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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 Additional Materials 9.1 to 9.7

These Additional Materials were not formatted or edited by HEI. This document was part of the HEI Panel's review process.

Correspondence concerning the Special Report may be addressed to Dr. Hanna Boogaard at Health Effects Institute, 75 Federal Street, Suite 1400, Boston, Massachusetts, 02110; email: *jboogaard@healtheffects.org*.

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Chapter 9: Traffic-Related Air Pollution and Respiratory Outcomes

Additional Materials: All Analyses

- 9.1 Asthma Onset
- 9.2 Prevalence of Asthma Ever
- 9.3 Prevalence of Active Asthma
- 9.4 Acute Lower Respiratory Infections (ALRI)
- 9.5 Incidence of Chronic Obstructive Pulmonary Disease (COPD)
- 9.6 Prevalence of Active Wheeze
- 9.7 Prevalence of Wheeze Ever

Chapter 9 Additional Materials

9.1 Asthma onset





Footnote: The following increments were used: $10 \mu g/m^3$ for NO₂, $20 \mu g/m^3$ for NO_x, $1 \mu g/m^3$ for EC, and $5 \mu g/m^3$ 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.

NO₂ – Asthma onset - Adults

Primary meta-analysis

NO_2 - Incidence of asthma, Adults

Study	Study Name	Relative Risk	RR	95%-CI	Weight
Modig, 2006	Lulea Adults' Asthma Incidence		- 1.00	[0.37; 2.73]	0.6%
Jacquemin, 2009b	ECRHS	- 	+ 1.43	[1.02; 2.01]	4.5%
Modig, 2009	RHINE Sweden		➡ 1.54	[1.00; 2.37]	2.9%
Andersen, 2012	DDCH		1.18	[1.02; 1.37]	16.3%
Jacquemin, 2015	ESCAPE		1.10	[0.99; 1.22]	25.0%
Weichenthal, 2017	ONPHEC	+	1.04	[1.02; 1.06]	43.5%
Salimi, 2018	45 and Up Study		1.05	[0.81; 1.36]	7.3%
Random effects model Prediction interval		÷.	1.10	[1.01; 1.21] [0.92; 1.32]	100.0%
Heterogeneity: $I^2 = 42\%$,	$\tau^2 = 0.0033, p = 0.11$				
	0.6 (0.75 1 1.5	2		
	R	elative Risk per 10 µg/m ³			

NO₂ – Asthma onset – Adults

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high

Study	Study Name	Relative Risk			RR	95%-CI
Low/Moderate			Ĩ			
Jacquemin, 2009b	ECRHS				+ 1.43	[1.02; 2.01]
Modig, 2009	RHINE Sweden				1.54	[1.00; 2.37]
Andersen, 2012	DDCH			-	1.18	[1.02; 1.37]
Jacquemin, 2015	ESCAPE				1.10	[0.99; 1.22]
Weichenthal, 2017	ONPHEC		•		1.04	[1.02; 1.06]
Salimi, 2018	45 and Up Study				1.05	[0.81; 1.36]
Random effects mode	el		\sim		1.11	[0.99; 1.23]
Heterogeneity: $I^2 = 51$	%, $\tau^2 = 0.0034$, $p = 0.07$					
High						
Modig, 2006	Lulea Adults' Asthma Incidence 🗧		- B		→ 1.00	[0.37; 2.73]
	0.6	0.75	1	1.5	2	
		Rela	ative Risk per 10 µ	ig/m		

NO₂ – Asthma onset – Adults

Sensitivity analysis - risk of bias missing data domain - low/moderate vs high

Study	Study Name		Relative Risk	RR	95%-CI
Low/Moderate			Ĩ		
Modig, 2009	RHINE Sweden			• 1.54	[1.00; 2.37]
Andersen, 2012	DDCH			1.18	[1.02; 1.37]
Jacquemin, 2015	ESCAPE			1.10	[0.99; 1.22]
Weichenthal, 2017	ONPHEC		+	1.04	[1.02; 1.06]
Salimi, 2018	45 and Up Study	<u> </u>		1.05	[0.81; 1.36]
Random effects mode	el		\sim	1.08	[0.98; 1.19]
Heterogeneity: $l^2 = 439$	$\%, \tau^2 = 0.0020, \rho = 0.14$				
High					
Modig, 2006	Lulea Adults' Asthma Incidence 📼			₱ 1.00	[0.37; 2.73]
Jacquemin, 2009b	ECRHS			▶ 1.43	[1.02; 2.01]
	_				
	0.6	0.75	1 1	.5 2	
		Re	lative Risk per 10 µg/n	1 [°]	

NO₂ – Asthma onset – Adults Subgroup analysis – region

Study	Study Name			Relative Ris	k	RR	95%-CI
North America				Ĩ.			
Weichenthal, 2017	ONPHEC			+		1.04	[1.02; 1.06]
Western Europe							
Modig, 2006	Lulea Adults' Asthma Incidence	•		_		1.00	[0.37; 2.73]
Jacquemin, 2009b	ECRHS					• 1.43	[1.02; 2.01]
Modig, 2009	RHINE Sweden					1.54	[1.00; 2.37]
Andersen, 2012	DDCH				_	1.18	[1.02; 1.37]
Jacquemin, 2015	ESCAPE			- 10 - 1		1.10	[0.99; 1.22]
Random effects model				\sim	-	1.17	[1.02; 1.33]
Heterogeneity: $l^2 = 7\%$, τ	² = 0.0018, <i>p</i> = 0.37						
Australia/New Zealand							
Salimi, 2018	45 and Up Study		1. <u>.</u>			1.05	[0.81; 1.36]
				1			
			_	1			
	0	.6	0.75	1	1.5	2	
			Relat	tive Risk per 10	µg/m ³		

NO₂ – Asthma onset – Adults Subgroup analysis – year of publication



NO₂ – Asthma onset – Adults Subgroup analysis – traffic specificity



NO₂ – Asthma onset – Adults Subgroup analysis – smoking adjustment

Study	Study Name			Relative Ris	sk	RR	95%-CI
Yes				Ĩ			
Modig, 2006	Lulea Adults' Asthma Incidence 🖪	•		_		+ 1.00	[0.37; 2.73]
Jacquemin, 2009b	ECRHS					• 1.43	[1.02; 2.01]
Modig, 2009	RHINE Sweden					1.54	[1.00; 2.37]
Andersen, 2012	DDCH					1.18	[1.02; 1.37]
Jacquemin, 2015	ESCAPE			- 10 -		1.10	[0.99; 1.22]
Salimi, 2018	45 and Up Study		0.			1.05	[0.81; 1.36]
Random effects mode	1			\sim	-	1.14	[1.04; 1.26]
Heterogeneity: $I^2 = 0\%$	$, \tau^2 = 0, \rho = 0.45$						
No							
Weichenthal, 2017	ONPHEC			-		1.04	[1.02; 1.06]
	- -						
	0.6	6	0.75	1	1.5	2	
	0.0	0	0.75 Rela	tive Risk per 1	с.т 0 µg/m ³	2	

NO₂ – Asthma onset - Children

Primary meta-analysis

NO₂ - Incidence of asthma - Children (<18 years)

Study	Study Name	Exposure window	Relative Risk	RR	95%-CI	Weight
Clougherty et al. 2007	EBNHC	Annual average for the year of diagnos	is 🕂 💷	1.28	[0.96; 1.70]	2.9%
Jerrett et al. 2008	CHS	Annual average		1.24	[1.06; 1.46]	6.5%
Krämer et al. 2009	GINI, LISA: Wesel	Annual average at birth		1.19	[0.85; 1.67]	2.2%
Oftedal et al. 2009	Oslo Birth Cohort	Average first year		0.93	[0.86; 1.00]	11.8%
Gehring et al. 2010	PIAMA	Annual average at birth		1.16	[0.96: 1.40]	5.4%
Carlsten et al. 2011	Vancouver High Risk Asthma Infants	Annual average at birth		- 1.76	0.86: 3.571	0.6%
Ranzi et al. 2014	GASPI	Annual average at birth		1.07	[0.76: 1.52]	2.2%
Gehring et al. 2015	ESCAPE	Annual average at birth	÷ • •	1.13	[1.02; 1.25]	10.0%
Sbihi et al. 2016	BC 99/02 Birth Cohort	Entire pregnancy		0.95	[0.89; 1.01]	12.9%
Tétreault et al. 2016	Quebec Birth Cohort	Annual average at birth	+	1.04	[1.02: 1.05]	15.2%
Lavigne et al. 2018	BORN Ontario	Entire pregnancy	÷	1.05	[1.04: 1.07]	15.2%
Lavigne et al. 2019	BORN Toronto	Entire pregnancy		1.01	[0.99; 1.03]	15.0%
Random effects mode	ł		÷	1.05	[0.99; 1.12]	100.0%
Prediction interval					[0.89; 1.25]	
Heterogeneity: $I^2 = 73\%$,	$\tau^2 = 0.0051, p < 0.01$					
- · · · · · · · · · · · · · · · · · · ·	an an assessed a second the second second		0.7 1 1.5	2		
			Relative Risk per 10 µg/m ³			

Chapter 9 Additional Materials

NO₂ – Asthma onset – Children Funnel plot



Footnote: 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.

NO₂ – Asthma onset – Children

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate				
Clougherty et al. 2007	EBNHC		1.28	[0.96; 1.70]
Jerrett et al. 2008	CHS		1.24	[1.06; 1.46]
Krämer et al. 2009	GINI, LISA: Wesel		1.19	[0.85; 1.67]
Oftedal et al. 2009	Oslo Birth Cohort		0.93	[0.86; 1.00]
Gehring et al. 2010	PIAMA		1.16	[0.96; 1.40]
Carlsten et al. 2011	Vancouver High Risk Asthma Infant	is	···· 1.76	[0.86; 3.57]
Ranzi et al. 2014	GASPII		1.07	[0.76; 1.52]
Gehring et al. 2015	ESCAPE		1.13	[1.02; 1.25]
Tétreault et al. 2016	Quebec Birth Cohort	-	1.04	[1.02; 1.05]
Lavigne et al. 2018	BORN Ontario	-	1.05	[1.04; 1.07]
Lavigne et al. 2019	BORN Toronto	÷	1.01	[0.99; 1.03]
Random effects model		\diamond	1.07	[1.00; 1.14]
Heterogeneity: $l^2 = 69\%$,	$\tau^2 = 0.0044, p < 0.01$			
High				
Sbihi et al. 2016	BC 99/02 Birth Cohort		0.95	[0.89; 1.01]
		0.7 1 1.5	2	

Relative Risk per 10 µg/m³

NO₂ – Asthma onset – Children

Sensitivity analysis - risk of bias missing data domain - low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate		Ĩ.		
Clougherty et al. 2007	EBNHC		1.28	[0.96; 1.70]
Jerrett et al. 2008	CHS		1.24	[1.06; 1.46]
Krämer et al. 2009	GINI, LISA: Wesel		1.19	[0.85; 1.67]
Oftedal et al. 2009	Oslo Birth Cohort		0.93	[0.86; 1.00]
Gehring et al. 2010	PIAMA		1.16	[0.96; 1.40]
Carlsten et al. 2011	Vancouver High Risk Asthma Infants		1.76	[0.86; 3.57]
Ranzi et al. 2014	GASPII		1.07	[0.76; 1.52]
Gehring et al. 2015	ESCAPE		1.13	[1.02; 1.25]
Sbihi et al. 2016	BC 99/02 Birth Cohort		0.95	[0.89; 1.01]
Tétreault et al. 2016	Quebec Birth Cohort	-	1.04	[1.02; 1.05]
Lavigne et al. 2019	BORN Toronto	÷	1.01	[0.99; 1.03]
Random effects model			1.06	[0.98; 1.14]
Heterogeneity: $I^2 = 70\%$,	$\tau^2 = 0.0071, p < 0.01$			
High				
Lavigne et al. 2018	BORN Ontario	-	1.05	[1.04; 1.07]
		0.7 1 1.5	2	
		Relative Risk per 10 µg/m ³		

NO₂ – Asthma onset – Children Subgroup analysis – region

Study	Study Name		Relative Ris	k	RR	95%-CI
North America			l l			
Clougherty et al. 2007	EBNHC		-	-	1.28	[0.96; 1.70]
Jerrett et al. 2008	CHS				1.24	[1.06; 1.46]
Carlsten et al. 2011	Vancouver High Risk Asthma Infants				• 1.76	[0.86; 3.57]
Tétreault et al. 2016	Quebec Birth Cohort		+		1.04	[1.02; 1.05]
Sbihi et al. 2016	BC 99/02 Birth Cohort		-		0.95	[0.89; 1.01]
Lavigne et al. 2018	BORN Ontario		Ξ.		1.05	[1.04; 1.07]
Lavigne et al. 2019	BORN Toronto		- B		1.01	[0.99; 1.03]
Random effects model			\Rightarrow		1.04	[0.96; 1.13]
Heterogeneity: 1 ² = 79%	$, \tau^2 = 0.0031, p < 0.01$					
Western Europe			2.1			
Oftedal et al. 2009	Oslo Birth Cohort				0.93	[0.86; 1.00]
Krämer et al. 2009	GINI, LISA: Wesel				1.19	[0.85; 1.67]
Gehring et al. 2010	PIAMA		-	-	1.16	[0.96; 1.40]
Ranzi et al. 2014	GASPII				1.07	[0.76; 1.52]
Gehring et al. 2015	ESCAPE				1.13	[1.02; 1.25]
Random effects model					1.07	[0.93; 1.22]
Heterogeneity: /2 = 67%	$\tau^2 = 0.0094, p = 0.02$				17.10	
		1-1-				
		0.7	1	1.5	2	
			Relative Risk per 1	0 µg/m		

NO₂ – Asthma onset – Children Sensitivity analysis – year of publication

Study	Study Name		Relative Ris	sk	RR	95%-CI
Before 2008			ľ.			
Clougherty et al. 2007	EBNHC				1.28	[0.96; 1.70]
Jerrett et al. 2008	CHS				1.24	[1.06; 1.46]
After 2009						
Offedel et al. 2000	Osla Bith Cabat				0.02	10 96: 1 001
Krämer et al. 2009	CINI LISA: Wasal				1 10	[0.80, 1.00]
Cebring et al. 2005	PIAMA				1.15	[0.05, 1.07]
Corleton et al. 2010	Vancouver High Risk Asthma Infants					[0.96: 3.57]
Ranzi et al. 2014	GASPII				1.07	[0.76: 1.52]
Gebring et al. 2015	ESCAPE				1 13	[1 02: 1 25]
Tétrepult et al. 2015	Quebec Birth Cohort				1.13	[1.02, 1.25]
Shihi et al. 2016	BC 99/02 Birth Cohort				0.95	[0.89:1.01]
Lavigne et al. 2018	BORN Ontario		-		1.05	[1 04: 1 07]
Lavigne et al. 2019	BORN Toronto		L.		1.00	[0.99:1.03]
Random effects model			5		1.03	[0.97:1.09]
Heterogeneity: 12 - 74%	$r^2 = 0.0027$ $p < 0.01$					[olori, lice]
neterogenety. / = / +/0,	t = 0.0027, p = 0.01			10		
	(0.7	1	1.5	2	
			Relative Risk per 1	0 µg/m ³		

NO₂ – Asthma onset – Children Sensitivity analysis – traffic specificity

Study	Study Name		Relative Risk	C	RR	95%-CI
High			Ē			
Clougherty et al. 2007	EBNHC				1.28	[0.96; 1.70]
Oftedal et al. 2009	Oslo Birth Cohort				0.93	[0.86; 1.00]
Krämer et al. 2009	GINI, LISA: Wesel				1.19	[0.85; 1.67]
Gehring et al. 2010	PIAMA			-	1.16	[0.96; 1.40]
Carlsten et al. 2011	Vancouver High Risk Asthma Infant	S	-		→ 1.76	[0.86; 3.57]
Ranzi et al. 2014	GASPII	_	10.0 . 0	1	1.07	[0.76; 1.52]
Gehring et al. 2015	ESCAPE				1.13	[1.02; 1.25]
Tétreault et al. 2016	Quebec Birth Cohort				1.04	[1.02; 1.05]
Sbihi et al. 2016	BC 99/02 Birth Cohort				0.95	[0.89; 1.01]
Lavigne et al. 2019	BORN Toronto		÷		1.01	[0.99; 1.03]
Random effects model			\Rightarrow		1.03	[0.96; 1.11]
Heterogeneity: $I^2 = 68\%$,	$\tau^2 = 0.0044, p < 0.01$					
Moderate						
Jerrett et al. 2008	CHS				1.24	[1.06; 1.46]
Lavigne et al. 2018	BORN Ontario		-		1.05	[1.04; 1.07]
		11		0.15		
		0.7	1	1.5	2	
			Relative Risk per 10	µg/m		

NO₂ – Asthma onset – Children Subgroup analysis – smoking adjustment

Study Study Name **Relative Risk** RR 95%-CI Yes Clougherty et al. 2007 EBNHC 1.28 [0.96; 1.70] Oftedal et al. 2009 Oslo Birth Cohort 0.93 [0.86; 1.00] GINI, LISA: Wesel Krämer et al. 2009 1.19 [0.85; 1.67] Gehring et al. 2010 PIAMA 1.16 [0.96; 1.40] Vancouver High Risk Asthma Infants 1.76 [0.86; 3.57] Carlsten et al. 2011 Ranzi et al. 2014 GASPII 1.07 [0.76; 1.52] Gehring et al. 2015 ESCAPE 1.13 [1.02; 1.25] Lavigne et al. 2018 **BORN Ontario** 1.05 [1.04; 1.07] BORN Toronto Lavigne et al. 2019 1.01 [0.99; 1.03] Random effects model 1.06 [0.98; 1.14] Heterogeneity: $l^2 = 71\%$, $\tau^2 = 0.0046$, p < 0.01No Jerrett et al. 2008 CHS 1.24 [1.06; 1.46] Tétreault et al. 2016 Quebec Birth Cohort 1.04 [1.02; 1.05] Sbihi et al. 2016 BC 99/02 Birth Cohort 0.95 [0.89; 1.01] Random effects model 1.05 [0.76; 1.45] Heterogeneity: $l^2 = 85\%$, $\tau^2 = 0.0128$, $\rho < 0.01$ т 0.7 1 1.5 2 Relative Risk per 10 µg/m

NO₂ – Asthma onset – Children Sensitivity analysis – reverse selection

NO₂ - Incidence of asthma - Children (<18 years)

Study	Study Name	Exposure window		Relativ	e Risk	RR	95%-CI	Weight
Clougherty et al. 2007	EBNHC	Annual average for the year of diagnos	is	+:		1.28	[0.96; 1.70]	2.4%
Jerrett et al. 2008	CHS	Annual average		i	-	1.24	[1.06; 1.46]	5.9%
Krämer et al. 2009	GINI, LISA: Wesel	Annual average at birth		<u>i</u>	•	1.19	[0.85; 1.67]	1.8%
Oftedal et al. 2009	Oslo Birth Cohort	Cumulative average		-		0.90	[0.81; 1.01]	9.4%
Gehring et al. 2010	PIAMA	Annual average at birth		÷ •		1.16	[0.96; 1.40]	4.7%
Carlsten et al. 2011	Vancouver High Risk Asthma Infants	Annual average at birth				+ 1.76	[0.86; 3.57]	0.4%
Ranzi et al. 2014	GASPII	Cumulative average				1.09	[0.78; 1.52]	1.8%
Gehring et al. 2015	ESCAPE	Annual average current year		-	-	1.03	[0.89; 1.20]	6.4%
Sbihi et al. 2016	BC 99/02 Birth Cohort	Entire pregnancy				0.95	[0.89; 1.01]	14.0%
Tétreault et al. 2016	Quebec Birth Cohort	Cumulative average		-		1.04	[1.02; 1.05]	17.9%
Lavigne et al. 2018	BORN Ontario	Cumulative average		+		1.00	[0.99; 1.01]	17.9%
Lavigne et al. 2019	BORN Toronto	Cumulative average		* 1:		1.01	[0.98; 1.03]	17.3%
Random effects mode Prediction interval			_	÷		1.03	[0.97; 1.09] [0.89; 1.18]	100.0%
Heterogeneity: $I^2 = 73\%$, 1	$c^2 = 0.0032, p < 0.01$		11		12000	1		
			0.7	1	1.5	2		
				Relative Risk	per 10 µg/m ³			

Recent years > cumulative average > first year of life > at birth > pregnancy

NO_x – Asthma onset - Children

Primary meta-analysis

NO_X - Incidence of asthma - Children (<18 years)



EC – Asthma onset - Children

Primary meta-analysis

EC - Incidence of asthma - Children (<18 years)



Relative Risk per 1 µg/m³

EC – Asthma onset – Children

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low vs high

Refid	Study	Study Name	Study Name		Relative Risk		95%-CI
	Low						
	Krämer et al. 2009	GINI, LISA: Wesel			• 1.31	[0.78; 2.20]	
	Gehring et al. 2010	PIAMA			*	1.28	[0.93; 1.77]
	Carlsten et al. 2011	Vancouver High Risk Asthma Inf			1.07	[0.76; 1.49]	
	Gehring et al. 2015	ESCAPE			1.26	[1.00; 1.59]	
	Random effects model				-	1.22	[1.07; 1.40]
	Heterogeneity: $I^2 = 0\%$,						
	High						
	Sbihi et al. 2016	BC 99/02 Birth Cohort		÷.		0.99	[0.95; 1.03]
			_				
						1	
			0.7	1	1.5	2	
				Relative Risk	per 1 µg/m		

