pan 2010	Liaoning Survey 2002	High	Low	Low	Mod	Low	Low
Puklová 2019	Czech Respiratory Cohort	High	Low	Low	Low	Low	Low
Svendsen 2012	El Paso Children's Health	Low	Mod	Low	Mod	Low	Low
Zhou 2013	French Six Cities	Low	Mod	Low	Mod	Low	Low

Mod = moderate.

Appendix Table 9B-4. Risk of bias assessment for individual studies: acute lower respiratory infections in children.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Aguilera 2013	INMA	Mod	Low	Low	Mod	Low	Low
Hirsch 1999	ISAAC Dresden	Low	Low	Low	Mod	Low	Low
Janssen 2003	ISAAC Southwestern Netherlands	Low	Low	Low	Mod	Low	Low
Karr 2009	Georgia Air Basin Birth Cohort	Mod	Low	Low	Low	Low	Low
Liu 2016	CCHH Shanghai	Low	Low	Low	Mod	Low	Low
MacIntyre 2014	ESCAPE	Low	Low	Mod	Mod	Low	Low
Madsen 2017	MoBa	Low	Low	Low	Mod	Mod	Low
Morgenstern 2007	GINI, LISA: Munich	Low	Low	Low	Mod	Low	Low
Pedersen 2013	EDEN	Low	Low	Low	Mod	Mod	Low
Ranzi 2014	GASPII	Low	Low	Low	Mod	Mod	Low
Svendsen 2012	El Paso Children's Health	Low	Mod	Low	Mod	Low	Low

Mod = moderate.

Appendix Table 9B-5. Risk of bias assessment for individual studies: asthma onset in adults.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Andersen 2012	DDCH	Low	Low	Low	Low	Low	Low
Jacquemin 2009	ECRHS	Low	Low	Mod	Mod	High	Low
Jacquemin 2015	ESCAPE	Low	Low	Mod	Mod	Low	Low
Modig 2006	Lulea Adults' Asthma Incidence	High	Low	Mod	Low	High	Low
Modig 2009	RHINE Sweden	Mod	Low	Mod	Mod	Mod	Low
Salimi 2018	45 and Up Study	Low	Low	Low	Low	Low	Low
Weichenthal 2017	ONPHEC	Mod	Low	Mod	Low	Mod	Low

Mod = moderate.

Appendix Table 9B-6. Risk of bias assessment for individual studies: acute lower respiratory infections in adults.

Reference	Study Name	Confounding	Selection Bias	Exposure Assessment	Outcome Measurement	Missing Data	Selective Reporting
Carey 2016	CPRD London	Mod	Low	Low	Low	Low	Low
Neupane 2010	Hamilton Pneumonia	Low	Mod	Low	Low	Low	Low
Salimi 2018	45 and Up Study	Low	Low	Low	Low	Low	Low

Mod = moderate.

Appendix Table 9B-7. Risk of bias assessment for individual studies: chronic obstructive pulmonary disease incidence in adults.

Reference	**Study Name**	**Confounding**	**Selection Bias**	**Exposure Assessment**	**Outcome Measurement**	**Missing Data**	**Selective Reporting**
Andersen 2011	DDCH	Mod	Low	Mod	Low	Low	Low
Atkinson 2015	CPRD	Mod	Low	Low	Low	Low	Low
Carey 2016	CPRD London	Mod	Low	Low	Low	Low	Low
Gan 2013	Vancouver Administrative	High	Low	Mod	Low	Low	Low
Salimi 2018	45 and Up Study	Low	Low	Low	Low	Low	Low
Schikowski 2014	ESCAPE	Low	Low	Mod	Low	Low	Low
Weichenthal 2017	ONPHEC	Mod	Low	Mod	Low	Mod	Low

Mod = moderate.

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