EC – Asthma onset – Children Subgroup analysis – region

Study	Study Name		Relative Risk	RR	95%-CI
North America			1		
Carlsten et al. 2011	Vancouver High Risk Asthma Infan	ts —		1.07	[0.76; 1.49]
Sbihi et al. 2016	BC 99/02 Birth Cohort		÷	0.99	[0.95; 1.03]
			I		
Western Europe					
Krämer et al. 2009	GINI, LISA: Wesel	3		• 1.31	[0.78; 2.20]
Gehring et al. 2010	PIAMA			1.28	[0.93; 1.77]
Gehring et al. 2015	ESCAPE			1.26	[1.00; 1.59]
Random effects mode	el		\diamond	1.27	[1.22; 1.33]
Heterogeneity: $l^2 = 0\%$	$\tau^2 = 0, p = 0.99$				
		0.7	1 1.5	2	
			Relative Risk per 1 µg/m3		

Subgroup analysis – traffic specificity All studies rated high traffic specificity EC – Asthma onset – Children

Subgroup analysis – smoking adjustment



PM_{2.5} – Asthma onset - Children

Primary meta-analysis

PM_{2.5} - Incidence of Asthma - Children (<18 years)



PM_{2.5} – Asthma onset – Children

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low vs high



PM_{2.5} – Asthma onset – Children

Sensitivity analysis - risk of bias missing data domain - low/moderate vs high



PM_{2.5} – Asthma onset – Children Subgroup analysis – region



Subgroup analysis – traffic specificity

All rated as moderate

PM_{2.5} – Asthma onset – Children

Subgroup analysis – smoking adjustment



.9 1 1.1 Relative Risk per 5 µg/m³

Distance measures – Asthma onset – Adults

Reference	Study Name				Categories	RR	95% CI
Modig et al. 2009	RHINE Sweden			-	→ <50 vs. >50 m	3.88	[1.93, 7.82]
Andersen et al. 2012	DDCH	-■			<100 vs. >100 m	0.98	[0.81, 1.19]
Fisher et al. 2016	Nurses' Health	+■			<50 vs. >200 m	1.13	[0.93, 1.38]
Fisher et al. 2016	Nurses' Health	⊦∎⊣			50-199 vs. >200 m	0.90	[0.77, 1.07]
Bowatte et al. 2018	TAHS				<200 vs. >200 m	1.60	[0.71, 3.60]
	0	1	2 3 Relative Risk	4	5		

Distance measures - Incidence of asthma - Adults

Distance measures – Asthma onset – Children

Reference	Study Name					Categories	RR	95% CI
Shima, 2003	Chiba Cohort					<50 m vs. rural areas	4.03	[0.90, 17.96]
Shima, 2003	Chiba Cohort			2 P	>	<50 m vs. rural areas	3.77	[1.00, 14.16]
Shima, 2003	Chiba Cohort					>50 m vs. rural areas	1.99	[0.79, 4.99]
Shima, 2003	Chiba Cohort	1				>50 m vs. rural areas	1.74	[0.63, 4.81]
Krämer, 2009	GINI, LISA: Wesel	⊢ ∎∔i				<50 vs. >50 m	0.86	[0.66, 1.14]
Oftedal, 2009	Oslo Birth Cohort	-				per 541m	0.99	[0.90, 1.08]
Clark, 2010	BC 99/00 Birth Cohort	H				<50 m to major road or <150 m to highway vs. higher	0.97	[0.82, 1.15]
Ranzi, 2014	GASPI	H				<86.1 vs. >86.1 m	0.69	[0.40, 1.20]
Sbihi, 2016	BC 99/02 Birth Cohort	H a H				<50 m to major road or <150 m to highway vs. higher	1.06	[0.92, 1.21]
Lee, 2018b	CHEER				\rightarrow	<75 m vs. >75 m and no bronchiolitis	1.88	[0.67, 5.29]
Lee, 2018b	CHEER				>	${<}75\text{m}$ and bronchiolitis vs. ${<}75\text{m}$ and no bronchiolitis	3.62	[1.07, 12.26]
Lee, 2018b	CHEER		-			bronchiolitis only vs. >75 m and no bronchiolitis	1.93	[1.01, 3.39]
		0 1	2 3 Relative Risł	4	5			

Distance measures - Incidence of asthma - Children (<18 years)

Shima et al. 2003 estimates were stratified by sex.

Density measures – Asthma onset – Adults





Density measures – Asthma onset – Children

Density measures - Incidence of asthma - Children (<18 years)



9.2 Prevalence of asthma ever

Meta-analysis overview – Children (<18).



Footnote: The following increments were used: $10 \ \mu g/m^3$ for NO₂, $20 \ \mu g/m^3$ for NO_x, $1 \ mg/m^3$ for CO, $1 \ \mu g/m^3$ for EC, $10 \ \mu g/m^3$ for PM₁₀ and $5 \ \mu g/m^3$ 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.

NO₂ – Prevalence of asthma ever - children

Primary meta-analysis

Study	Study Name	Study Design	Exposure window	Relative Risk	RR	95%-CI	Weight
Study Hirsch et al. 1999 Krämer et al. 2000 Janssen et al. 2003 Morgenstern et al. 2008 Rosenlund et al. 2009 Pénard-Morand et al. 2009 Pénard-Morand et al. 2009 Svendsen et al. 2019 Liu et al. 2013 Pedersen et al. 2013 Abidin et al. 2014 Dell et al. 2014 Liu et al. 2014 Ranzi et al. 2014 Möter et al. 2015 Wood et al. 2016 Liu et al. 2016	Study Name ISAAC Dresden Düsseldorf School Survey ISAAC Southwestern Netherlands GINI, LISA: Munich ISAAC Rome ISAAC Hamilton French Six Cities EI Paso Children's Health SNEC Kindergarten EDEN ISAAC Malaysia T-CHEQ SNEC GASPII ESCAPE ISAAC East London CCHH Changsha CCHH Shanghai	Study Design Cross sectional Cross sectional Cohort Cross sectional Cross sectional Cross sectional Cross sectional Cross sectional Cohort Cross sectional Case-control Cross sectional Cohort Cross sectional Cohort Cross sectional Cohort Cohort Cross sectional Cross sectional Cross sectional	Exposure window Annual mean Annual average current year Annual average current year Annual average at current address Exposure in 2000-2001 (recent year Cumulative average Annual average current year Average recent Three year average at baseline Entire pregnancy Annual average current year Average first year Three year average at baseline Annual average at birth Cumulative average Annual average current year Entire pregnancy Entire pregnancy		 RR 1.16 0.90 1.21 1.06 0.85 2.12 1.05 1.00 1.16 0.78 1.50 1.09 1.25 1.03 1.10 0.74 1.42 1.08 	95%-Cl [0.94; 1.43] [0.52; 1.56] [0.85; 1.71] [0.60; 1.88] [0.69; 1.06] [1.00; 4.48] [0.92; 1.20] [0.86; 1.17] [0.86; 1.17] [0.86; 1.17] [0.86; 1.17] [0.87; 2.58] [0.92; 1.30] [1.15; 1.35] [0.71; 1.49] [0.81; 1.49] [0.81; 1.77] [1.14; 1.77] [0.91; 1.29]	Weight 5.6% 1.3% 2.8% 1.2% 5.3% 0.7% 8.2% 7.7% 2.2% 1.3% 6.7% 2.2% 1.3% 6.5% 3.4% 1.7% 5.2%
Oudin et al. 2017 Knibbs et al. 2018 Puklová et al. 2019 Random effects model Prediction interval Heterogeneity: $I^2 = 55\%$, $\tau^2 =$	SIMSAM Medication ACHAPS Czech Respiratory Cohort 0.0091, <i>p</i> < 0.01	Cohort Cross sectional Cross sectional	Baseline year average Previous year annual average Five year average at baseline	0.6 0.75 1 Relative Risk per 10	■ 1.06 1.40 0.87 1.09 1.5 2 µg/m ³	[1.02; 1.11] [1.08; 1.81] [0.70; 1.09] [1.01; 1.18] [0.88; 1.35]	11.7% 4.3% 5.1%

NO₂ - Prevalence of asthma ever - Children (<18 years)

NO_2 – Prevalence of asthma ever – Children

Funnel plot



Footnote: 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.
Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate		I		
Hirsch et al. 1999	ISAAC Dresden	+	1.16	[0.94; 1.43]
Krämer et al. 2000	Düsseldorf School Survey	• • • • • • • • • • • • • • • • • • •	0.90	[0.52; 1.56]
Janssen et al. 2003	ISAAC Southwestern Netherlands	s	1.21	[0.85; 1.71]
Morgenstern et al. 2008	GINI, LISA: Munich	· · · · · ·	1.06	[0.60; 1.88]
Rosenlund et al. 2009	ISAAC Rome		0.85	[0.69; 1.06]
Pénard-Morand et al. 2010	French Six Cities		1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health		1.00	[0.86; 1.17]
Liu et al. 2013	SNEC Kindergarten		1.16	[0.98; 1.38]
Pedersen et al. 2013	EDEN	• • • • • • • • • • • • • • • • • • •	0.78	[0.52; 1.16]
Abidin et al. 2014	ISAAC Malaysia		+ 1.50	[0.87; 2.58]
Dell et al. 2014	T-CHEQ		1.09	[0.92; 1.30]
Liu et al. 2014	SNEC		1.25	[1.15; 1.35]
Ranzi et al. 2014	GASPII	· · · ·	1.03	[0.71; 1.49]
Mölter et al. 2015	ESCAPE		1.10	[0.81; 1.49]
Wood et al. 2015	ISAAC East London	• • • ·	0.74	[0.46; 1.17]
Liu et al. 2016	CCHH Shanghai	-+	1.08	[0.91; 1.29]
Oudin et al. 2017	SIMSAM Medication	+	1.06	[1.02; 1.11]
Knibbs et al. 2018	ACHAPS		- 1.40	[1.08; 1.81]
Random effects model			1.09	[1.02; 1.16]
Heterogeneity: $l^2 = 47\%$, τ^2	² = 0.0054, <i>p</i> = 0.02			
High				
Sahsuvaroglu et al. 2009	ISAAC Hamilton		> 2.12	[1.00; 4.48]
Deng et al. 2016	CCHH Changsha		1.42	[1.14; 1.77]
Puklová et al. 2019	Czech Respiratory Cohort		0.87	[0.70; 1.09]
Random effects model			1.27	[0.45; 3.54]
Heterogeneity: $l^2 = 83\%$, τ^2	² = 0.1238, <i>p</i> < 0.01			
			_	
		U.D U./5 1 1.5	2	
		Relative Risk per 10 µg/m		

Sensitivity analysis - risk of bias selection bias domain - low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate		Ĩ		
Hirsch et al. 1999	ISAAC Dresden	+	1.16	[0.94; 1.43]
Krämer et al. 2000	Düsseldorf School Survey	• • • • • • • • • • • • • • • • • • •	0.90	[0.52; 1.56]
Janssen et al. 2003	ISAAC Southwestern Netherland	s	- 1.21	[0.85; 1.71]
Morgenstern et al. 2008	GINI, LISA: Munich		1.06	[0.60; 1.88]
Rosenlund et al. 2009	ISAAC Rome	_ • +	0.85	[0.69; 1.06]
Sahsuvaroglu et al. 2009	ISAAC Hamilton		- 2.12	[1.00; 4.48]
Pénard-Morand et al. 2010	French Six Cities	- .	1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health	<u> </u>	1.00	[0.86; 1.17]
Liu et al. 2013	SNEC Kindergarten	—	1.16	[0.98; 1.38]
Pedersen et al. 2013	EDEN	• • • • • • • • • • • • • • • • • • •	0.78	[0.52; 1.16]
Abidin et al. 2014	ISAAC Malaysia	· · · · · ·	• 1.50	[0.87; 2.58]
Dell et al. 2014	T-CHEQ	- 1 * -	1.09	[0.92; 1.30]
Liu et al. 2014	SNEC		1.25	[1.15; 1.35]
Ranzi et al. 2014	GASPII	· · · · · · · · · · · · · · · · · · ·	1.03	[0.71; 1.49]
Mölter et al. 2015	ESCAPE		1.10	[0.81; 1.49]
Liu et al. 2016	CCHH Shanghai	-+	1.08	[0.91; 1.29]
Oudin et al. 2017	SIMSAM Medication	+	1.06	[1.02; 1.11]
Knibbs et al. 2018	ACHAPS	· · · · · ·	1.40	[1.08; 1.81]
Puklová et al. 2019	Czech Respiratory Cohort	— • • •	0.87	[0.70; 1.09]
Random effects model		\diamond	1.09	[1.01; 1.16]
Heterogeneity: $l^2 = 50\%$, τ	² = 0.0064, <i>p</i> < 0.01			
High				
Wood et al. 2015	ISAAC East London	• =	0.74	[0.46; 1.17]
Deng et al. 2016	CCHH Changsha		- 1.42	[1.14; 1.77]
		I		
		0.6 0.75 1 1.5	2	

Sensitivity analysis - risk of bias outcome measurement domain - low/moderate vs high

Study	Study Name			Relative Risk		RR	95%-CI
Low/Moderate				Ĩ			
Hirsch et al. 1999	ISAAC Dresden					1.16	[0.94; 1.43]
Krämer et al. 2000	Düsseldorf School Survey	-		•		0.90	[0.52; 1.56]
Janssen et al. 2003	ISAAC Southwestern Netherland	s	0			1.21	[0.85; 1.71]
Morgenstern et al. 2008	GINI, LISA: Munich					1.06	[0.60; 1.88]
Rosenlund et al. 2009	ISAAC Rome		\rightarrow	_		0.85	[0.69; 1.06]
Sahsuvaroglu et al. 2009	ISAAC Hamilton			-		• 2.12	[1.00; 4.48]
Pénard-Morand et al. 2010	French Six Cities					1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health			_ 		1.00	[0.86; 1.17]
Liu et al. 2013	SNEC Kindergarten				-	1.16	[0.98; 1.38]
Pedersen et al. 2013	EDEN	+		_		0.78	[0.52; 1.16]
Abidin et al. 2014	ISAAC Malaysia					+ 1.50	[0.87; 2.58]
Dell et al. 2014	T-CHEQ			+		1.09	[0.92; 1.30]
Liu et al. 2014	SNEC					1.25	[1.15; 1.35]
Ranzi et al. 2014	GASPII		<u>.</u>			1.03	[0.71; 1.49]
Mölter et al. 2015	ESCAPE		1			1.10	[0.81; 1.49]
Deng et al. 2016	CCHH Changsha					1.42	[1.14; 1.77]
Liu et al. 2016	CCHH Shanghai			+		1.08	[0.91; 1.29]
Oudin et al. 2017	SIMSAM Medication			-		1.06	[1.02; 1.11]
Knibbs et al. 2018	ACHAPS			<u> </u>	•	1.40	[1.08; 1.81]
Puklová et al. 2019	Czech Respiratory Cohort		100	•+-		0.87	[0.70; 1.09]
Random effects model				\diamond		1.10	[1.02; 1.18]
Heterogeneity: $l^2 = 54\%$, τ^2	= 0.0085, <i>p</i> < 0.01						
High							
Wood et al. 2015	ISAAC East London	-	•			0.74	[0.46; 1.17]
		_		_		_	
		0.6	0.75	1	1.5	2	
			Rel	ative Risk per 10	µg/m ³		

Subgroup analysis – region

Study	Study Name	Relative Risk	RR	95%-CI
North America		l l		
Sahsuvaroglu et al. 2009	ISAAC Hamilton		- 2.12	[1.00; 4.48]
Svendsen et al. 2012	El Paso Children's Health		1.00	[0.86; 1.17]
Dell et al. 2014	T-CHEQ		1.09	[0.92; 1.30]
Random effects model			1.06	[0.74; 1.50]
Heterogeneity: $I^2 = 49\%$, $\tau^2 = 4\%$	= < 0.0001, <i>p</i> = 0.14			
Western Europe				
Hirsch et al. 1999	ISAAC Dresden		1 16	[0 94 1 43]
Krämer et al 2000	Düsseldorf School Survey	•	0.90	[0 52 1 56]
Janssen et al. 2003	ISAAC Southwestern Netherlands		1.21	[0 85 1 71]
Morgenstern et al 2008	GINL LISA: Munich		- 1.06	[0 60 1 88]
Rosenlund et al. 2009	ISAAC Rome		0.85	[0.69: 1.06]
Pénard-Morand et al. 2010) French Six Cities		1.05	[0.92 1.20]
Pedersen et al 2013	EDEN	• • • • • • • • • • • • • • • • • • •	0.78	[0 52 1 16]
Ranzi et al 2014	GASPII		1.03	[0 71 1 49]
Mölter et al. 2015	ESCAPE		1.10	[0.81: 1.49]
Wood et al. 2015	ISAAC East London	• • • • • • • • • • • • • • • • • • •	0 74	[0 46 1 17]
Oudin et al. 2017	SIMSAM Medication	+	1.06	[1.02: 1.11]
Random effects model		♦	1.05	[1.01; 1.10]
Heterogeneity: $l^2 = 1\%$, $\tau^2 =$	0, <i>p</i> = 0.43			
Asia				
Liu et al. 2013	SNEC Kindergarten		1.16	[0.98: 1.38]
Abidin et al. 2014	ISAAC Malavsia		- 1.50	[0.87: 2.58]
Liu et al. 2014	SNEC		1.25	[1.15: 1.35]
Deng et al. 2016	CCHH Changsha		1.42	[1.14: 1.77]
Liu et al. 2016	CCHH Shanghai		1.08	[0.91; 1.29]
Random effects model	3	\diamond	1.23	[1.11; 1.36]
Heterogeneity: $l^2 = 17\%$, $\tau^2 = 17\%$	= 0.0004, <i>p</i> = 0.31			
Australia/New Zealand				
Knibbs et al. 2018	ACHAPS		1.40	[1.08; 1.81]
Eastern Europe				
Puklová et al. 2019	Czech Respiratory Cohort		0 87	[0 70- 1 09]
		1		
).6 0.75 1 1.5 Relative Risk per 10 ug/m ³	2	
		resolutive real per re pg/m		

NO_2 – Prevalence of asthma ever – Children

Subgroup analysis – year of publication

Study	Study Name	Relative Risk	RR	95%-CI
Before 2008		1		
Hirsch et al. 1999	ISAAC Dresden		1.16	[0.94; 1.43]
Krämer et al. 2000	Düsseldorf School Survey	• =	0.90	[0.52; 1.56]
Janssen et al. 2003	ISAAC Southwestern Netherlands		1.21	[0.85; 1.71]
Morgenstern et al. 2008	GINI, LISA: Munich		1.06	[0.60; 1.88]
Random effects model			1.14	[0.99; 1.31]
Heterogeneity: $l^2 = 0\%$, $\tau^2 =$: 0, <i>p</i> = 0.83			
After 2008				
Rosenlund et al. 2009	ISAAC Rome		0.85	[0.69; 1.06]
Sahsuvaroglu et al. 2009	ISAAC Hamilton		2.12	[1.00; 4.48]
Pénard-Morand et al. 2010	French Six Cities		1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health		1.00	[0.86; 1.17]
Liu et al. 2013	SNEC Kindergarten	-	1.16	[0.98; 1.38]
Pedersen et al. 2013	EDEN	• • • • • •	0.78	[0.52; 1.16]
Dell et al. 2014	T-CHEQ		1.09	[0.92; 1.30]
Ranzi et al. 2014	GASPII	· · · · · · · · · · · · · · · · · · ·	1.03	[0.71; 1.49]
Liu et al. 2014	SNEC		1.25	[1.15; 1.35]
Abidin et al. 2014	ISAAC Malaysia		+ 1.50	[0.87; 2.58]
Mölter et al. 2015	ESCAPE	· · · ·	1.10	[0.81; 1.49]
Wood et al. 2015	ISAAC East London	<	0.74	[0.46; 1.17]
Deng et al. 2016	CCHH Changsha		1.42	[1.14; 1.77]
Liu et al. 2016	CCHH Shanghai		1.08	[0.91; 1.29]
Oudin et al. 2017	SIMSAM Medication	-	1.06	[1.02; 1.11]
Knibbs et al. 2018	ACHAPS	· · · ·	- 1.40	[1.08; 1.81]
Puklová et al. 2019	Czech Respiratory Cohort		0.87	[0.70; 1.09]
Random effects model			1.09	[0.99; 1.19]
Heterogeneity: $l^2 = 63\%$, τ^2	= 0.0118, p < 0.01			
-				
	4	0.6 0.75 1 1.5	2	

NO_2 – Prevalence of asthma ever – Children

Subgroup analysis – traffic specificity

Study	Study Name			Relative Risk		RR	95%-CI
High				T I			
Morgenstern et al. 2008	GINI, LISA: Munich	-				1.06	[0.60; 1.88]
Rosenlund et al. 2009	ISAAC Rome		-			0.85	[0.69; 1.06]
Sahsuvaroglu et al. 2009	ISAAC Hamilton					+ 2.12	[1.00; 4.48]
Pénard-Morand et al. 2010	French Six Cities					1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health					1.00	[0.86; 1.17]
Pedersen et al. 2013	EDEN	<u> </u>	-	<u> </u>		0.78	[0.52; 1.16]
Dell et al. 2014	T-CHEQ					1.09	[0.92; 1.30]
Ranzi et al. 2014	GASPII		10		-	1.03	[0.71; 1.49]
Mölter et al. 2015	ESCAPE		-		- 25	1.10	[0.81; 1.49]
Wood et al. 2015	ISAAC East London	<u> </u>	-	_		0.74	[0.46; 1.17]
Oudin et al. 2017	SIMSAM Medication					1.06	[1.02; 1.11]
Knibbs et al. 2018	ACHAPS					1.40	[1.08; 1.81]
Puklová et al. 2019	Czech Respiratory Cohort			-		0.87	[0.70; 1.09]
Random effects model						1.04	[0.98; 1.11]
Heterogeneity: $I^2 = 39\%$, τ^2	² = 0.0006, <i>p</i> = 0.07						
Moderate							
Hirsch et al. 1999	ISAAC Dresden			-		1.16	[0.94; 1.43]
Krämer et al. 2000	Düsseldorf School Survey	-				0.90	[0.52; 1.56]
Janssen et al. 2003	ISAAC Southwestern Netherlands			-		1.21	[0.85; 1.71]
Liu et al. 2013	SNEC Kindergarten					1.16	[0.98; 1.38]
Liu et al. 2014	SNEC					1.25	[1.15; 1.35]
Abidin et al. 2014	ISAAC Malaysia			-		→ 1.50	[0.87; 2.58]
Deng et al. 2016	CCHH Changsha				_	1.42	[1.14; 1.77]
Liu et al. 2016	CCHH Shanghai					1.08	[0.91; 1.29]
Random effects model				\diamond		1.22	[1.14; 1.30]
Heterogeneity: $l^2 = 0\%$, τ^2 :	= 0, p = 0.51					_	
		-		1		1	
	(0.6	0.75	1	1.5	2	
			Rel	ative Risk per 10 µg/	m		

NO_2 – Prevalence of asthma ever – Children

Subgroup analysis – smoking adjustment

Study	Study Name		F	Relative Risk	RR	95%-C
Yes				T. C.		
Hirsch et al. 1999	ISAAC Dresden				1.16	[0.94; 1.43]
Janssen et al. 2003	ISAAC Southwestern Netherlands	3	-		- 1.21	[0.85; 1.71]
Morgenstern et al. 2008	GINI, LISA: Munich	-			1.06	[0.60; 1.88]
Rosenlund et al. 2009	ISAAC Rome		-	-	0.85	[0.69; 1.06]
Sahsuvaroglu et al. 2009	ISAAC Hamilton			7	• 2.12	[1.00; 4.48]
Pénard-Morand et al. 2010	French Six Cities		3		1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health				1.00	[0.86; 1.17]
Liu et al. 2013	SNEC Kindergarten				1.16	[0.98; 1.38]
Pedersen et al. 2013	EDEN	-			0.78	[0.52; 1.16]
Dell et al. 2014	T-CHEQ		3		1.09	[0.92; 1.30]
Ranzi et al. 2014	GASPII		<u></u>		1.03	[0.71; 1.49]
Liu et al. 2014	SNEC				1.25	[1.15: 1.35
Abidin et al. 2014	ISAAC Malaysia		-		+ 1.50	10.87: 2.58
Mölter et al. 2015	ESCAPE		_	· · · ·	1.10	[0.81: 1.49]
Wood et al. 2015	ISAAC East London				0.74	[0.46; 1.17]
Deng et al. 2016	CCHH Changsha				1.42	[1.14; 1.77
Liu et al. 2016	CCHH Shanghai			-	1.08	10.91: 1.29
Oudin et al. 2017	SIMSAM Medication			+	1.06	[1.02: 1.11]
Random effects model				\diamond	1.10	[1.02: 1.18]
Heterogeneity: $l^2 = 53\%$, τ^2	= 0.0065, <i>p</i> < 0.01					
No						
Krämer et al. 2000	Düsseldorf School Survey	-			0.90	[0.52; 1.56]
Knibbs et al. 2018	ACHAPS				1.40	[1.08; 1.81]
Puklová et al. 2019	Czech Respiratory Cohort		-		0.87	[0.70; 1.09
Random effects model						[0.53; 2.08]
Heterogeneity: $l^2 = 74\%$, τ^2	= 0.0589, p = 0.02	_				
		0.6	0.75	1 1.5	2	
			Relativ	/e Risk per 10 µg/m		

Sensitivity analysis - reverse selection

NO₂ - Prevalence of asthma ever - Children (<18 years)

Study	Study Name	Exposure window	Relative Risk	RR	95%-CI	Weight
Hirsch et al. 1999 Krämer et al. 2000 Janssen et al. 2003 Morgenstern et al. 2008 Rosenlund et al. 2009 Sahsuvaroglu et al. 2009 Pénard-Morand et al. 2010 Svendsen et al. 2012 Liu et al. 2013 Pedersen et al. 2013 Abidin et al. 2014 Dell et al. 2014 Liu et al. 2014 Ranzi et al. 2014 Mölter et al. 2015 Deng et al. 2015 Deng et al. 2016 Liu et al. 2017 Knibbs et al. 2017 Knibbs et al. 2019 Random effects model Prediction interval Heterogeneity: $I^2 = 55\%$, $\tau^2 =$	ISAAC Dresden Düsseldorf School Survey ISAAC Southwestern Netherlands GINI, LISA: Munich ISAAC Rome ISAAC Hamilton French Six Cities El Paso Children's Health SNEC Kindergarten EDEN ISAAC Malaysia T-CHEQ SNEC GASPII ESCAPE ISAAC East London CCHH Changsha CCHH Shanghai SIMSAM Medication ACHAPS Czech Respiratory Cohort	Annual mean Annual average current year Annual average current year Annual average at current address Exposure in 2000-2001 (recent yea Currulative average Annual average current year Average recent Three year average at baseline Entire pregnancy Annual average current year Annual average current year Annual average current year Currulative average Currulative average Annual average current year Currulative average Annual average current year Annual average current year Previous year annual average Five year average at baseline	Sar)	1.16 0.90 1.21 1.06 0.85 1.05 1.05 1.05 1.00 1.16 0.78 1.150 1.17 1.25 1.01 1.10 0.74 1.45 1.17 1.06 1.40 0.87 1.10	$\begin{matrix} [0.94; 1.43]\\ [0.52; 1.56]\\ [0.85; 1.71]\\ [0.60; 1.88]\\ [0.69; 1.06]\\ [1.00; 4.48]\\ [0.92; 1.20]\\ [0.86; 1.17]\\ [0.98; 1.38]\\ [0.96; 1.43]\\ [0.52; 1.16]\\ [0.52; 1.16]\\ [0.52; 1.16]\\ [0.52; 1.53]\\ [0.69; 1.47]\\ [0.87; 2.58]\\ [0.96; 1.47]\\ [0.87; 2.58]\\ [0.96; 1.47]\\ [0.87; 2.58]\\ [0.96; 1.47]\\ [0.87; 1.35]\\ [0.69; 1.47]\\ [1.11; 1.88]\\ [1.01; 1.35]\\ [0.46; 1.17]\\ [1.11; 1.88]\\ [1.01; 1.36]\\ [1.02; 1.11]\\ [1.02; 1.11]\\ [1.02; 1.19]\\ [0.89; 1.36]\end{matrix}$	5.6% 1.3% 2.8% 5.4% 0.7% 8.2% 7.5% 6.8% 1.3% 5.8% 10.5% 2.4% 3.4% 10.5% 4.2% 7.6% 11.8% 4.2% 5.2%
			Relative Risk per 10 µg/m°			

Recent years > cumulative average > first year of life > at birth > pregnancy

Subgroup analysis – study design

Study	Study Name	Relative Risk	RR	95%-CI
Case-control		L		
Dell et al. 2014	T-CHEQ	+=	1.09	[0.92; 1.30]
Cohort		I		
Morgonstorn et al. 2009	CINIL LISA: Munich		1.06	10 60: 1 001
Pederson at al 2012	EDEN		0.79	[0.50, 1.00]
Panzi et al. 2014	CASPIL		1.02	[0.32, 1.10]
Mölter et al. 2014	ESCAPE		1.05	[0.91:1.49]
Oudin et al. 2017	SIMSAM Medication	+	1.06	[1 02: 1 11]
Random effects model	childen in medication		1.06	[1.01.1.11]
Heterogeneity: $l^2 = 0\%$, $\tau^2 =$	0, <i>p</i> = 0.67			[]
Cross sectional				
Hirsch et al. 1999	ISAAC Dresden		1.16	[0.94; 1.43]
Krämer et al. 2000	Düsseldorf School Survey	· · · · · · · · · · · · · · · · · · ·	0.90	[0.52; 1.56]
Janssen et al. 2003	ISAAC Southwestern Netherlands		1.21	[0.85; 1.71]
Rosenlund et al. 2009	ISAAC Rome	· · · · ·	0.85	[0.69; 1.06]
Sahsuvaroglu et al. 2009	ISAAC Hamilton		> 2.12	[1.00; 4.48]
Pénard-Morand et al. 2010	French Six Cities	-+	1.05	[0.92; 1.20]
Svendsen et al. 2012	El Paso Children's Health		1.00	[0.86; 1.17]
Liu et al. 2013	SNEC Kindergarten		1.16	[0.98; 1.38]
Liu et al. 2014	SNEC		1.25	[1.15; 1.35]
Abidin et al. 2014	ISAAC Malaysia		→ 1.50	[0.87; 2.58]
Wood et al. 2015	ISAAC East London	• • • • • • • • • • • • • • • • • • •	0.74	[0.46; 1.17]
Deng et al. 2016	CCHH Changsha	· · · · ·	1.42	[1.14; 1.77]
Liu et al. 2016	CCHH Shanghai		1.08	[0.91; 1.29]
Knibbs et al. 2018	ACHAPS	· · · ·	1.40	[1.08; 1.81]
Puklová et al. 2019	Czech Respiratory Cohort	· · ·	0.87	[0.70; 1.09]
Random effects model		\sim	1.11	[1.00; 1.24]
Heterogeneity: $l^2 = 62\%$, τ^2	= 0.0158, p < 0.01			
		0.6 0.75 1 1.5	2	
		Relative Risk per 10 µg/m		

44

Primary meta-analysis

NO_X - Prevalence of asthma ever - Children (<18 years)



Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias selection bias domain – low/moderate vs high

Study	Study Name		Re	ative Risk	RR	95%-CI
Low/Moderate				1		
Zhang et al. 2002	Chinese 4-City School Survey	y			0.98	[0.87; 1.12]
Hwang et al. 2005	ISAAC Taiwan				1.01	[0.94; 1.08]
McConnell et al. 2006	CHS			- -	1.04	[0.97; 1.11]
Pénard-Morand et al. 2010	French Six Cities				1.03	[0.96; 1.10]
Mölter et al. 2015	ESCAPE		-		1.07	[0.86; 1.33]
Random effects model				\diamond	1.02	[1.00; 1.05]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$	= 0, <i>p</i> = 0.91					
High						
Wood et al. 2015	ISAAC East London	•			0.82	[0.55; 1.23]
				1		
		0.6	0.75	1	1.5	
			Relative	Risk per 20 µg/m ³		

Sensitivity analysis - risk of bias outcome measurement domain - moderate vs high



$\mathrm{NO}_{\mathrm{x}}-\mathrm{Prevalence}$ of asthma ever – Children

Subgroup analysis – region

Study	Study Name			Relative Risk	RR	95%-CI
North America						
McConnell et al. 2006	CHS				1.04	[0.97; 1.11]
Master Furne						
western Europe	5 1 01 011			100		
Penard-Morand et al. 2010	French Six Cities				1.03	[0.96; 1.10]
Mölter et al. 2015	ESCAPE				1.07	[0.86; 1.33]
Wood et al. 2015	ISAAC East London	•			0.82	[0.55; 1.23]
Random effects model				\rightarrow	1.03	[0.91; 1.16]
Heterogeneity: $l^2 = 0\%$, $\tau^2 =$	= < 0.0001, <i>p</i> = 0.51					
Asia						
Zhang et al. 2002	Chinese 4-City School Survey	у			0.98	[0.87; 1.12]
Hwang et al. 2005	ISAAC Taiwan				1.01	[0.94; 1.08]
		_	-			
		0.6	0.75	1	1.5	

NO_x – Prevalence of asthma ever – Children Subgroup analysis – year of publication

Study	Study Name		Re	elative Risk	RR	95%-CI
Before 2008				1		
Zhang et al. 2002	Chinese 4-City School Surv	ey			0.98	[0.87; 1.12]
Hwang et al. 2005	ISAAC Taiwan			- 10 -10-10	1.01	[0.94; 1.08]
McConnell et al. 2006	CHS			- 1	1.04	[0.97; 1.11]
Random effects model				\Leftrightarrow	1.02	[0.96; 1.08]
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, <i>p</i> = 0.70					
After 2008						
Pénard-Morand et al. 2010	French Six Cities			-	1.03	[0.96; 1.10]
Mölter et al. 2015	ESCAPE				1.07	[0.86; 1.33]
Wood et al. 2015	ISAAC East London	+			0.82	[0.55; 1.23]
Random effects model					1.03	[0.91; 1.16]
Heterogeneity: $l^2 = 0\%$, $\tau^2 =$	< 0.0001, p = 0.51			2.72572		
				1		
		0.6	0.75	1	1.5	

NO_x – Prevalence of asthma ever – Children Subgroup analysis – traffic specificity

Study	Study Name	Relative Risk	RR	95%-CI
High				
McConnell et al. 2006	CHS		1.04 [0.97; 1.11]
Pénard-Morand et al. 2010	French Six Cities		1.03 [0.96; 1.10]
Mölter et al. 2015	ESCAPE		1.07 [0.86; 1.33]
Wood et al. 2015	ISAAC East London		0.82 [0.55; 1.23]
Random effects model		\diamond	1.03 [0.98; 1.09]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 4$: 0.0001, p = 0.70			
Moderate				
Zhang et al. 2002	Chinese 4-City School Survey		0.98 [0.87; 1.12]
Hwang et al. 2005	ISAAC Taiwan	-	1.01 [0.94; 1.08]
		0.75		

Subgroup analysis - smoking adjustment



EC – Prevalence of asthma ever – Children

Primary meta-analysis

EC - Prevalence of asthma ever - Children (<18 years)



Primary meta-analysis

PM₁₀ - Prevalence of asthma ever - Children (<18 years)



Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low		Ι		
Pénard-Morand et al. 2010	French Six Cities		1.27	[1.07; 1.50]
Pedersen et al. 2013	EDEN	• • • • • • • • • • • • • • • • • • •	0.38	[0.10; 1.41]
Mölter et al. 2015	ESCAPE		0.88	[0.63; 1.23]
Wood et al. 2015	ISAAC East London	• • • •	0.48	[0.10; 2.42]
Random effects model			0.94	[0.48; 1.86]
Heterogeneity: $l^2 = 60\%$, $\tau^2 =$	0.0871, <i>p</i> = 0.06			
High				
Puklová et al. 2019	Czech Respiratory Cohort	-=+	0.86	[0.70; 1.06]
		· · · · · · · · · · · · · · · · · · ·	-	

0.2

0.5 1 2 3 Relative Risk per 10 µg/m³

Sensitivity analysis - risk of bias selection bias domain - low/moderate vs high

Study	Study Name		Relati	ve Risk		RR	95%-CI
Low/Moderate				1			
Pénard-Morand et al. 201	0 French Six Cities					1.27	[1.07; 1.50]
Pedersen et al. 2013	EDEN			_		0.38	[0.10; 1.41]
Mölter et al. 2015	ESCAPE					0.88	[0.63; 1.23]
Puklová et al. 2019	Czech Respiratory Coho	t				0.86	[0.70; 1.06]
Random effects model					-11	0.96	[0.60; 1.55]
Heterogeneity: $l^2 = 74\%$, 1	$t^2 = 0.0454, p < 0.01$						
High							
Wood et al. 2015	ISAAC East London	-				0.48	[0.10; 2.42]
			1	-	1		
		0.2	0.5	1	2	3	
			Relative Ris	k per 10 µg/n	3		

Sensitivity analysis - risk of bias outcome measurement domain - low/moderate vs high

Study	Study Name		Relative	e Risk		RR	95%-CI
Low/Moderate				1			
Pénard-Morand et al. 2010	French Six Cities					1.27	[1.07; 1.50]
Pedersen et al. 2013	EDEN		•	-		0.38	[0.10; 1.41]
Mölter et al. 2015	ESCAPE			-		0.88	[0.63; 1.23]
Puklová et al. 2019	Czech Respiratory Cohort			-		0.86	[0.70; 1.06]
Random effects model						0.96	[0.60; 1.55]
Heterogeneity: $l^2 = 74\%$, τ^2	= 0.0454, <i>p</i> < 0.01						
High							
Wood et al. 2015	ISAAC East London	•				0.48	[0.10; 2.42]
				-	1		
		0.2	0.5	1	2	3	
			Relative Risk	per 10 µg/m ³			

PM_{10} – Prevalence of asthma ever – Children

Subgroup analysis – region



Subgroup analysis – year of publication



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Subgroup analysis – traffic specificity
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All studies moderate specificity

PM₁₀ – Prevalence of asthma ever – Children Subgroup analysis – smoking adjustment





Primary meta-analysis

PM_{2.5} - Prevalence of asthma ever - Children (<18 years)



CO – Prevalence of asthma ever – Children

Primary meta-analysis

CO - Prevalence of asthma ever - Children (<18)



Distance measures – Prevalence of asthma ever – Adults

Reference	Study Name				Categories	RR	95% CI
Cesaroni et al. 2008	SIDRIA				<50 vs. >200 m	1.01	[0.73, 1.39]
Cesaroni et al. 2008	SIDRIA	ļ			50-100 vs. >200 m	1.07	[0.76, 1.52]
Cesaroni et al. 2008	SIDRIA	F			100-200 vs. >200 m	1.00	[0.77, 1.29]
Nuvolone et al. 2011	Tuscany Health Survey				<100 vs. 250-800 m	1.68	[0.97, 2.88]
Nuvolone et al. 2011	Tuscany Health Survey) —			<100 vs. 250-800 m	1.59	[0.85, 2.98]
Nuvolone et al. 2011	Tuscany Health Survey	 			100-250 vs. 250-800 m	0.58	[0.30, 1.15]
Nuvolone et al. 2011	Tuscany Health Survey				100-250 vs. 250-800 m	1.55	[0.83, 2.87]
		0 1	2 Relative Risk	3			

Distance measures - Prevalence of asthma ever - Adults

Nuvolone et al. 2011 estimates were stratified by sex. All prevalence studies.

Distance measures – Prevalence of asthma ever – Children

Distance measures - Prevalence of asthma ever - Children (<18 years)

South Holland Respiratory Survey ISAAC Eastern UK ISAAC Eastern UK ISAAC Eastern UK CHS CHS CHS GINI, LISA: Munich		<100 vs. >100-1000 m <150 vs. >300 m <150 vs. >300 m 	1.68 0.85 1.05 1.03 1.29 1.06	[0.68, 4.14] [0.60, 1.05] [0.90, 1.25] [0.87, 1.23] [1.01, 1.66] [0.82, 1.36]
ISAAC Eastern UK ISAAC Eastern UK ISAAC Eastern UK CHS CHS GINI, LISA: Munich		<30 vs. >150 m 30-89 vs. >150 m 90-149 vs. >150 m <75 vs. >300 m 75-150 vs. >300 m 150-300 vs. >300 m	0.85 1.05 1.03 1.29 1.06	[0.60, 1.05] [0.90, 1.25] [0.87, 1.23] [1.01, 1.66] [0.82, 1.36]
ISAAC Eastern UK ISAAC Eastern UK CHS CHS CHS GINI, LISA: Munich		30-89 vs. >150 m 90-149 vs. >150 m <75 vs. >300 m 75-150 vs. >300 m 150-300 vs. >300 m	1.05 1.03 1.29 1.06	[0.90, 1.25] [0.87, 1.23] [1.01, 1.66] [0.82, 1.36]
ISAAC Eastern UK CHS CHS CHS GINI, LISA: Munich		90-149 vs. >150 m <75 vs. >300 m 75-150 vs. >300 m 150-300 vs. >300 m	1.03 1.29 1.06	[0.87, 1.23] [1.01, 1.66] [0.82, 1.36]
CHS CHS CHS GINI, LISA: Munich		<75 vs. >300 m 75-150 vs. >300 m 150-300 vs. >300 m	1.29 1.06	[1.01, 1.66] [0.82, 1.36]
CHS CHS GINI, LISA: Munich		75-150 vs. >300 m 150-300 vs. >300 m	1.06	[0.82, 1.36]
CHS GINI, LISA: Munich		150-300 vs. >300 m	0.00	
GINI, LISA: Munich			0.92	[0.73, 1.15]
		<50 vs. >50 m	1.23	[1.00, 1.51]
GINI, LISA: Munich		<50 vs. >50 m	1.66	[1.01, 2.59]
Liaoning Survey 2007		<20 vs. >100 m	1.17	[0.83, 1.63]
Liaoning Survey 2007		20-100 vs. >100 m	0.84	[0.63, 1.11]
ISAAC Rome	H	<100 vs. >100 m	0.70	[0.40, 1.10]
Health Survey England		<150 vs. >150 m	1.01	[0.95, 1.07]
OMCHS		<50 vs. >200 m	4.01	[1.44, 11.24]
OMCHS			1.39	[0.36, 4.54]
OMCHS			2.38	[0.91, 6.28]
ISAAC Bytom		<100 vs. >100 m	1.47	[0.95, 2.27]
T-CHEQ		<100 vs. >100 m	1.28	[0.33, 4.96]
GASPII	II	<86.1 vs. >86.1 m	0.62	[0.33, 1.13]
CHEER	I	<75 vs. >225 m	1.11	[0.84, 1.46]
CHEER		75-150 vs. >225 m	1.23	[0.98, 1.56]
CHEER		150-225 vs. >225 m	1.13	[0.81, 1.59]
CHEER		<75 vs. >700 m	1.79	[1.05, 3.06]
CHEER		75-700 vs. >700 m	1.36	[0.83, 2.24]
0	1 2	3		
	GINI, LISA: Munich GINI, LISA: Munich Liaoning Survey 2007 ISAAC Rome Health Survey England OMCHS OMCHS OMCHS ISAAC Bytom T-CHEQ GASPII CHEER CHEER CHEER CHEER CHEER CHEER CHEER CHEER	GINI, LISA: Munich GINI, LISA: Munich Liaoning Survey 2007 Liaoning Survey 2007 ISAAC Rome Health Survey England OMCHS OMCHS OMCHS ISAAC Bytom T-CHEQ GASPII CHEER	GINI, LISA: Munich GINI, LISA: Munich Liaoning Survey 2007 Liaoning Survey 2007 ISAAC Rome Health Survey England OMCHS OMCHS OMCHS OMCHS OMCHS OMCHS OMCHS OMCHS CHEER CH	GINI, LISA: Munich <50 vs. >50 m 1.23 GINI, LISA: Munich <50 vs. >50 m 1.66 Liaoning Survey 2007 20.100 vs. >100 m 0.84 ISAAC Rome <100 vs. >100 m 0.84 Vertex Pengland <150 vs. >100 m 0.70 Health Survey England <150 vs. >100 m 0.70 OMCHS <50 vs. >200 m 4.01 OMCHS <50 vs. >200 m 1.39 OMCHS <100 vs. >100 m 1.47 T-CHEQ <100 vs. >100 m 1.47 T-CHEQ <86.1 vs. >86.1 m 0.62 CHEER <86.1 vs. >86.1 m 0.62 CHEER 75 vs. >225 m 1.11 CHEER 75 vs. >700 m 1.38 CHEER 1.33 CHEER 1.33 CHEER 3<

All prevalence studies

Density measures - Prevalence of asthma ever - Adults



Density measures - Prevalence of asthma ever - Adults

All prevalence studies

Density measures – Prevalence of asthma ever – Children

Reference	Study Name		Per Increment/Categories	RR	95% CI
Wjst et al. 1993	Munich Asthma and Allergy	-	25000 vehicles/day	1.06	[0.97, 1.16]
van Vliet et al. 1997	South Holland Respiratory Survey	⊢ ∎	high vs. low car volume	0.30	[0.09, 0.97]
van Vliet et al. 1997	South Holland Respiratory Survey		high vs. low truck volume	0.54	[0.18, 1.60]
Nicolai et al. 2003	ISAAC Munich		>30000 vehicles/day vs. none	1.19	[0.76, 1.87]
Nicolai et al. 2003	ISAAC Munich	F	15001-30000 vehicles/day vs. none	0.93	[0.58, 1.51]
Nicolai et al. 2003	ISAAC Munich	⊢	2600-15000 vehicles/day vs. none	0.90	[0.55, 1.49]
Gordian et al. 2006	Anchorage Respiratory		>8000 vs. <4000 vehicle-km/day	2.83	[1.23, 6.51]
Gordian et al. 2006	Anchorage Respiratory	II	4000 to 8000 vs. <4000 vehicle-km/day	1.40	[0.77, 2.55]
Andersson et al. 2011	OLIN	L	>8000 vs. <8000 vehicles/day	1.40	[0.80, 2.50]
Andersson et al. 2011	OLIN	•	>500 vs. <500 heavy vehicles/day	1.50	[0.80, 2.90]
Skrzypek et al. 2013	ISAAC Bytom	•	>90th vs. <90th percentile	1.60	[1.07, 2.39]
		0 1 2 3 Relative Risk	4		

Density measures - Prevalence of asthma ever - Children (<18 years)

All prevalence studies

9.3 Prevalence of active asthma



Footnote: The following increments were used: $10 \ \mu g/m^3$ for NO₂, $20 \ \mu g/m^3$ for NO_x, $1 \ \mu g/m^3$ for EC and $10 \ \mu g/m^3$ for PM₁₀. 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.

NO₂ – Prevalence of active asthma – Children

Primary meta-analysis

NO₂ - Prevalence of active/current asthma - Children (<18 years)

Study	Study Name	Exposure window			Relative Ris	k	RR	95%-CI	Weight
Krämer et al. 2009	GINI, LISA: Wesel	Cumulative average	-		•		0.94	[0.56; 1.60]	1.9%
Gehring et al. 2010	PIAMA	Annual average at birth			- <u></u>		1.21	[0.95; 1.55]	6.3%
Pan et al. 2010	Liaoning Survey 2002	Four year average at baseline					1.12	[1.04; 1.20]	16.1%
Svendsen et al. 2012	El Paso Children's Health	Average recent					1.02	[0.88; 1.18]	11.2%
Liu et al. 2013	SNEC Kindergarten	Three year average at baseline	9				1.21	[0.93; 1.57]	5.8%
Zhou et al. 2013	French Six Cities	Annual average current year			- # *		1.00	[0.88; 1.14]	12.0%
Dell et al. 2014	T-CHEQ	Average first year				•	1.10	[0.91; 1.34]	8.4%
Liu et al. 2014	SNEC	Three year average at baseline	9				1.22	[1.06; 1.40]	11.6%
Gehring et al. 2015	ESCAPE	Annual average at birth					1.06	[0.89; 1.27]	9.2%
Cakmak et al. 2016	Windsor Children's Health 05	Annual average current year		-	=		1.07	[0.80; 1.42]	5.1%
Knibbs et al. 2018	ACHAPS	Previous year annual average					→ 1.77	[1.36; 2.29]	5.9%
Puklová et al. 2019	Czech Respiratory Cohort	Five year average at baseline			-		0.93	[0.73; 1.19]	6.4%
Random effects model					÷		1.12	[1.02; 1.23]	100.0%
Prediction interval								[0.90; 1.39]	
Heterogeneity: $I^2 = 49\%$, τ	$^{2} = 0.0078, p = 0.03$		<u> </u>					10000	
. , , , , , , , , , , , , , , , , , , ,			0.6	0.75	1	1.5	2		
				Relativ	e Risk per 1	0 µg/m ³			

NO_2 – Prevalence of active asthma – Children

Funnel plot



Footnote: 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.

NO₂ – Prevalence of active asthma – Children

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high

Study	Study Name		Relative Risk		RR	95%-CI
Low/Moderate						
Krämer et al. 2009	GINI, LISA: Wesel		·		0.94	[0.56; 1.60]
Gehring et al. 2010	PIAMA				1.21	[0.95; 1.55]
Svendsen et al. 2012	El Paso Children's Health	37			1.02	[0.88; 1.18]
Liu et al. 2013	SNEC Kindergarten		+	-	1.21	[0.93; 1.57]
Zhou et al. 2013	French Six Cities	_	+		1.00	[0.88; 1.14]
Dell et al. 2014	T-CHEQ				1.10	[0.91; 1.34]
Liu et al. 2014	SNEC			-	1.22	[1.06; 1.40]
Gehring et al. 2015	ESCAPE	-	*		1.06	[0.89; 1.27]
Knibbs et al. 2018	ACHAPS				• 1.77	[1.36; 2.29]
Random effects model			\sim		1.15	[1.01; 1.30]
Heterogeneity: 1 ² = 58%	$p, \tau^2 = 0.0146, p = 0.01$					
High						
Pan et al. 2010	Liaoning Survey 2002				1.12	[1.04; 1.20]
Cakmak et al. 2016	Windsor Children's Health 05				1.07	[0.80; 1.42]
Puklová et al. 2019	Czech Respiratory Cohort		-		0.93	[0.73; 1.19]
Random effects model		1			1.08	[0.89; 1.32]
Heterogeneity: /2 = 1%,	τ ² = 0.0019, p = 0.36					
		0.75		15		
	0.6	0.75	T Distance 40	1.5	2	
		Relati	ive Risk per 10 µ	g/m		

NO₂ – Prevalence of active asthma – Children

Subgroup analysis – region

1	
1.02	[0.88; 1.18]
1.10	[0.91; 1.34]
1.07	[0.80; 1.42]
1.05	[0.94; 1.17]
~ ~ ~	
• 0.94	[0.56; 1.60]
1.21	[0.95; 1.55]
1.00	[0.88; 1.14]
1.06	[0.89; 1.27]
1.05	[0.92; 1.19]
1.12	[1.04; 1.20]
1.21	[0.93; 1.57]
1.22	[1.06; 1.40]
1.15	[1.01; 1.29]
1 .77	[1.36; 2.29]
0.93	[0.73; 1.19]
— 	
1 1.5 2	
	1.03 1.12 1.21 1.22 1.15

Subgroup analysis – year of publication All published after 2008

NO₂ – Prevalence of active asthma – Children Subgroup analysis – traffic specificity

Study	Study Name			Relative Risk		RR	95%-CI
High							
Krämer et al. 2009	GINI, LISA: Wesel	.		-		0.94	[0.56; 1.60]
Gehring et al. 2010	PIAMA					1.21	[0.95; 1.55]
Svendsen et al. 2012	El Paso Children's Health			- -		1.02	[0.88; 1.18]
Zhou et al. 2013	French Six Cities			- <u>+</u>		1.00	[0.88; 1.14]
Dell et al. 2014	T-CHEQ					1.10	[0.91; 1.34]
Gehring et al. 2015	ESCAPE					1.06	[0.89; 1.27]
Cakmak et al. 2016	Windsor Children's Health 05		_			1.07	[0.80; 1.42]
Knibbs et al. 2018	ACHAPS					+ 1.77	[1.36; 2.29]
Puklová et al. 2019	Czech Respiratory Cohort					0.93	[0.73; 1.19]
Random effects model				+		1.10	[0.96; 1.26]
Heterogeneity: 1 ² = 56%	$t_{0}, \tau^{2} = 0.0172, p = 0.02$						
Moderate							
Pan et al. 2010	Liaoning Survey 2002					1.12	[1.04; 1.20]
Liu et al. 2013	SNEC Kindergarten				2.0	1.21	[0.93; 1.57]
Liu et al. 2014	SNEC				100	1.22	[1.06; 1.40]
Random effects model				\sim		1.15	[1.01; 1.29]
Heterogeneity: $I^2 = 0\%$,	$\tau^2 = 0.0003, p = 0.49$						
		—					
	0).6	0.75	1	1.5	2	
			Rela	ative Risk per 10 p	ug/m"		

$\mathsf{NO}_2-\mathsf{Prevalence}$ of active asthma – Children

Subgroup analysis – smoking adjustment

Study	Study Name	Relative Risk	RR	95%-CI
Yes				
Krämer et al. 2009	GINI, LISA: Wesel	• • • • • • • • • • • • • • • • • • • •	0.94	[0.56; 1.60]
Gehring et al. 2010	PIAMA		1.21	[0.95; 1.55]
Pan et al. 2010	Liaoning Survey 2002		1.12	[1.04; 1.20]
Svendsen et al. 2012	El Paso Children's Health		1.02	[0.88; 1.18]
Liu et al. 2013	SNEC Kindergarten	2 	1.21	[0.93; 1.57]
Zhou et al. 2013	French Six Cities		1.00	[0.88; 1.14]
Dell et al. 2014	T-CHEQ		1.10	[0.91; 1.34]
Liu et al. 2014	SNEC		1.22	[1.06; 1.40]
Gehring et al. 2015	ESCAPE		1.06	[0.89; 1.27]
Cakmak et al. 2016	Windsor Children's Health 05		1.07	[0.80; 1.42]
Random effects model		\diamond	1.10	[1.05; 1.15]
Heterogeneity: $l^2 = 0\%$,	$\tau^2 = 0, \rho = 0.64$			
No				
Knibbs et al. 2018	ACHAPS		• • 1.77	[1.36; 2.29]
Puklová et al. 2019	Czech Respiratory Cohort		0.93	[0.73; 1.19]
	0	6 075 1	15 2	
	č	Relative Risk per 10 µ	g/m ³	
NO_2 – Prevalence of active asthma – Children

Sensitivity analysis – reverse selection

NO₂ - Prevalence of active/current asthma - Children (<18 years)

Study	Study Name	Exposure window		Relative Risk	C RR	95%-CI	Weight
Krämer et al. 2009 Gehring et al. 2010 Pan et al. 2010 Svendsen et al. 2012 Liu et al. 2013 Zhou et al. 2013 Dell et al. 2014 Liu et al. 2014 Gehring et al. 2015 Cakmak et al. 2016 Knibbs et al. 2018 Puklová et al. 2019	GINI, LISA: Wesel PIAMA Liaoning Survey 2002 EI Paso Children's Health SNEC Kindergarten French Six Cities T-CHEQ SNEC ESCAPE Windsor Children's Health 05 ACHAPS Czech Respiratory Cohort	Cumulative average Annual average at birth Four year average at baseline Average recent Three year average at baseline Annual average current year Annual average current year Annual average current year Annual average current year Previous year annual average Five year average at baseline	e e e				1.9% 6.2% 15.4% 10.8% 5.7% 11.6% 7.0% 11.2% 13.1% 5.1% 5.8% 6.3%
Random effects model Prediction interval Heterogeneity: $I^2 = 51\%$, τ^2	² = 0.0083, <i>p</i> = 0.02		0.7 F	1 1 Relative Risk per 10	1.11 1.5 2 0 µg/m ³	[1.02; 1.22] [0.89; 1.39]	100.0%

Recent years > cumulative average > first year of life > at birth > pregnancy

NO_x – Prevalence of active asthma – Children

Primary meta-analysis

NO_X - Prevalence of active/current asthma - Children (<18 years)



EC – Prevalence of active asthma – Children

Primary meta-analysis

EC - Prevalence of active/current asthma - Children (<18 years)



PM₁₀ – Prevalence of active asthma – Children

Primary meta-analysis

PM₁₀ - Prevalence of active/current asthma - Children (<18 years)



PM₁₀ – Prevalence of active asthma – Children

Sensitivity and subgroup analyses notes:

Risk of bias confounding domain – Gruzieva et al. 2013 and Puklova et al. 2019 high risk of bias; other two low risk of bias.

Smoking adjustment: Gruzieva et al. 2013 and Puklova et al. 2019 no smoking adjustment.

Year of publication: All studies published after 2008

PM₁₀ – Prevalence of active asthma – Children Subgroup analysis – region

Study Study Name **Relative Risk** RR 95%-CI Western Europe Gruzieva et al. 2013 BAMSE 1.38 [0.65; 2.93] Zhou et al. 2013 French Six Cities 1.02 [0.84; 1.24] Gehring et al. 2015 ESCAPE 1.10 [0.74; 1.63] 1.05 [0.85; 1.30] Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, p = 0.73Eastern Europe Puklová et al. 2019 Czech Respiratory Cohort -----0.78 [0.61; 0.99] n -0.1 0.5 1 2 3 Relative Risk per 10 µg/m³

PM₁₀ – Prevalence of active asthma – Children Subgroup analysis – traffic specificity

Study	Study Name	Relative Risk	RR	95%-CI
High		1		
Gruzieva et al. 2013	BAMSE		1.38	[0.65; 2.93]
Moderate		1		
Zhou et al. 2013	French Six Cities	+	1.02	[0.84; 1.24]
Gehring et al. 2015	ESCAPE		1.10	[0.74; 1.63]
Puklová et al. 2019	Czech Respiratory Cohort	-	0.78	[0.61; 0.99]
Random effects mode	4	\rightarrow	0.94	[0.60; 1.46]
Heterogeneity: 12 = 469	$6, \tau^2 = 0.0154, \rho = 0.16$			
	0.1	0.5 1	2 3	
		Relative Risk per 10 µg/m ³		

Distance measures - Prevalence of active asthma – Adults

Reference	Study Name								Categories	RR	95% CI
Livingstone et al. 1996	Tower Hamlets GP	ļ							<150 vs. >150 m	1.00	[0.84, 1.19]
Morris et al. 2000	Tower Hamlets Respiratory	⊢ ∎							<150 vs. >150 m	0.78	[0.46, 1.32]
Balmes et al. 2014	Asthma Rhinitis Cohort, Severe Asthma Cohort								<131 vs. >334 m	0.77	[0.47, 1.26]
Balmes et al. 2014	Asthma Rhinitis Cohort, Severe Asthma Cohort	ŀ	•						131-334 vs. >334 m	1.26	[0.77, 2.06]
Bowatte et al. 2017a	TAHS		-∎	-					<200 vs. >200m	1.49	[1.09, 2.05]
Bowatte et al. 2017b	TAHS		╠╼╌┤						<200 vs. >200 m	1.21	[0.91, 1.59]
Bowatte et al. 2018	TAHS		-			•		\longrightarrow	<200 vs. >200 m	5.21	[1.54, 17.60]
				1							
		0		2	4 Relativ	e Risk	6	8			

Distance measures - Prevalence of active/current asthma - Adults

Note: Bowatte et al 2017a & b and 2018 refer to different study designs and study selections. All prevalence studies

Distance measures - Prevalence of active asthma – Children

Reference	Study Name		incidence/Prevalence	Categories	RR	95% CI
Pereira et al. 2009	Perth Asthma ED Visits		Incidence	-1 km	1.20	[0.96, 1.49]
Li et al. 2011	Detroit Medicaid Children's Asthma		Incidence	1000 m	0.98	[0.93, 1.03]
Livingstone et al. 1996	Tower Hamlets GP	•	Prevalence	<150 vs. >150 m	0.96	[0.78, 1.22]
van Vliet et al. 1997	South Holland Respiratory Survey	H-	Prevalence	<100 vs. 100-1000 m	0.87	[0.32, 2.37]
Lin et al. 2002	Erie County Children's Asthma	H - -I	Prevalence	<200 vs. >600 m	1.24	[0.87, 1.77]
Lin et al. 2002	Erie County Children's Asthma	H H H	Prevalence	201-400 vs. >600 m	0.88	[0.61, 1.28]
Lin et al. 2002	Erie County Children's Asthma	•	Prevalence	401-600 vs. >600 m	0.73	[0.50, 1.09]
Yang et al. 2002	Kaohsiung Respiratory Survey	-	Prevalence	150 vs. 1500 m	0.94	[0.78, 1.13]
McConnell et al. 2006	CHS	H H H	Prevalence	<75 vs. >300 m	1.50	[1.16, 1.95]
McConnell et al. 2006	CHS	• -1	Prevalence	75-150 vs. >300 m	1.33	[1.02, 1.72]
McConnell et al. 2006	CHS	•	Prevalence	150-300 vs. >300 m	1.04	[0.82, 1.33]
Dong et al. 2008	Liaoning Survey 2007	H 1	Prevalence	<20 vs. >100 m	1.25	[0.79, 1.98]
Dong et al. 2008	Liaoning Survey 2007	+	Prevalence	20-100 vs. >100 m	0.89	[0.56, 1.44]
Kim et al. 2008	EBCRHS		Prevalence	<75 vs. >300 m	3.80	[1.20, 11.71]
Kim et al. 2008	EBCRHS	H	Prevalence	75-150 vs. >300 m	1.87	[0.71, 4.90]
Kim et al. 2008	EBCRHS		Prevalence	150-300 vs. >300 m	1.25	[0.50, 3.11]
Krämer et al. 2009	GINI, LISA: Wesel	H.	Prevalence	<50 vs. >50 m	0.82	[0.51, 1.32]
Patel et al. 2011	CCCEH	µ − −1	Prevalence	-0.96 km	1.31	[0.88, 1.96]
Dell et al. 2014	T-CHEQ		Prevalence	<100 vs. >100 m	1.91	[0.46, 7.94]
Jung et al. 2015	CHEER	H e -H	Prevalence	<75 vs. >225 m	1.08	[0.69, 1.68]
Jung et al. 2015	CHEER	H H H	Prevalence	75-150 vs. >225 m	1.00	[0.68, 1.49]
Jung et al. 2015	CHEER	H -	Prevalence	150-225 vs. >225 m	1.12	[0.64, 1.96]
Yi et al. 2017	Seoul Atopy Friendly School	•	Prevalence	<150 vs. >500 m	0.93	[0.78, 1.11]
Yi et al. 2017	Seoul Atopy Friendly School	•	Prevalence	150-300 vs. >500 m	1.11	[0.93, 1.32]
Yi et al. 2017	Seoul Atopy Friendly School	-	Prevalence	300-500 vs. >500 m	1.00	[0.83, 1.20]

Distance measures - Prevalence of active/current asthma - Children (<18 years)

0 2 4 6 8 Relative Risk

Density measures - Prevalence of active asthma – Adults

Reference	Study Name		Stratification	Per Increment/Categories	RR	95% CI
Lindgren et al. 2009	Scania Respiratory Survey 2000	L	only non-allergic asthma	>10 vehicles/minute vs. no heavy road	0.96	[0.47, 1.96]
Lindgren et al. 2009	Scania Respiratory Survey 2000	⊢	only allergic asthma	>10 vehicles/minute vs. no heavy road	1.83	[1.23, 2.72]
Lindgren et al. 2009	Scania Respiratory Survey 2000	-	only non-allergic asthma	6-10 vehicles/minute vs. no heavy road	0.95	[0.54, 1.69]
Lindgren et al. 2009	Scania Respiratory Survey 2000	H	only allergic asthma	6-10 vehicles/minute vs. no heavy road	1.34	[0.92, 1.96]
Lindgren et al. 2009	Scania Respiratory Survey 2000	⊢	only non-allergic asthma	2-5 vehicles/minute vs. no heavy road	0.98	[0.63, 1.53]
Lindgren et al. 2009	Scania Respiratory Survey 2000	⊢− −1	only allergic asthma	2-5 vehicles/minute vs. no heavy road	0.96	[0.69, 1.33]
Lindgren et al. 2009	Scania Respiratory Survey 2000	- -	only non-allergic asthma	<2 vehicles/minute vs. no heavy road	0.82	[0.53, 1.28]
Lindgren et al. 2009	Scania Respiratory Survey 2000	H -	only allergic asthma	<2 vehicles/minute vs. no heavy road	1.13	[0.84, 1.51]
Havet et al. 2018	EGEA	H		4000 vehicle-km/day	1.14	[0.94, 1.37]
		0.4 1 2 3				

Density measures - Prevalence of active/current asthma - Adults

All prevalence studies.

Density measures - Prevalence of active asthma – Children

Reference	Study Name		incidence/Prevalence	Per Increment/Categories	RR	95% CI
Wilkinson et al. 1999	London Children's Asthma		Incidence	>50 vs. <1.5 vehicle-km/hour	0.88	[0.74, 1.06]
Wilkinson et al. 1999	London Children's Asthma	•	Incidence	15-50 vs. <1.5 vehicle-km/hour	0.80	[0.68, 0.95]
Wilkinson et al. 1999	London Children's Asthma	i ∎-1	Incidence	1.5-15 vs. <1.5 vehicle-km/hour	1.03	[0.87, 1.22]
Pereira et al. 2009	Perth Asthma ED Visits		Incidence	1000 vehicle-km/peak morning hour	0.73	[0.62, 0.85]
Wjst et al. 1993	Munich Asthma and Allergy	.	Prevalence	25000 vehicles/day	1.04	[0.89, 1.21]
van Vliet et al. 1997	South Holland Respiratory Survey	H 	Prevalence	high vs. low car volume	0.38	[0.13, 1.12]
van Vliet et al. 1997	South Holland Respiratory Survey	H	Prevalence	high vs. low truck volume	1.78	[0.66, 4.77]
English et al. 1999	San Diego Children's Asthma	H H H	Prevalence	>50100 vs. <9100 vehicles/day	1.05	[0.88, 1.26]
English et al. 1999	San Diego Children's Asthma	P ≣ -I	Prevalence	25001-50100 vs. <9100 cars/day	1.00	[0.83, 1.19]
English et al. 1999	San Diego Children's Asthma		Prevalence	16701-25000 vs. <9100 cars/day	0.76	[0.63, 0.91]
English et al. 1999	San Diego Children's Asthma	•	Prevalence	9101-16700 vs. <9100 cars/day	0.83	[0.69, 1.00]
Lin et al. 2002	Erie County Children's Asthma	I	Prevalence	>4043 vs. no vehicle-miles/day	1.93	[1.13, 3.29]
Lin et al. 2002	Erie County Children's Asthma	H	Prevalence	2367-4042 vs. no vehicle-miles/day	1.06	[0.64, 1.76]
Lin et al. 2002	Erie County Children's Asthma	+	Prevalence	<2366 vs. no vehicle-miles/day	1.31	[0.79, 2.16]
Nicolai et al. 2003	ISAAC Munich		Prevalence	>30000 vehicles/day vs. none	1.79	[1.05, 3.05]
Nicolai et al. 2003	ISAAC Munich	⊢I I	Prevalence	15001-30000 vehicles/day vs. none	1.18	[0.64, 2.17]
Nicolai et al. 2003	ISAAC Munich	⊢− ■−−−−−	Prevalence	2600-15000 vehicles/day vs. none	0.61	[0.26, 1.40]
Kim et al. 2008	EBCRHS		Prevalence	9414-74041 vehicles-km/day vs. none	2.37	[1.05, 5.36]
Kim et al. 2008	EBCRHS)	Prevalence	4403-9413 vehicles-km/day vs. none	1.40	[0.60, 3.30]
Kim et al. 2008	EBCRHS	+	Prevalence	1920-4402 vehicles-km/day vs. none	1.96	[0.85, 4.52]
Kim et al. 2008	EBCRHS	⊢	Prevalence	<1919 vehicles-km/day vs. none	1.23	[0.53, 2.83]

Density measures - Prevalence of active/current asthma - Children (<18 years)

0 1 2 3 4 5 Relative Risk

9.4 Acute lower respiratory infections (ALRI)

Meta-analysis overview – Children (<18).



Footnote: The following increments were used: $10 \ \mu g/m^3$ for NO₂ and $1 \ \mu g/m^3$ for EC. 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.

NO₂ – ALRI – Adults

Primary meta-analysis

NO₂ - ALRI - Adults (18+ years)



NO₂ – ALRI – Children

Primary meta-analysis

NO₂ - ALRI - Children (<18 years)

Study	Study Name	Exposure window			Relative R	lisk	RR	95%-CI	Weight
Hirsch et al. 1999	ISAAC Dresden	Annual mean			:	-	1.23	[1.10; 1.37]	12.1%
Janssen et al. 2003	ISAAC Southwestern Netherlands	Annual average current year	ar	08			- 1.20	[0.75; 1.91]	1.2%
Morgenstern et al. 2007	GINI, LISA: Munich	Annual average at birth		<u></u>			1.14	[0.71; 1.83]	1.2%
Karr et al. 2009	Georgia Air Basin Birth Cohort	Cumulative average					1.06	[1.02; 1.09]	22.5%
Svendsen et al. 2012	El Paso Children's Health	Average recent			-		1.12	[0.93; 1.34]	6.4%
Aguilera et al. 2013	INMA	Entire pregnancy					1.05	[0.98; 1.12]	17.8%
Pedersen et al. 2013	EDEN	Entire pregnancy		-			0.95	[0.75; 1.21]	4.1%
MacIntyre et al. 2014	ESCAPE	Annual average at birth				*	1.30	[1.02; 1.65]	4.1%
Ranzi et al. 2014	GASPI	Annual average at birth		0			0.87	[0.69; 1.09]	4.6%
Liu et al. 2016	CCHH Shanghai	Entire pregnancy				_	1.17	[1.07; 1.30]	13.5%
Madsen et al. 2017	МоВа	Entire pregnancy			-		1.05	[0.95; 1.17]	12.6%
Random effects model Prediction interval			-		\$		1.09	[1.03; 1.16] [0.95; 1.25]	100.0%
Heterogeneity: $I^2 = 45\%$, τ	$^{2} = 0.0030, p = 0.05$			1.0			0		
			0.6	0.75	1	1.5	2		
				Relat	ive Risk per	10 µg/m ³			





Footnote: 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.

NO₂ – ALRI – Children Subgroup analysis – region

Study	Study Name			Relative Ris	sk	RR	95%-CI
North America				E a			
Karr et al. 2009	Georgia Air Basin Birth Cohort			-		1.06	[1.02; 1.09]
Svendsen et al. 2012	El Paso Children's Health			-		1.12	[0.93; 1.34]
Western Europe						10002	
Hirsch et al. 1999	ISAAC Dresden					1.23	[1.10; 1.37]
Janssen et al. 2003	ISAAC Southwestern Netherlands		-			1.20	[0.75; 1.91]
Morgenstern et al. 2007	GINI, LISA: Munich		-	- I ·		- 1.14	[0.71; 1.83]
Aguilera et al. 2013	INMA			- - -		1.05	[0.98; 1.12]
Pedersen et al. 2013	EDEN			-		0.95	[0.75; 1.21]
MacIntyre et al. 2014	ESCAPE				•	1.30	[1.02; 1.65]
Ranzi et al. 2014	GASPII			-		0.87	[0.69; 1.09]
Madsen et al. 2017	MoBa			- -		1.05	[0.95; 1.17]
Random effects model				\Rightarrow		1.08	[0.97; 1.20]
Heterogeneity: / ² = 49%,	$\tau^2 = 0.0071, p = 0.06$						
Asia							
Liu et al. 2016	CCHH Shanghai				-	1.17	[1.07: 1.30]
Random effects model	States to			4			
			-		- 1		
		0.6	0.75	1	1.5	2	
			Rela	tive Risk per 1	10 µg/m ³		

NO₂ – ALRI – Children

Subgroup analysis – year of publication

Study	Study Name			Relative Risk	c	RR	95%-CI
Before 2008							
Hirsch et al. 1999	ISAAC Dresden					1.23	[1.10; 1.37]
Janssen et al. 2003	ISAAC Southwestern Netherlands		8			1.20	[0.75; 1.91]
Morgenstern et al. 2007	GINI, LISA: Munich			-		1.14	[0.71; 1.83]
Random effects model				\diamond		1.22	[1.16; 1.29]
Heterogeneity: $l^2 = 0\%$, t	$c^2 = 0, p = 0.95$						
After 2008							
Karr et al. 2009	Georgia Air Basin Birth Cohort			-		1.06	[1.02; 1.09]
Svendsen et al. 2012	El Paso Children's Health			- · ·		1.12	[0.93; 1.34]
Aguilera et al. 2013	INMA			- -		1.05	[0.98; 1.12]
Pedersen et al. 2013	EDEN					0.95	[0.75; 1.21]
MacIntyre et al. 2014	ESCAPE					1.30	[1.02; 1.65]
Ranzi et al. 2014	GASPII					0.87	[0.69; 1.09]
Liu et al. 2016	CCHH Shanghai			-		1.17	[1.07; 1.30]
Madsen et al. 2017	MoBa					1.05	[0.95; 1.17]
Random effects model				\diamond		1.06	[1.02; 1.11]
Heterogeneity: /2 = 38%,	$\tau^2 = < 0.0001, p = 0.12$	_					
		0.6	0.75	1	1.5	2	
			Rela	ative Risk per 10	µg/m		

NO₂ – ALRI – Children Subgroup analysis – traffic specificity

Study	Study Name		Relative Risk	RR	95%-CI
High			÷		
Morgenstern et al. 2007	GINI, LISA: Munich		· · ·	1.14	[0.71; 1.83]
Karr et al. 2009	Georgia Air Basin Birth Cohort		T	1.06	[1.02; 1.09]
Svendsen et al. 2012	El Paso Children's Health			1.12	[0.93; 1.34]
Aguilera et al. 2013	INMA			1.05	[0.98; 1.12]
Pedersen et al. 2013	EDEN		-	0.95	[0.75; 1.21]
MacIntyre et al. 2014	ESCAPE			- 1.30	[1.02; 1.65]
Ranzi et al. 2014	GASPII		-	0.87	[0.69; 1.09]
Madsen et al. 2017	MoBa			1.05	[0.95; 1.17]
Random effects model			♦	1.05	[1.02; 1.09]
Heterogeneity: $l^2 = 2\%$,	$\tau^2 = < 0.0001, p = 0.42$				
Moderate					
Hirsch et al. 1999	ISAAC Dresden			1.23	[1.10; 1.37]
Janssen et al. 2003	ISAAC Southwestern Netherlands	-	- · ·	1.20	[0.75; 1.91]
Liu et al. 2016	CCHH Shanghai		1	1.17	[1.07; 1.30]
Random effects model			\diamond	1.20	[1.12; 1.28]
Heterogeneity: /2 = 0%,	$\tau^2 = 0, p = 0.83$				
		-	1		
	0.6	6 0.75	1 1.5	2	
		Re	lative Risk per 10 µg/m		

Subgroup analysis – smoking adjustment

All corrected for smoking

NO₂ – ALRI – Children Subgroup analysis – study design

Study	Study Name			Relative Risk		RR	95%-CI
Case-control				E.			
Karr et al. 2009	Georgia Air Basin Birth Cohort			-		1.06	[1.02; 1.09]
Cohort							
Morgenstern et al. 2007	GINI, LISA: Munich			<u> </u>		- 1.14	[0.71: 1.83]
Aquilera et al. 2013	INMA					1.05	[0.98: 1.12]
Pedersen et al. 2013	EDEN		_			0.95	[0.75; 1.21]
MacIntyre et al. 2014	ESCAPE					1.30	[1.02; 1.65]
Ranzi et al. 2014	GASPII					0.87	[0.69; 1.09]
Madsen et al. 2017	MoBa			- 		1.05	[0.95; 1.17]
Random effects model				\Rightarrow		1.05	[0.97; 1.13]
Heterogeneity: $I^2 = 24\%$,	$\tau^2 = < 0.0001, p = 0.25$						
Cross sectional				1.100			
Hirsch et al. 1999	ISAAC Dresden					1.23	[1.10; 1.37]
Janssen et al. 2003	ISAAC Southwestern Netherlands	5	1			1.20	[0.75; 1.91]
Svendsen et al. 2012	El Paso Children's Health			-		1.12	[0.93; 1.34]
Liu et al. 2016	CCHH Shanghai			-		1.17	[1.07; 1.30]
Random effects model				\diamond		1.19	[1.12; 1.26]
Heterogeneity: $I^2 = 0\%$, τ^2	f = 0, p = 0.84	_			_	_	
		0.6	0.75		1 5		
		0.0	U.75 Dala	tive Diek ner 10 i	1.0	2	
			Reid	uve max per 10 p	grin		

NO₂ – ALRI – Children Sensitivity analysis – reverse selection

NO₂ - ALRI - Children (<18 years)



Recent years > cumulative average > first year of life > at birth > pregnancy

EC-ALRI - Children

Primary meta-analysis

EC - ALRI - Children (<18 years)



EC – ALRI – Children Subgroup analysis – region

Study	Study Name	Relative Risk	RR 95	%-CI
North America				
Karr et al. 2009	Georgia Air Basin Birth Cohort	÷	0.99 [0.96;	1.02]



EC – ALRI – Children

Subgroup analysis – traffic specificity

Study	Study Name		1	Relative Risk	RR	95%-CI
High			1			
Morgenstern et al. 2007	GINI, LISA: Munich	-	_	*	• 1.22	[0.46; 3.26]
Karr et al. 2009	Georgia Air Basin Birth Cohort		- 慶二		0.99	[0.96; 1.02]
MacIntyre et al. 2014	ESCAPE		2222		1.87	[1.39; 2.51]
Random effects model					1 .31	[0.53; 3.20]
Heterogeneity: $l^2 = 89\%$,	$\tau^2 = 0.1274, p < 0.01$					
Moderate						
Janssen et al. 2003	ISAAC Southwestern Netherlands	•			• 1.31	[0.45; 3.83]
		_				
		0.7		15		
		0.7	1	1.5	3	
			Relat	ive Risk per 1 ug/m"		

Chapter 9 Additional Materials

EC – ALRI – Children

Subgroup analysis notes:

Year of publication: Jansen 2003 and Morgenstern before 2008 Smoking adjustment: All corrected for smoking Study design: Karr 2009 case-control; Jansen 2003 cross-sectional, the other two cohorts

Distance measures – ALRI – Adults



Distance measures – ALRI – Children

Reference	Study Name		Categories	RR	95% CI
van Vliet et al. 1997	South Holland Respiratory Survey		<100 vs. 100-1000 m	0.99	[0.39, 2.52]
Yang et al. 2002	Kaohsiung Respiratory Survey	- - 1	150 vs. 1500 m	0.99	[0.88, 1.12]
Morgenstern et al. 2007	GINI, LISA: Munich	⊢	<50 vs. >50 m	1.15	[0.87, 1.53]
Ranzi et al. 2014	GASPII	⊢	<86.1 vs. > 86.1 m	1.03	[0.72, 1.48]
Rice et al. 2015	VIVA	Jj	<100 vs. >1000 m	1.38	[1.11, <mark>1.63]</mark>
Lee et al. 2018	CHEER	⊢I	<75 vs. >700 m	1.12	[0.71, 1.79]
Lee et al. 2018	CHEER	⊨	75-700 vs. >700 m	1.17	[0.81, 1 .68]
	0	1 2 Relative Risk			

Distance measures - ALRI - Children (<18 years)

Density measures – ALRI – Adults



Density measures – ALRI – Children



Density measures - ALRI - Children (<18 years)

9.5 Incidence of chronic obstructive pulmonary disease (COPD)

Meta-analysis overview



Footnote: The following increments were used: $10 \mu g/m^3$ for NO₂, $20 \mu g/m^3$ for NO_x and $5 \mu g/m^3$ 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.

NO₂ – Incidence of COPD – Adults

Primary meta-analysis

Study	Study Name	Relative Risk	RR	95%-CI	Weight
Andersen et al. 2011	DDCH		1.14	[1.04; 1.26]	14.9%
Gan et al. 2013	Vancouver Administrative		1.00	[0.95; 1.05]	18.0%
Schikowski et al. 2014	ESCAPE		0.99	[0.86; 1.13]	11.9%
Atkinson et al. 2015	CPRD		1.03	[0.96; 1.10]	17.0%
Carey et al. 2016	CPRD London		0.98	[0.82; 1.18]	9.0%
Weichenthal et al. 2017	ONPHEC		1.14	[1.09; 1.20]	18.4%
Salimi et al. 2018	45 and Up Study		0.84	[0.72; 0.97]	10.8%
Random effects model		÷	1.03	[0.94; 1.13]	100.0%
Prediction interval				[0.81; 1.30]	
Heterogeneity: $I^2 = 79\%$, τ	$^{2} = 0.0071, p < 0.01$		1		
	C	0.7 0.8 1 1.25	5		
		Relative Risk per 10 µg/m ³			

NO₂ – Incidence of COPD – Adults

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate		1		
Andersen et al. 2011	DDCH		- 1.14	[1.04; 1.26]
Schikowski et al. 2014	ESCAPE		0.99	[0.86; 1.13]
Atkinson et al. 2015	CPRD		1.03	[0.96; 1.10]
Carey et al. 2016	CPRD London		0.98	[0.82; 1.18]
Weichenthal et al. 2017	ONPHEC		1.14	[1.09; 1.20]
Salimi et al. 2018	45 and Up Study -		0.84	[0.72; 0.97]
Random effects model			1.03	[0.91; 1.16]
Heterogeneity: / ² = 78%,	$\tau^2 = 0.0094, p < 0.01$			
High				
Gan et al. 2013	Vancouver Administrative		1.00	[0.95; 1.05]
		- I		
	0.7	0.8 1 1.	25	

Relative Risk per 10 µg/m³

NO_2 – Incidence of COPD – Adults

Subgroup analysis – region

Study	Study Name		Relative Risk	R	R 95	%-CI
North America Gan et al. 2013 Weichenthal et al. 2017	Vancouver Administrative ONPHEC		╉	1.0 ————————————————————————————————————	0 [0.95; 4 [1.09;	1.05] 1.20]
Western Europe Andersen et al. 2011 Schikowski et al. 2014 Atkinson et al. 2015 Carey et al. 2016 Random effects model Heterogeneity: $J^2 = 34\%$:	DDCH ESCAPE CPRD CPRD London $c^2 = 0.0018, \rho = 0.21$			1.1 0.9 1.0 0.9 0.9 0.9 1.0	4 [1.04; 9 [0.86; 3 [0.96; 8 [0.82; 5 [0.94; 1	1.26] 1.13] 1.10] 1.18] 1.17]
Australia/New Zealand Salimi et al. 2018	45 and Up Study	0.7 0.8 R	+ 1 lelative Risk per 10 ur	0.8 1.25 a/m ³	4 [0.72; (0.97]

Subgroup analysis – year of publication All post 2008

NO₂ – Incidence of COPD – Adults Subgroup analysis – traffic specificity

Study	Study Name			Relative Risk	RR	95%-CI
High				1		
Andersen et al. 2011	DDCH				1.14	[1.04; 1.26]
Gan et al. 2013	Vancouver Administrative			-+	1.00	[0.95; 1.05]
Schikowski et al. 2014	ESCAPE				0.99	[0.86; 1.13]
Carey et al. 2016	CPRD London				0.98	[0.82; 1.18]
Weichenthal et al. 2017	ONPHEC				1.14	[1.09; 1.20]
Salimi et al. 2018	45 and Up Study	-			0.84	[0.72; 0.97]
Random effects model					1.02	[0.91; 1.15]
Heterogeneity: $I^2 = 82\%$,	$\tau^2 = 0.0097, p < 0.01$					
Moderate						
Atkinson et al. 2015	CPRD			-	1.03	[0.96; 1.10]
		0.7	0.8	1	1.25	

Relative Risk per 10 µg/m³

NO₂ – Incidence of COPD – Adults Subgroup analysis – smoking adjustment

Study Study Name **Relative Risk** RR 95%-CI Yes Andersen et al. 2011 DDCH 1.14 [1.04; 1.26] Schikowski et al. 2014 ESCAPE 0.99 [0.86; 1.13] Atkinson et al. 2015 CPRD 1.03 [0.96; 1.10] CPRD London 0.98 [0.82; 1.18] Carey et al. 2016 Salimi et al. 2018 45 and Up Study 0.84 [0.72; 0.97] Random effects model 1.00 [0.87; 1.15] Heterogeneity: $l^2 = 68\%$, $\tau^2 = 0.0083$, p = 0.02No Gan et al. 2013 Vancouver Administrative 1.00 [0.95; 1.05] -Weichenthal et al. 2017 ONPHEC 1.14 [1.09; 1.20] r 0.6 0.75 1.5 2 1 Relative Risk per 10 µg/m³

NO_x – Incidence of COPD – Adults

Primary meta-analysis

NO_{X} - Incidence of COPD

Study	Study Name	Rela	tive Risk	R	R 95%-CI	Weight
Andersen et al. 2011 Schikowski et al. 2014 Carev et al. 2016	DDCH ESCAPE CPRD London		-	- 1.0 - 0.9	8 [1.01; 1.16] 7 [0.85; 1.10] 9 [0.86; 1.13]	51.3% 25.5% 23.2%
Ourcy cr ul. 2010	OF IND EXHIBIT			0.5	5 [0.00, 1.10]	20.270
Random effects mode	I		-	1.0	3 [0.88; 1.20]	100.0%
Prediction interval					[0.51; 2.07]	
Heterogeneity: $I^2 = 31\%$, a	$c^2 = 0.0017$, $p = 0.24$		1			
· · · · · ·	0.8	0.9	1 .	1.1 1.2		
	F	Relative Ri	sk per 20 µ	ıg/m ³		

PM_{2.5} – Incidence of COPD – Adults

Primary meta-analysis

$\ensuremath{\mathsf{PM}_{2.5}}\xspace$ - Incidence of COPD

Study	Study Name	Relative Risk	RR	95%-CI	Weight
Gan et al. 2013 Schikowski et al. 2014 Atkinson et al. 2015 Salimi et al. 2018	Vancouver Administrative ESCAPE CPRD 45 and Up Study		1.06 0.73 0.98 0.48	[0.94; 1.21] [0.51; 1.04] [0.84; 1.15] [0.22; 1.04]	38.6% 19.7% 35.5% 6.3%
Random effects mode Prediction interval Heterogeneity: $I^2 = 60\%$,	$\tau^2 = 0.0253, p = 0.06$	0.8 1 1.25 Relative Risk per 5 μg/m ³	0.91 T	[0.62; 1.36] [0.38; 2.18]	100.0%
PM_{2.5} – Incidence of COPD – Adults

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high



PM_{2.5} – Incidence of COPD – Adults Subgroup analysis – smoking adjustment

Study	Study Name		Relative Risk		RR	95%-CI
Yes			1			
Schikowski et al. 2014	ESCAPE		-		0.73	[0.51; 1.04]
Atkinson et al. 2015	CPRD				0.98	[0.84; 1.15]
Salimi et al. 2018	45 and Up Study		100		0.48	[0.22; 1.04]
Random effects model		_			0.80	[0.38; 1.70]
Heterogeneity: 1 ² = 61%	$\tau^2 = 0.0497, p = 0.08$					
No						
Gan et al. 2013	Vancouver Administrative		-		1.06	[0.94; 1.21]
			1			
	ſ	1	1			
	0.6	6 0.75	1	1.5	2	
			Relative Risk per 5 j	ug/m ³		

PM_{2.5} – Incidence of COPD – Adults

Subgroup analysis – region Gan 2013 North America; Schikowski 2014 and Atkinson 2015 Western Europe, and Salimi 2018 Australia/New Zealand

Subgroup analysis – year of publication All post 2008

Subgroup analysis – traffic specificity All moderate

Distance measures – Incidence of COPD – Adults



Distance measures - Incidence of COPD

Density measures – Incidence of COPD – Adults



Density measures - Incidence of COPD

9.6 Prevalence of active wheeze

Meta-analysis overview – Children (<18)



Footnote: The following increments were used: $10 \ \mu g/m^3$ for NO₂, $20 \ \mu g/m^3$ for NO_x, $1 \ \mu g/m^3$ for EC, $10 \ \mu g/m^3$ for PM₁₀ and $5 \ \mu g/m^3$ 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.

Primary meta-analysis

Study	Study Name	Exposure window	Relative Risk	RR	95%-CI	Weight
Pikhart et al. 1997	SAVIAH	Annual average current year		0.98	[0.82; 1.18]	3.3%
Hirsch et al. 1999	ISAAC Dresden	Annual mean	+	1.13	[0.93; 1.37]	3.0%
Krämer et al. 2000	Düsseldorf School Survey	Annual average current year		→ 1.70	[0.90; 3.20]	0.3%
Janssen et al. 2003	ISAAC Southwestern Netherlands	Annual average current year		1.37	[1.00; 1.89]	1.2%
Krämer et al. 2009	GINI, LISA: Wesel	Cumulative average	••••	0.61	[0.36; 1.03]	0.4%
Oftedal et al. 2009	Oslo Birth Cohort	Annual average at birth	-+	1.01	[0.90; 1.12]	7.5%
Rosenlund et al. 2009	ISAAC Rome	Exposure in 2000-2001 (recent year	r)	1.00	[0.65; 1.54]	0.6%
Gehring et al. 2010	PIAMA	Annual average at birth	·	1.01	[0.87; 1.17]	4.7%
Pan et al. 2010	Liaoning Survey 2002	Four year average at baseline		0.95	[0.91; 1.00]	18.7%
Pénard-Morand et al. 2010	French Six Cities	Annual average current year	+	1.19	[0.92; 1.52]	1.9%
Ebisu et al. 2011	Yale Childhood Asthma Study	Average first year		1.12	[0.99; 1.27]	6.0%
Svendsen et al. 2012	El Paso Children's Health	Average recent		0.94	[0.80; 1.10]	4.2%
Altuğ et al. 2013	ISAAC Eskisehir	Annual average current year		0.92	[0.80; 1.07]	4.7%
Liu et al. 2013	SNEC Kindergarten	Three year average at baseline		0.96	[0.82; 1.12]	4.3%
Abidin et al. 2014	ISAAC Malaysia	Annual average current year		→ 1.90	[1.02; 3.53]	0.3%
Dell et al. 2014	T-CHEQ	Average first year		0.98	[0.83; 1.16]	3.9%
Liu et al. 2014	SNEC	Three year average at baseline		0.92	[0.84; 1.01]	9.5%
Wood et al. 2015	ISAAC East London	Annual average current year		1.10	[0.78; 1.57]	1.0%
Deng et al. 2016	CCHH Changsha	Entire pregnancy		0.97	[0.85; 1.11]	5.4%
Madsen et al. 2017	MoBa	Entire pregnancy	÷	1.02	[0.97; 1.07]	17.9%
Knibbs et al. 2018	ACHAPS	Previous year annual average		1.34	[0.99; 1.82]	1.3%
Random effects model			4	1.00	[0.96; 1.05]	100.0%
Prediction interval				_	[0.92; 1.09]	
Heterogeneity: $I^2 = 41\%$, $\tau^2 =$	0.0012, p = 0.03		1	1		
-	to see the cost of the cost of the		0.5 1 2	2.5		
			Relative Risk per 10µg/m ³			

NO₂ - Prevalence of wheeze 12 months - Children (<18 years)

NO_2 – Prevalence of active wheeze– Children

Funnel plot



Footnote: 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.

Trim and fill

Study	Relative Risk	RR	95%-CI	Weight
Pikhart et al 1997 SAVIAH	+	0.98	[0 82 [.] 1 18]	3.3%
Hirsch et al. 1999, ISAAC Dresden	4	1.13	[0.93: 1.37]	2.9%
Krämer et al. 2000. Düsseldorf School Survey	· · · · · · · · · · · · · · · · · · ·	1.70	[0.90: 3.20]	0.3%
Janssen et al. 2003, ISAAC Southwestern Netherlands	<u> </u>	1.37	[1.00; 1.89]	1.2%
Krämer et al. 2009, GINI, LISA: Wesel		0.61	[0.36; 1.03]	0.4%
Oftedal et al. 2009, Oslo Birth Cohort	+	1.01	[0.90; 1.12]	7.3%
Rosenlund et al. 2009, ISAAC Rome		1.00	[0.65; 1.54]	0.6%
Gehring et al. 2010, PIAMA	+	1.01	[0.87; 1.17]	4.6%
Pan et al. 2010, Liaoning Survey 2002		0.95	[0.91; 1.00]	17.7%
Pénard-Morand et al. 2010, French Six Cities	 • -	1.19	[0.92; 1.52]	1.9%
Ebisu et al. 2011, Yale Childhood Asthma Study		1.12	[0.99; 1.27]	5.9%
Svendsen et al. 2012, El Paso Children's Health		0.94	[0.80; 1.10]	4.1%
Altuğ et al. 2013, ISAAC Eskisehir		0.92	[0.80; 1.07]	4.6%
Liu et al. 2013, SNEC Kindergarten	+	0.96	[0.82; 1.12]	4.2%
Abidin et al. 2014, ISAAC Malaysia	· · · · · · · · · · · · · · · · · · ·	1.90	[1.02; 3.53]	0.3%
Dell et al. 2014, T-CHEQ	+	0.98	[0.83; 1.16]	3.8%
Liu et al. 2014, SNEC	-	0.92	[0.84; 1.01]	9.2%
Wood et al. 2015, ISAAC East London	- 	1.10	[0.78; 1.57]	1.0%
Deng et al. 2016, CCHH Changsha	主	0.97	[0.85; 1.11]	5.3%
Madsen et al. 2017, MoBa	7	1.02	[0.97; 1.07]	17.0%
Knibbs et al. 2018, ACHAPS		1.34	[0.99; 1.82]	1.3%
Filled: Knibbs et al. 2018, ACHAPS		0.72	[0.53; 0.98]	1.3%
Filled: Janssen et al. 2003, ISAAC Southwestern Netherlands		0.71	[0.52; 0.98]	1.2%
Filled: Krämer et al. 2000, Düsseldorf School Survey	-	0.57	[0.30; 1.08]	0.3%
Filled: Abidin et al. 2014, ISAAC Malaysia -		0.51	[0.28; 0.95]	0.3%
Random effects model	\$	0.99	[0.94; 1.04]	100.0%
Prediction interval	<u>+</u>		[0.90; 1.08]	
Heterogeneity: $I^2 = 51\%$, $\tau^2 = 0.0013$, $p < 0.01$				
	0.5 1 2			
	Relative Risk per 10 µg/m ²			

NO₂ - Prevalence of active wheeze - Children (<18 years)

Study			RR	95%-CI	Weights
Pikhart et al. 1997, SAVIAH			0.98	[0.82, 1.18]	3.30
Hirsch et al. 1999, ISAAC Dresden			1.13	[0.93, 1.37]	2.95
Krämer et al. 2000, Düsseldorf School Survey			▶ 1.70	[0.90, 3.20]	0.31
Janssen et al. 2003, ISAAC Southwestern Netherlan	B		1.37	[1.00, 1.89]	1.16
Krämer et al. 2009, GINI, LISA: Wesel	<		0.61	[0.36, 1.03]	0.44
Oftedal et al. 2009, Oslo Birth Cohort			1.01	[0.90, 1.12]	7.47
Rosenlund et al. 2009, ISAAC Rome	<		1.00	[0.65, 1.54]	0.65
Gehring et al. 2010, PIAMA			1.01	[0.87, 1.17]	4.69
Pan et al. 2010, Liaoning Survey 2002	_		0.95	[0.91, 1.00]	18.72
Pénard-Morand et al. 2010, French Six Cities			1.19	[0.92, 1.52]	1.88
Ebisu et al. 2011, Yale Childhood Asthma Study			1.12	[0.99, 1.27]	6.03
Svendsen et al. 2012, El Paso Children's Health			0.94	[0.80, 1.10]	4.19
Altuğ et al. 2013, ISAAC Eskisehir			0.92	[0.80, 1.07]	4.67
Liu et al. 2013, SNEC Kindergarten			0.96	[0.82, 1.12]	4.30
Abidin et al. 2014, ISAAC Malaysia			> 1.90	[1.02, 3.53]	0.32
Dell et al. 2014, T-CHEQ			0.98	[0.83, 1.16]	3.87
Liu et al. 2014, SNEC			0.92	[0.84, 1.01]	9.53
Wood et al. 2015, ISAAC East London			1.10	[0.78, 1.57]	0.99
Deng et al. 2016, CCHH Changsha	_		0.97	[0.85, 1.11]	5.39
Madsen et al. 2017, MoBa			1.02	[0.97, 1.07]	17.87
Knibbs et al. 2018, ACHAPS		<u></u> .	1.34	[0.99, 1.82]	1.28
Pooled Est.			1.00	[0.96, 1.05]	100%
Trim-n-fill Pooled est			0.99	[0.94, 1.04]	l
).7 1	1.5	2		
N imputed studies= 4	Relative Risk per 10 µg/	/m ³			

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate				
Hirsch et al. 1999	ISAAC Dresden		1 13	[0 93: 1 37]
Krämer et al. 2000	Düsseldorf School Survey	· · · · · · · · · · · · · · · · · · ·	-+ 170	[0.90: 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherlands		1.37	[1.00: 1.89]
Krämer et al. 2009	GINL LISA: Wesel	• · · · · · · · · · · · · · · · · · · ·	0.61	[0.36:1.03]
Oftedal et al. 2009	Oslo Birth Cohort	_ _	1.01	[0.90: 1.12]
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65: 1.54]
Gehring et al. 2010	PIAMA	_ _	1.01	[0.87; 1.17]
Pénard-Morand et al. 2010	French Six Cities		1.19	[0.92; 1.52]
Ebisu et al. 2011	Yale Childhood Asthma Study		1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health	+-	0.94	[0.80; 1.10]
Altuğ et al. 2013	ISAAC Eskisehir		0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten		0.96	[0.82; 1.12]
Abidin et al. 2014	ISAAC Malaysia		→ 1.90	[1.02; 3.53]
Dell et al. 2014	T-CHEQ		0.98	[0.83; 1.16]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
Madsen et al. 2017	MoBa	÷	1.02	[0.97; 1.07]
Knibbs et al. 2018	ACHAPS		1.34	[0.99; 1.82]
Random effects model			1.02	[0.96; 1.08]
Heterogeneity: $I^2 = 42\%$, τ^2	= 0.0016, <i>p</i> = 0.03			
High				
Pikhart et al. 1997	SAVIAH		0.98	[0.82; 1.18]
Pan et al. 2010	Liaoning Survey 2002	-	0.95	[0.91; 1.00]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
Random effects model		0	0.96	[0.94; 0.98]
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0\%$	= 0, <i>p</i> = 0.95			
			2.5	
	l	J.D 1 2 Deletive Diek ses 10 us/m ³	2.5	
		Relative Risk per 10 µg/m		

Sensitivity analysis - risk of bias selection bias domain - low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate		Ĩ		
Pikhart et al. 1997	SAVIAH	_ _	0.98	[0.82; 1.18]
Hirsch et al. 1999	ISAAC Dresden	++	1.13	[0.93; 1.37]
Krämer et al. 2000	Düsseldorf School Survey		• 1.70	[0.90; 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherlands	· · · ·	1.37	[1.00; 1.89]
Krämer et al. 2009	GINI, LISA: Wesel	• · · · · · · · · · · · · · · · · · · ·	0.61	[0.36; 1.03]
Oftedal et al. 2009	Oslo Birth Cohort		1.01	[0.90; 1.12]
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65; 1.54]
Gehring et al. 2010	PIAMA	_ 	1.01	[0.87; 1.17]
Pan et al. 2010	Liaoning Survey 2002	+	0.95	[0.91; 1.00]
Pénard-Morand et al. 2010	French Six Cities	++	1.19	[0.92; 1.52]
Ebisu et al. 2011	Yale Childhood Asthma Study		1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health	+ -	0.94	[0.80; 1.10]
Altuğ et al. 2013	ISAAC Eskisehir		0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten	<u> </u>	0.96	[0.82; 1.12]
Abidin et al. 2014	ISAAC Malaysia		• 1.90	[1.02; 3.53]
Dell et al. 2014	T-CHEQ		0.98	[0.83; 1.16]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Madsen et al. 2017	MoBa	÷	1.02	[0.97; 1.07]
Knibbs et al. 2018	ACHAPS	— • — •	1.34	[0.99; 1.82]
Random effects model			1.00	[0.95; 1.05]
Heterogeneity: $I^2 = 46\%$, τ^2	= 0.0015, <i>p</i> = 0.01			
High				
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
		-		
		r	٦	
	C	0.5 1 2 2	2.5	

Relative Risk per 10 µg/m³

Sensitivity analysis - risk of bias outcome measurement domain - low/moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low/Moderate		Ĩ		
Pikhart et al. 1997	SAVIAH		0.98	[0.82; 1.18]
Hirsch et al. 1999	ISAAC Dresden	+	1.13	[0.93; 1.37]
Krämer et al. 2000	Düsseldorf School Survey		→ 1.70	[0.90; 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherlands	· · · · · · · · · · · · · · · · · · ·	1.37	[1.00; 1.89]
Krämer et al. 2009	GINI, LISA: Wesel	• • • • • • • • • • • • • • • • • • •	0.61	[0.36; 1.03]
Oftedal et al. 2009	Oslo Birth Cohort	-+-	1.01	[0.90; 1.12]
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65; 1.54]
Gehring et al. 2010	PIAMA		1.01	[0.87; 1.17]
Pan et al. 2010	Liaoning Survey 2002	+	0.95	[0.91; 1.00]
Pénard-Morand et al. 2010	French Six Cities	+ •	1.19	[0.92; 1.52]
Ebisu et al. 2011	Yale Childhood Asthma Study	⊢ ⊷	1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health	-+	0.94	[0.80; 1.10]
Altuğ et al. 2013	ISAAC Eskisehir	+-	0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten	+	0.96	[0.82; 1.12]
Abidin et al. 2014	ISAAC Malaysia		- 1.90	[1.02; 3.53]
Dell et al. 2014	T-CHEQ		0.98	[0.83; 1.16]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
Madsen et al. 2017	MoBa	+	1.02	[0.97; 1.07]
Knibbs et al. 2018	ACHAPS		1.34	[0.99; 1.82]
Random effects model			1.00	[0.95; 1.05]
Heterogeneity: $l^2 = 43\%$, τ^2	= 0.0012, <i>p</i> = 0.02			
High				
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
		·	_	
	0	.5 1 2	2.5	



Subgroup analysis – region

Study	Study Name	Relative Risk	RR	95%-CI
North America		Ĩ		
Ebisu et al. 2011	Yale Childhood Asthma Study	-	1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health		0.94	[0.80; 1.10]
Dell et al. 2014	T-CHEQ.		0.98	[0.83; 1.16]
Random effects model			1.02	[0.81; 1.29]
Heterogeneity: $l^2 = 40\%$, τ	$c^2 = 0.0041, p = 0.19$	200 million (100 - 100 -		
Western Furope				
Hirsch et al. 1999	ISAAC Dresden		1.13	[0.93; 1.37]
Krämer et al. 2000	Düsseldorf School Survey		1.70	[0.90: 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherlands	· · · · · · · · · · · · · · · · · · ·	1.37	[1.00; 1.89]
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65; 1.54]
Oftedal et al. 2009	Oslo Birth Cohort	+-	1.01	[0.90; 1.12]
Krämer et al. 2009	GINI, LISA: Wesel	• • • • • • • • • • • • • • • • • • • •	0.61	[0.36; 1.03]
Gehring et al. 2010	PIAMA	<u> </u>	1.01	[0.87; 1.17]
Pénard-Morand et al. 201	0 French Six Cities	++	1.19	[0.92; 1.52]
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
Madsen et al. 2017	МоВа	÷	1.02	[0.97; 1.07]
Random effects model			1.03	[0.98; 1.09]
Heterogeneity: 12 = 25%, a	$t^2 = < 0.0001, p = 0.21$			
Asia				
Pan et al. 2010	Liaoning Survey 2002	*	0.95	[0.91; 1.00]
Altuğ et al. 2013	ISAAC Eskisehir	-++	0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten	+	0.96	[0.82; 1.12]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Abidin et al. 2014	ISAAC Malaysia	•	1.90	[1.02; 3.53]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
Random effects model		4	0.95	[0.90; 1.00]
Heterogeneity: /2 = 10%, a	$t^2 = < 0.0001, p = 0.35$			
Australia/New Zealand				
Knibbs et al. 2018	ACHAPS	-	1.34	[0.99; 1.82]
		I		
Eastern Europe				
Pikhart et al. 1997	SAVIAH		0.98	[0.82; 1.18]
	0	1.5 1 2 2	5	

Relative Risk per 10 µg/m³

Subgroup analysis – year of publication

Study	Study Name	Relative Risk	RR	95%-CI
Before 2008				
Pikhart et al. 1997	SAVIAH		0.98	[0.82; 1.18]
Hirsch et al. 1999	ISAAC Dresden		1.13	[0.93; 1.37]
Krämer et al. 2000	Düsseldorf School Survey		• 1.70	[0.90; 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherland	is .	1.37	[1.00; 1.89]
Random effects model			1.15	[0.85; 1.54]
Heterogeneity: $l^2 = 43\%$, τ^2	= 0.0126, p = 0.16			
After 2008				
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65: 1.54]
Oftedal et al. 2009	Oslo Birth Cohort	+	1.01	[0.90; 1.12]
Krämer et al. 2009	GINI, LISA: Wesel	• • • • • • • • • • • • • • • • • • •	0.61	[0.36; 1.03]
Gehring et al. 2010	PIAMA	_ _	1.01	[0.87; 1.17]
Pénard-Morand et al. 2010	French Six Cities		1.19	[0.92; 1.52]
Pan et al. 2010	Liaoning Survey 2002	-	0.95	[0.91; 1.00]
Ebisu et al. 2011	Yale Childhood Asthma Study		1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health		0.94	[0.80; 1.10]
Altuğ et al. 2013	ISAAC Eskisehir		0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten		0.96	[0.82; 1.12]
Dell et al. 2014	T-CHEQ	<u> </u>	0.98	[0.83; 1.16]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Abidin et al. 2014	ISAAC Malaysia		• 1.90	[1.02; 3.53]
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
Madsen et al. 2017	MoBa	÷	1.02	[0.97; 1.07]
Knibbs et al. 2018	ACHAPS		1.34	[0.99; 1.82]
Random effects model			0.99	[0.95; 1.03]
Heterogeneity: $l^2 = 37\%$, τ^2	= 0.0009, p = 0.06			
		0.5 1	0 05	
		U.D I Delative Disk per 10 volm ³	2 2.5	
		Relative Risk per 10 µg/m		

Subgroup analysis – traffic specificity

Study	Study Name	Relative Risk	RR	95%-CI
High				
Pikhart et al. 1997	SAVIAH		0.98	[0.82; 1.18]
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65; 1.54]
Oftedal et al. 2009	Oslo Birth Cohort	- + -	1.01	[0.90; 1.12]
Krämer et al. 2009	GINI, LISA: Wesel	• • • • • • •	0.61	[0.36; 1.03]
Gehring et al. 2010	PIAMA		1.01	[0.87; 1.17]
Pénard-Morand et al. 2010	French Six Cities		1.19	[0.92; 1.52]
Ebisu et al. 2011	Yale Childhood Asthma Study		1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health		0.94	[0.80; 1.10]
Dell et al. 2014	T-CHEQ		0.98	[0.83; 1.16]
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
Madsen et al. 2017	MoBa		1.02	[0.97; 1.07]
Knibbs et al. 2018	ACHAPS		1.34	[0.99; 1.82]
Random effects model		\$	1.02	[0.98; 1.07]
Heterogeneity: $l^2 = 9\%$, $\tau^2 = 10\%$	= < 0.0001, <i>p</i> = 0.36			
Moderate				
Hirsch et al. 1999	ISAAC Dresden		1.13	[0.93; 1.37]
Krämer et al. 2000	Düsseldorf School Survey	· · · · ·	- 1.70	[0.90; 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherlands	· · ·	1.37	[1.00; 1.89]
Pan et al. 2010	Liaoning Survey 2002	-	0.95	[0.91; 1.00]
Altuğ et al. 2013	ISAAC Eskisehir		0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten		0.96	[0.82; 1.12]
Liu et al. 2014	SNEC	-	0.92	[0.84; 1.01]
Abidin et al. 2014	ISAAC Malaysia		1.90	[1.02; 3.53]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
Random effects model		4	0.96	[0.91; 1.02]
Heterogeneity: $l^2 = 51\%$, τ^2	² = < 0.0001, p = 0.04			
	8			
	C	0.5 1 2	2.5	
		Relative Risk per 10 µg/m		

123

Subgroup analysis – smoking adjustment

Study	Study Name	Relative Risk	RR	95%-CI
Yes				
Hirsch et al. 1999	ISAAC Dresden	++	1.13	[0.93; 1.37]
Janssen et al. 2003	ISAAC Southwestern Netherlands	s <u></u>	1.37	[1.00; 1.89]
Rosenlund et al. 2009	ISAAC Rome		1.00	[0.65; 1.54]
Oftedal et al. 2009	Oslo Birth Cohort		1.01	[0.90; 1.12]
Krämer et al. 2009	GINI, LISA: Wesel	•	0.61	[0.36; 1.03]
Gehring et al. 2010	PIAMA	_ 	1.01	[0.87; 1.17]
Pénard-Morand et al. 201	0 French Six Cities	+	1.19	[0.92; 1.52]
Pan et al. 2010	Liaoning Survey 2002	-	0.95	[0.91; 1.00]
Ebisu et al. 2011	Yale Childhood Asthma Study		1.12	[0.99; 1.27]
Svendsen et al. 2012	El Paso Children's Health	-+-	0.94	[0.80; 1.10]
Altuğ et al. 2013	ISAAC Eskisehir	-++	0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten		0.96	[0.82; 1.12]
Dell et al. 2014	T-CHEQ		0.98	[0.83; 1.16]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Abidin et al. 2014	ISAAC Malaysia			[1.02; 3.53]
Wood et al. 2015	ISAAC East London	— + +	1.10	[0.78; 1.57]
Deng et al. 2016	CCHH Changsha	+	0.97	[0.85; 1.11]
Madsen et al. 2017	MoBa	÷	1.02	[0.97; 1.07]
Random effects model			0.99	[0.95; 1.04]
Heterogeneity: I ² = 38%, a	² = 0.0010, <i>p</i> = 0.05			
No				
Pikhart et al. 1997	SAVIAH		0.98	[0.82; 1.18]
Krämer et al. 2000	Düsseldorf School Survey			[0.90; 3.20]
Knibbs et al. 2018	ACHAPS		1.34	[0.99; 1.82]
Random effects model			=- 1.20	[0.64; 2.26]
Heterogeneity: $I^2 = 60\%$, τ	² = 0.0393, p = 0.08			
		0.5 1 2	2.5	

Relative Risk per 10 µg/m³

Subgroup analysis – study design

Study	Study Name	Relative Risk	RR	95%-CI
Case-control		1		
Dell et al. 2014	T-CHEQ		0.98	[0.83; 1.16]
Cohort				
Offedal et al. 2009	Oslo Bith Cobot		1.01	10 00: 1 121
Krämer et al. 2009	CINI LISA: Wesel	•	0.61	[0.36: 1.03]
Cebring et al. 2003	PIAMA		1.01	[0.30, 1.03]
Ehisu et al 2011	Vale Childhood Asthma Study		1 12	[0.00; 1.27]
Madsen et al. 2017	MoBa	<u>_</u>	1.02	[0.00, 1.27]
Random effects model	intega	E C	1.02	[0.96: 1.10]
Heterogeneity: $l^2 = 32\%$, τ^2	= < 0.0001, p = 0.21			[one of mol
Cross sectional				
Pikhart et al. 1997	SAVIAH	· · · · ·	0.98	[0.82; 1.18]
Hirsch et al. 1999	ISAAC Dresden	- 	1.13	[0.93; 1.37]
Krämer et al. 2000	Düsseldorf School Survey		+ 1.70	[0.90; 3.20]
Janssen et al. 2003	ISAAC Southwestern Netherlands	•	1.37	[1.00; 1.89]
Rosenlund et al. 2009	ISAAC Rome	······································	1.00	[0.65; 1.54]
Pénard-Morand et al. 2010	French Six Cities		1.19	[0.92; 1.52]
Pan et al. 2010	Liaoning Survey 2002	-	0.95	[0.91; 1.00]
Svendsen et al. 2012	El Paso Children's Health		0.94	[0.80; 1.10]
Altuğ et al. 2013	ISAAC Eskisehir		0.92	[0.80; 1.07]
Liu et al. 2013	SNEC Kindergarten		0.96	[0.82; 1.12]
Liu et al. 2014	SNEC		0.92	[0.84; 1.01]
Abidin et al. 2014	ISAAC Malaysia		+ 1.90	[1.02; 3.53]
Wood et al. 2015	ISAAC East London		1.10	[0.78; 1.57]
Deng et al. 2016	CCHH Changsha		0.97	[0.85; 1.11]
Knibbs et al. 2018	ACHAPS	· · · · ·	1.34	[0.99; 1.82]
Random effects model		\$	0.99	[0.93; 1.05]
Heterogeneity: $l^2 = 42\%$, τ^2	= 0.0014, p = 0.04			
			1	
		0.0 0.75 T 1.5	2	

Sensitivity analysis – reverse selection

Study	Study Name	Exposure Window	Rel	lative Risk	RR	95%-CI	Weight
Pikhart et al. 1997	SAVIAH	Annual average current year	1 <u>.</u>		0.98	[0.82; 1.18]	3.5%
Hirsch et al. 1999	ISAAC Dresden	Annual mean		+	1.13	[0.93; 1.37]	3.1%
Krämer et al. 2000	Düsseldorf School Survey	Annual average current year	-	+	-+ 1.70	[0.90; 3.20]	0.3%
Janssen et al. 2003	ISAAC Southwestern Netherlands	Annual average current year		—	1.37	[1.00; 1.89]	1.3%
Krämer et al. 2009	GINI, LISA: Wesel	Cumulative average	• ·	+	0.61	[0.36; 1.03]	0.5%
Oftedal et al. 2009	Oslo Birth Cohort	Annual average at birth	-	+	1.01	[0.90; 1.12]	7.7%
Rosenlund et al. 2009	ISAAC Rome	Exposure in 2000-2001 (recent year	r)	-	1.00	[0.65; 1.54]	0.7%
Gehring et al. 2010	PIAMA	Annual average at birth		+	1.01	[0.87; 1.17]	4.9%
Pan et al. 2010	Liaoning Survey 2002	Four year average at baseline	ł	-	0.95	[0.91; 1.00]	17.9%
Pénard-Morand et al. 2010	French Six Cities	Annual average current year		+	1.19	[0.92; 1.52]	2.0%
Ebisu et al. 2011	Yale Childhood Asthma Study	Average first year			1.12	[0.99; 1.27]	6.3%
Svendsen et al. 2012	El Paso Children's Health	Average recent		-	0.94	[0.80; 1.10]	4.4%
Altuğ et al. 2013	ISAAC Eskisehir	Annual average current year		-	0.92	[0.80; 1.07]	4.9%
Liu et al. 2013	SNEC Kindergarten	Three year average at baseline		4 -	0.96	[0.82; 1.12]	4.5%
Abidin et al. 2014	ISAAC Malaysia	Annual average current year			→ 1.90	[1.02; 3.53]	0.3%
Dell et al. 2014	T-CHEQ	Annual average current year	-		1.05	[0.89; 1.24]	4.2%
Liu et al. 2014	SNEC	Three year average at baseline		4	0.92	[0.84; 1.01]	9.7%
Wood et al. 2015	ISAAC East London	Annual average current year		- •	1.10	[0.78; 1.57]	1.1%
Deng et al. 2016	CCHH Changsha	Cumulative average		4	0.96	[0.81; 1.13]	4.1%
Madsen et al. 2017	MoBa	Entire pregnancy		÷.	1.02	[0.97; 1.07]	17.2%
Knibbs et al. 2018	ACHAPS	Previous year annual average			1.34	[0.99; 1.82]	1.4%
Random effects model				\$	1.00	[0.96; 1.05]	100.0%
Prediction interval						[0.92; 1.10]	
Heterogeneity: $I^2 = 42\%$, $\tau^2 =$	0.0014, p = 0.02						
			0.5	1 2	2.5		
			Relative F	Risk per 10µg/m ³			

NO₂ - Prevalence of wheeze 12 months - Children (<18 years)

Recent years > cumulative average > first year of life > at birth > pregnancy

Primary meta-analysis

NO_X - Prevalence of wheeze 12 months - Children (<18 years)



Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low vs high

Study	Study Name		Relative Risk	RR	95%-CI
Low			1		
McConnell et al. 2006	CHS			1.06	[0.99; 1.13]
Pénard-Morand et al. 201	0 French Six Cities			1.11	[0.98; 1.26]
Mölter et al. 2015	ESCAPE			1.01	[0.87; 1.17]
Wood et al. 2015	ISAAC East Londor	n —		1.00	[0.74; 1.35]
Random effects model			\sim	1.06	[1.01; 1.12]
Heterogeneity: $I^2 = 0\%$, τ^2	$p^{2} = 0, p = 0.76$				
High					
Gruzieva et al. 2013	BAMSE			1.05	[0.93; 1.19]
			1		
		0.70.75	1	1.5	
			Relative Risk per 20 µg/m ³		

Sensitivity analysis - risk of bias selection bias domain - low/moderate vs high

Study	Study Name		Relative Risk	RR	95%-CI
Low/Moderate					
McConnell et al. 2006	CHS			1.06	[0.99; 1.13]
Pénard-Morand et al. 2	010 French Six Cities			1.11	[0.98; 1.26]
Gruzieva et al. 2013	BAMSE			1.05	[0.93; 1.19]
Mölter et al. 2015	ESCAPE			1.01	[0.87; 1.17]
Random effects mode	el 🛛		\diamond	1.06	[1.01; 1.11]
Heterogeneity: 1 ² = 0%	$\tau^2 = 0, p = 0.79$				
High					
Wood et al. 2015	ISAAC East London			1.00	[0.74; 1.35]
	(0.70.75	1	1.5	
			Relative Risk per 20 µg/m ³		

Sensitivity analysis - risk of bias outcome measurement domain - moderate vs high

Study	Study Name		Relative Risk	RR	95%-CI
Moderate			1		
McConnell et al. 2006	CHS			1.06	[0.99; 1.13]
Pénard-Morand et al. 2	010 French Six Cities			1.11	[0.98; 1.26]
Gruzieva et al. 2013	BAMSE		-	1.05	[0.93; 1.19]
Mölter et al. 2015	ESCAPE			1.01	[0.87; 1.17]
Random effects mode	ł		\diamond	1.06	[1.01; 1.11]
Heterogeneity: $I^2 = 0\%$,	$\tau^2 = 0, \rho = 0.79$				
High					
Wood et al. 2015	ISAAC East Londor	n		1.00	[0.74; 1.35]
			1		
			1		
		0.70.75	1	1.5	
			Relative Risk per 20 µg/m ³		

NO_x – Prevalence of active wheeze – Children Subgroup analysis – region

Study	Study Name		Relative Risk	RR	95%-CI
North America			2		
McConnell et al. 2006	CHS			1.06	[0.99; 1.13]
Western Europe					
Pénard-Morand et al. 20	10 French Six Cities			1.11	[0.98; 1.26]
Gruzieva et al. 2013	BAMSE			1.05	[0.93; 1.19]
Mölter et al. 2015	ESCAPE			1.01	[0.87; 1.17]
Wood et al. 2015	ISAAC East London			- 1.00	[0.74; 1.35]
Random effects model			\leftarrow	1.06	[0.98; 1.14]
Heterogeneity: $I^2 = 0\%$,	$\tau^2 = 0, p = 0.76$				
	(0.70.75	1	1.5	
			Relative Risk per 20 µg/m3		

NO_x – Prevalence of active wheeze – Children Subgroup analysis – year of publication

Study Study Name **Relative Risk** RR 95%-CI Before 2008 McConnell et al. 2006 CHS 1.06 [0.99; 1.13] After 2008 1.11 [0.98; 1.26] 1.05 [0.93; 1.19] 1.01 [0.87; 1.17] Pénard-Morand et al. 2010 French Six Cities Gruzieva et al. 2013 BAMSE ESCAPE Mölter et al. 2015 Wood et al. 2015 ISAAC East London 1.00 [0.74; 1.35] Random effects model ----1.06 [0.98; 1.14] Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $\rho = 0.76$ 0.70.75 1.5 1 Relative Risk per 20 µg/m3

Subgroup analysis – traffic specificity

All high traffic specificity

NO_x – Prevalence of active wheeze – Children Subgroup analysis – smoking adjustment

Study	Study Name	Relative Risk	RR	95%-CI
Yes				
Pénard-Morand et al. 20	10 French Six Cities		1.11	[0.98; 1.26]
Mölter et al. 2015	ESCAPE		1.01	[0.87; 1.17]
Wood et al. 2015	ISAAC East London		1.00	[0.74; 1.35]
Random effects model			1.06	[0.92; 1.23]
Heterogeneity: / ² = 0%, 1	$c^2 = 0, p = 0.56$			
No		1.07.0		
McConnell et al. 2006	CHS		1.06	[0.99; 1.13]
Gruzieva et al. 2013	BAMSE		1.05	[0.93; 1.19]
	0.7	1 1	1.5	
		Relative Risk per 20 µg/m"		

NO_x – Prevalence of active wheeze – Children Subgroup analysis – study design

Study	Study Name		Relative Risk		RR	95%-CI
Cohort			1			
Gruzieva et al. 2013	BAMSE			1.	05	[0.93; 1.19]
Mölter et al. 2015	ESCAPE			1.	01	[0.87; 1.17]
Cross sectional McConnell et al. 2006 Pénard-Morand et al. 201	CHS 10 French Six Cities		-	1. 1.	06 11	[0.99; 1.13] [0.98; 1.26]
Wood et al. 2015	ISAAC East London		_	1.	00	[0.74; 1.35]
Random effects model			\diamond	1.	07	[0.99; 1.15]
Heterogeneity: $I^2 = 0\%$, τ	² = 0, p = 0.72		_			
	0.6	0.75	1	1.5 2		
		Rela	ative Risk per 20 µ	g/m ³		

NO_x – Prevalence of active wheeze– Children Sensitivity analysis – reverse selection

NO_X - Prevalence of wheeze 12 months - Children (<18 years)



Recent years > cumulative average > first year of life > at birth > pregnancy

EC - Prevalence of active wheeze – Children

Primary meta-analysis

EC - Prevalence of wheeze 12 months - Children (<18)



EC – Prevalence of active wheeze – Children

Subgroup analysis – year of publication

Study	Study Name		Relative Risk	RR	95%-CI
Before 2008			1		
Janssen et al. 2003	ISAAC Southwestern Netherlands			• 1.42	[0.67; 3.01]
			1		
After 2008					
Krämer et al. 2009	GINI, LISA: Wesel	•		0.59	[0.28; 1.28]
Gehring et al. 2010	PIAMA	5	-	1.05	[0.82; 1.34]
Mölter et al. 2015	ESCAPE			1.17	[0.83; 1.64]
Random effects mode				- 1.05	[0.65; 1.69]
Heterogeneity: /2 = 219	$6, \tau^2 = < 0.0001, p = 0.28$				
			1 1		
		0.7	1 <u>1.5</u>	2	
			Relative Risk per 1 µg/m3		

Subgroup analysis – traffic specificity

Study	Study Name		Relative Ris	k	RR	95%-CI
High			1			
Krämer et al. 2009	GINI, LISA: Wesel	•			0.59	[0.28; 1.28]
Gehring et al. 2010	PIAMA		-		1.05	[0.82; 1.34]
Mölter et al. 2015	ESCAPE	2			1.17	[0.83; 1.64]
Random effects mode	-				1.05	[0.65; 1.69]
Heterogeneity: $l^2 = 21\%$	$b, \tau^2 = < 0.0001, p = 0.28$					
Moderate						
Janssen et al. 2003	ISAAC Southwestern Netherlands	•		•	• 1.42	[0.67; 3.01]
			1	1		
		0.7	1	1.5	2	
			Relative Risk per 1	µg/m ³		

EC – Prevalence of active wheeze – Children

Subgroup analysis – study design

Study	Study Name		Relative Risk	RR	95%-CI
Cohort					
Krämer et al. 2009	GINI, LISA: Wesel	2		0.59	[0.28; 1.28]
Gehring et al. 2010	PIAMA	-	-	1.05	[0.82; 1.34]
Mölter et al. 2015	ESCAPE	1		1.17	[0.83; 1.64]
Random effects mode				— 1.05	[0.65; 1.69]
Heterogeneity: $l^2 = 21\%$	$6, \tau^2 = < 0.0001, p = 0.28$				
Cross sectional					
Janssen et al. 2003	ISAAC Southwestern Netherlands	-		• 1.42	[0.67; 3.01]
		82	1	<u></u>	
	0.6	0.75	1 1	.5 2	
		R	elative Risk per 1 µg/m	3	

Chapter 9 Additional Materials

EC – Prevalence of active wheeze – Children

Subgroup analyses notes:

Subgroup analysis – region

All Western Europe

Subgroup analysis – smoking adjustment

All studies controlled for smoking

Primary meta-analysis

PM10 - Prevalence of wheeze 12 months - Children (<18)



Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low vs high

Study	Study Name		Relative Risk	(I	RR	95%-CI
Low						
Pénard-Morand et al. 20	10 French Six Cities			<u> </u>	29	[0.90; 1.85]
Mölter et al. 2015	ESCAPE	. <u> </u>		<u> </u>	11	[0.70; 1.76]
Wood et al. 2015	ISAAC East London	-		1.	79	[0.41; 7.76]
Random effects model			-+	<u> </u>	24	[0.91; 1.69]
Heterogeneity: 1 ² = 0%,	$t^2 = 0, p = 0.77$					
High						
Gruzieva et al. 2013	BAMSE	1.5		1.	21	[0.75; 1.97]
		0.7	1	1.5 2		
			Relative Risk per 10	µg/m ³		

Sensitivity analysis - risk of bias selection bias domain - low/moderate vs high

Study	Stu	dy Name	Relative Risk	RR	95%-CI
Low/Moder	ate		1		
Pénard-Mol	rand et al. 2010 Frenc	h Six Cities		1.29	[0.90; 1.85]
Gruzieva et	al. 2013 E	BAMSE		1.21	[0.75; 1.97]
Mölter et al.	2015 E	SCAPE	-	1.11	[0.70; 1.76]
Random ef	fects model			1.22	[1.00; 1.48]
Heterogene	eity: $l^2 = 0\%$, $\tau^2 = 0$, $\rho = 0$.88			
High					
Wood et al.	2015 ISAAC I	East London 🔹	2.4	• • 1.79	[0.41; 7.76]
		0.7	1 1.	5 2	
			Relative Risk per 10 µg/	m ³	
PM₁₀ – Prevalence of active wheeze – Children

Sensitivity analysis - risk of bias outcome measurement domain - moderate vs high



PM₁₀ – Prevalence of active wheeze – Children Subgroup analysis – traffic specificity



PM₁₀ – Prevalence of active wheeze – Children Subgroup analysis – smoking adjustment

Study	Study Name		Relativ	ve Risk	RR	95%-CI
Yes						
Pénard-Morand et al. 2010	French Six Cities		_		1.29	[0.90; 1.85]
Mölter et al. 2015	ESCAPE		-		- 1.11	[0.70; 1.76]
Wood et al. 2015	ISAAC East London	e			• 1.79	[0.41; 7.76]
Random effects model			-+		1.24	[0.91; 1.69]
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$: 0, <i>p</i> = 0.77					
No						
Gruzieva et al. 2013	BAMSE	<u>.</u>			1.21	[0.75; 1.97]
		·				
		-				
	1	0.7	1	1.5	2	
			Relative Risk	per 10 µg/m		

 $\mathsf{PM}_{10}-\mathsf{Prevalence}$ of active wheeze – Children

Sensitivity analysis - reverse selection

PM10 - Prevalence of wheeze 12 months - Children (<18)



Recent years > cumulative average > first year of life > at birth > pregnancy

Chapter 9 Additional Materials

PM₁₀ – Prevalence of active wheeze – Children

Subgroup analyses notes:

Subgroup analysis – region All Western Europe

Subgroup analysis – year of publication All after 2008

Subgroup analysis – study design Gruzieva 2013 and Molter 2015 cohorts; the other two cross sectional studies

PM_{2.5} – Prevalence of active wheeze – Children

Primary meta-analysis

PM_{2.5}- Prevalence of wheeze 12 months - Children (<18)



PM_{2.5} – Prevalence of active wheeze – Children

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias selection bias domain – low vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low				
Morgenstern et al. 2008	GINI, LISA: Munich		0.86	[0.65; 1.14]
Gehring et al. 2010	PIAMA		1.06	[0.77; 1.46]
Mölter et al. 2015	ESCAPE		0.96	[0.62; 1.49]
Random effects model			0.95	[0.71; 1.27]
Heterogeneity: $l^2 = 0\%$, τ^2	$p^2 = 0, p = 0.62$			
High				
Wood et al. 2015	ISAAC East London		⇒ 2.10	10.37: 12.061
	0.4 0.	5 1 Relative Risk per 5 μg/m ³	2	

PM_{2.5} – Prevalence of active wheeze – Children

Sensitivity analysis - risk of bias outcome measurement domain - moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Moderate				
Morgenstern et al. 2008	GINI, LISA: Munich		0.86	[0.65; 1.14]
Gehring et al. 2010	PIAMA		1.06	[0.77; 1.46]
Mölter et al. 2015	ESCAPE		0.96	[0.62; 1.49]
Random effects model			0.95	[0.71; 1.27]
Heterogeneity: $l^2 = 0\%$, τ^2	= 0, p = 0.62			
High				
Wood et al. 2015	ISAAC East London		→ 2.10	[0.37; 12.06]
	0.4 0.	5 1 Relative Risk per 5 μg/m ³	2	

PM_{2.5} – Prevalence of active wheeze – Children Subgroup analysis – year of publication

Study	Study Name		Relative Risk	RR	95%-CI
Before 2008					
Morgenstern et al. 2008	GINI, LISA: Munich			0.86	[0.65; 1.14]
Affar 2000			I.		
Cabring at al. 2010	DIAMA			1.06	10 77: 1 46
Möltor of al. 2015				0.06	[0.77, 1.40]
Wood et al. 2015	ISAAC East London	-		2 10	[0.02, 1.49]
Random effects model	2			1.04	[0.74; 1.48]
Heterogeneity: /~ = 0%, 1	f = 0, p = 0.68				
	0	.4 0.5	1 Relative Risk per 5 µg/m ³	2	

PM_{2.5} – Prevalence of active wheeze – Children Subgroup analysis – study design

Study	Study Name		Relative Risk		RR	95%-CI
Cohort			1			
Morgenstern et al. 2008	GINI, LISA: Munich				0.86	[0.65; 1.14]
Gehring et al. 2010	PIAMA	0,	-		1.06	[0.77; 1.46]
Mölter et al. 2015	ESCAPE			-	0.96	[0.62; 1.49]
Random effects model					0.95	[0.71; 1.27]
Heterogeneity: $l^2 = 0\%$, τ^2	= 0, <i>p</i> = 0.62					
Cross sectional						
Wood et al. 2015	ISAAC East London			3	2.10	[0.37; 12.06]
	r		1	1	1	
	0.	6 0.75	1	1.5	2	
		Rela	ative Risk per 5 µg	/m ³		

Chapter 9 Additional Materials

PM_{2.5} – Prevalence of active wheeze – Children

Subgroup analyses notes:

Subgroup analysis – traffic specificity

All moderate specificity

Subgroup analysis – smoking

All yes

Subgroup analysis – region

All Western Europe

Distance measures - Prevalence of active wheeze - Adults

Distance measures - Prev	alence of w	heeze 12 mc	onths - Adults
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Reference	Study Name		Categories	RR	95% CI
Nitta et al. 1993	Tokyo Respiratory Survey	⊢ • →	<20 vs. 20-150 m	2.75	[1.65, 4.73]
Nitta et al. 1993	Tokyo Respiratory Survey	F	<20 vs. 50-150 m	1.52	[0.91, 2.55]
Nitta et al. 1993	Tokyo Respiratory Survey	⊢	20-50 vs. 50-150 m	1.17	[0.69, 2.00]
Nitta et al. 1993	Tokyo Respiratory Survey	⊢I	<20 vs. 20-150 m	0.94	[0.61, 1.42]
Garshick et al. 2003	ATS US Veterans	—	<50 vs. >50 m	1.31	[1.00, 1.71]
Venn et al. 2005	Jimma Respiratory Survey	•>	<30 vs. 120-150 m	1.83	[0.78, 4.23]
Venn et al. 2005	Jimma Respiratory Survey	· · · · · · · · · · · · · · · · · · ·	30-60 vs. >120-150 m	1.59	[0.65, 3.90]
Venn et al. 2005	Jimma Respiratory Survey		60-90 vs. >120-150 m	1.65	[0.65, 4.10]
Venn et al. 2005	Jimma Respiratory Survey)	90-120 vs. >120-150 m	0.96	[0.30, 2.96]
Bayer-Oglesby et al. 2006	SAPALDIA		<20 vs. >20 m	0.94	[0.78, 1.12]
Pujades-Rodríguez et al. 2009	Nottingham Cohort	H	<50 vs. >100-150 m	1.60	[0.96, 2.68]
Pujades-Rodríguez et al. 2009	Nottingham Cohort	ii	50-100 vs. 100-150 m	1.00	[0.61, 1.66]
Nuvolone et al. 2011	Tuscany Health Survey		<100 vs. 250-800 m	1.32	[0.76, 2.28]
Nuvolone et al. 2011	Tuscany Health Survey	II	<100 vs. 250-800 m	1.76	[1.08, 2.87]
Nuvolone et al. 2011	Tuscany Health Survey	L	100-250 vs. 250-800 m	0.77	[0.42, 1.42]
Nuvolone et al. 2011	Tuscany Health Survey	L	100-250 vs. 250-800 m	1.54	[0.94, 2.53]
Hazenkamp-von Arx et al. 2011	MfMU	·	<200 vs. >200 m	3.10	[1.27, 7.55]
Bowatte et al. 2017a	TAHS	F	<200 vs. >200 m	1.61	[1.19, 2.19]
Bowatte et al. 2017b	TAHS		<200 vs. >200 m	1.38	[1.06, 1.80]
		0 1 2 3			
		Relative Risk			

Nitta et al. 1993 – results from different years; Nuvolone et al. results stratified by sex. Bowatte et al. 2017a and b refer to different study designs.

Distance measures - Prevalence of active wheeze - Children

Reference	Study Name					Categories	RR	95% CI
van Vliet et al. 1997	South Holland Respiratory Survey	-		•		<100 vs. 100-1000 m	2.00	[0.99, 2.74]
Venn et al. 2001	Nottingham School Survey					<30 vs. >150 m	1.38	[0.96, 1.92]
Venn et al. 2001	Nottingham School Survey					30-60 vs. >150 m	1.20	[0.85, 1.70]
Venn et al. 2001	Nottingham School Survey					60-90 vs. >150 m	1.07	[0.78, 1.49]
Venn et al. 2001	Nottingham School Survey		·			90-120 vs. >150 m	1.03	[0.78, 1.40]
Venn et al. 2001	Nottingham School Survey		-		÷	<30 vs. >150 m	1.84	[1.05. 3.22]
Venn et al. 2001	Nottingham School Survey					30-60 vs. >150 m	1.22	[0.69. 2.17]
Venn et al. 2001	Nottingham School Survey					60-90 vs. >150 m	1.09	[0.61, 1.92]
Venn et al. 2001	Nottingham School Survey					90-120 vs >150 m	0.91	10 54 1 611
Minake et al. 2002	ISAAC Suita	h				Facing road vs. >100 m	1.08	0.69 1.611
Miyake et al. 2002	ISAAC Suita	1				<100 vs >100 m	1.27	0.97 1.661
Vang et al. 2002	Kaohsiung Respiratory Survey					150 vs. 1500 m	1.01	[0.84 1 21]
Shima et al 2003	Chiba Cohort					<50 m vs. rural areas	1 35	10 34 5 321
Shima at al. 2003	Chiba Cohort					<50 m vs. rural areas	0.78	[0.09 7.00]
Shima at al. 2003	Chiba Cohort					50 m vs. rural areas	1.02	[0.00, 7.00]
Shima et al. 2003	Chiba Cohort	· · · · · · · · · · · · · · · · · · ·				>50 m vs. rural areas	0.79	[0.94, 2.30]
Shima et al. 2005	Chiba Conort	i				200 m vs. rural areas	0.75	[0.20, 2.39]
Lewis et al. 2005	ISAAC Eastern UK					<30 vs. >100 m	0.95	[0.73, 1.23]
Lewis et al. 2005	ISAAC Eastern UK					30-89 vs. >150 m	1.05	[0.89, 1.23]
Lewis et al. 2005	ISAAC Eastern UK		-			90-149 vs. >150 m	1.14	[0.97, 1.35]
Ryan et al. 2005	CCAAPS					<100 vs. >100 m	2.50	[1.15, 5.42]
McConnell et al. 2006	CHS					<75 vs. >300 m	1.40	[1.09, 1.78]
McConnell et al. 2006	CHS					75-150 vs. >300 m	1.30	[1.02, 1.66]
McConnell et al. 2006	CHS					150-300 vs. >300 m	1.02	[0.82, 1.27]
Dong et al. 2008	Liaoning Survey 2007		•			<20 vs. >100 m	1.32	[1.02, 1.73]
Dong et al. 2008	Liaoning Survey 2007					20-100 vs. >100 m	0.84	[0.65, 1.09]
Kim et al. 2008	EBCRHS	<u> </u>				<75 vs. >300 m	2.81	[0.94, 8.39]
Kim et al. 2008	EBCRHS	-	-			75-150 vs. >300 m	1.82	[0.75, 4.40]
Kim et al. 2008	EBCRHS	1.1		•		150-300 vs. >300 m	2.00	[0.93, 4.29]
Rosenlund et al. 2009	ISAAC Rome	-				<100 vs. >100 m	0.50	[0.20, 1.30]
Oftedal et al. 2009	Oslo Birth Cohort					580.3 m	1.00	[0.91, 1.11]
Krämer et al. 2009	GINI, LISA: Wesel					<50 vs. >50 m	0.76	[0.45, 1.28]
Pujades-Rodríguez et al. 2009	Health Survey England	H				<150 vs. >150 m	0.93	[0.88, 0.98]
Mivake et al. 2010	OMCHS					<50 vs. >200 m	0.85	[0,48, 1,47]
Mivake et al. 2010	OMCHS					50-100 vs. >200 m	1.10	10.65. 1.811
Mivake et al. 2010	OMCHS					100-200 vs. >200 m	1.04	10.66. 1.641
Middleton et al. 2010	ISAAC Cyprus	· · · · ·				<50 vs. >300 m	1.30	[0.86. 1.97]
Middleton et al. 2010	ISAAC Cyprus		-	-		50-100 vs. >300 m	1.08	[0.61, 1.89]
Middleton et al. 2010	ISAAC Cyprus					100-150 vs. >300 m	1.01	[0.51. 2.00]
Middleton et al. 2010	ISAAC Cyprus					150-300 vs ≥300 m	0.89	[0.52 1.50]
Patel et al. 2011	CCCEH	ji ji				-0.96 km	1.28	[0.98 1.62]
Dellet al 2014	T-CHEO				\rightarrow	<100 vs >100 m	1.35	10 38 4 821
lung et al. 2015	CHEER					675 vs. 5225 m	1.18	[0.91 1.49]
Jung et al. 2015	CHEER		1			75.150 us 5225 m	0.92	10.65 1.041
Jung et al. 2015	CHEER					150 225 vs. >225 m	1.02	[0.00, 1.04]
Jung et al. 2019	CHEER					100-220 VS220 ml <75 m vs. >75 m and no branchiolitic	1.02	[0.74, 1.40]
Lee et al. 2010	CHEER					<75 as and hereable bis us <75 as an hereable bis	1.01	[0.00, 1.09]
Lee et al. 2010	CHEER		a	20			1.05	[0.65, 5.20]
Lee et al. 2018	CHEER			1		prononiolitis only vs. >/o m and no prononiolitis	1.01	1.03, 2.03
		0 1		2	3			
			Relative Risk					

Distance measures - Prevalence of wheeze 12 months - Children (<18 years)

Venn et al. 2001 results stratified by sex; Miyake et al. 2002 results for residence and school; Shima et al. 2003 results stratified by sex

Density measures - Prevalence of active wheeze - Adults



Density measures - Prevalence of wheeze 12mths - Adults

Density measures - Prevalence of active wheeze - Children

Reference	Study Name						Per Increment/Categories	RR	95% CI
Oosterlee et al. 1996	Haarlem Respiratory Survey	H		•			high vs. low	1.50	[0.60, 3.70]
van Vliet et al. 1997	South Holland Respiratory Survey		-				high vs. low car volume	0.82	[0.34, 1.93]
van Vliet et al. 1997	South Holland Respiratory Survey	H				>	high vs. low truck volume	1.71	[0.72, 4.08]
Venn et al. 2000	Nottingham School Survey		-				10 thousand km/day/km ²	1.00	[0.99, 1.02]
Venn et al. 2000	Nottingham School Survey		-				10 thousand km/day/km ²	1.00	[0.99, 1.01]
Nicolai et al. 2003	ISAAC Munich		ŀ				>30000 vehicles/day vs. none	1.66	[1.07, 2.58]
Nicolai et al. 2003	ISAAC Munich		-				15001-30000 vehicles/day vs. none	1.01	[0.61, 1.67]
Nicolai et al. 2003	ISAAC Munich		•				2600-15000 vehicles/day vs. none	0.85	[0.48, 1.49]
Kim et al. 2008	EBCRHS		-				9414-74041 vehicles-km/day vs. none	1.16	[0.57, 2.36]
Kim et al. 2008	EBCRHS		1				4403-9413 vehicles-km/day vs. none	0.78	[0.36, 1.67]
Kim et al. 2008	EBCRHS	ŀ		-			1920-4402 vehicle-km/day vs. none	1.47	[0.73, 2.95]
Kim et al. 2008	EBCRHS			4			<1919 vehicle-km/day vs. none	0.58	[0.27, 1.25]
Andersson et al. 2011	OLIN		-	•			>500 vs. <500 heavy vehicles/day	1.70	[1.00, 2.70]
Andersson et al. 2011	OLIN		+				>8000 vs. <8000 vehicles/day	1.40	[0.90, 2.10]
Lindgren et al. 2013	Scania Birth Cohort 05/11		H				<8640 vs. >8640 vehicles/day	0.90	[0.80, 1.00]
		1				- 10			
		0	1	2 Relative R	3 isk	4			

Density measures - Prevalence of wheeze 12mths - Children (<18 months)

Chapter 9 Additional Materials

9.7 Prevalence of wheeze ever

NO₂ – Prevalence of wheeze ever – Children

Primary meta-analysis

NO₂ - Prevalence of wheeze ever - Children (<18 years)



NO₂ – Prevalence of wheeze ever – Children

Plots not shown for risk of bias domains if all studies were rated low or moderate. Sensitivity analysis – risk of bias confounding domain – low vs moderate vs high

Study	Study Name	Relative Risk	RR	95%-CI
Low		1		
Rosenlund et al. 2009	ISAAC Rome		0.78	[0.63; 0.96]
Pedersen et al. 2013	EDEN -		0.81	[0.62; 1.05]
Dell et al. 2014	T-CHEQ		1.11	[0.98; 1.26]
Ranzi et al. 2014	GASPII		0.97	[0.80; 1.17]
Random effects model			0.93	[0.71; 1.21]
Heterogeneity: / ² = 72%	$\tau^{2} = 0.0212, p = 0.01$			
High				
Pikhart et al. 1997	SAVIAH		0.94	[0.82; 1.07]
Cakmak et al. 2016	Windsor Children's Health 05		1.05	[0.92; 1.19]
	_	i i		

0.6

0.8 1 1.25 1.4 Relative Risk per 10 μg/m³

$\mathsf{NO}_2-\mathsf{Prevalence}$ of wheeze $\mathsf{ever}-\mathsf{Children}$

Subgroup analysis – region

Study	Study Name	Relative Risk	RR	95%-CI
North America		1		
Dell et al. 2014	T-CHEQ		1.11	[0.98; 1.26]
Cakmak et al. 2016	Windsor Children's Health 0	5	1.05	[0.92; 1.19]
Western Europe		I		
Recentlund et al. 2000	ISAAC Rome	3000 m	0.78	10 63: 0 961
Redercon et al. 2003	EDEN		0.01	[0.62: 1.05]
Pedersen et al. 2013	CASPIL	-	0.01	[0.02, 1.03]
Ralizi et al. 2014	GASEI		0.97	[0.60, 1.17]
Random effects model	2	T	0.80	[0.05; 1.17]
Heterogeneity: / = 25%,	$\tau = 0.0053, p = 0.26$			
Eastern Europe				
Pikhart et al. 1997	SAVIAH		0.94	[0.82; 1.07]
		1 1 1		
		0.6 0.8 1	1.25 1.4	

6 0.8 1 1.25 1.4 Relative Risk per 10 μg/m³

NO₂ – Prevalence of wheeze ever – Children Subgroup analysis – year of publication

Study	Study Name	Relative Risk	RR	95%-CI
Before 2008		1		
Pikhart et al. 1997	SAVIAH		0.94	[0.82; 1.07]
A4 2000				
After 2008	10110 8-00		0.70	10.00.0.001
Roseniund et al. 2009	ISAAC Rome -		0.78	[0.63; 0.96]
Pedersen et al. 2013	EDEN -	•	0.81	[0.62; 1.05]
Dell et al. 2014	T-CHEQ	-	1.11	[0.98; 1.26]
Ranzi et al. 2014	GASPII		0.97	[0.80; 1.17]
Cakmak et al. 2016	Windsor Children's Health 05		1.05	[0.92; 1.19]
Random effects model			0.96	[0.79; 1.16]
Heterogeneity: $l^2 = 65\%$	$\tau^2 = 0.0154 \ \rho = 0.02$			(7.9 m) (9 m) (9 m)
	0.6	0.8 1 1.2	25 1.4	
		Relative Risk per 10 µg/m3		

Subgroup analysis – traffic specificity All high specificity

NO_2 – Prevalence of wheeze ever – Children

Subgroup analysis – smoking adjustment

Study	Study Name		Relativ	e Risk		RR	95%-CI
Yes				T			
Rosenlund et al. 2009	ISAAC Rome		-			0.78	[0.63; 0.96]
Pedersen et al. 2013	EDEN			-		0.81	[0.62; 1.05]
Dell et al. 2014	T-CHEQ			- 	-	1.11	[0.98; 1.26]
Ranzi et al. 2014	GASPII					0.97	[0.80; 1.17]
Cakmak et al. 2016	Windsor Children's Health 05					1.05	[0.92; 1.19]
Random effects model			_		-	0.96	[0.79; 1.16]
Heterogeneity: / 2 = 65%	, τ ² = 0.0154, <i>p</i> = 0.02						
No							
Pikhart et al. 1997	SAVIAH					0.94	[0.82; 1.07]
	r		1		18		
	0.	6	0.8	1	1.25	1.4	



NO_2 – Prevalence of wheeze ever – Children

Subgroup analysis – by study design

Study	Study Name	Relative Risk	RR	95%-CI
Case-control Dell et al. 2014	T-CHEQ	-	1.11	[0.98; 1.26]
Cohort Pedersen et al. 2013 Ranzi et al. 2014	EDEN - GASPII		0.81 0.97	[0.62; 1.05] [0.80; 1.17]
Cross sectional Pikhart et al. 1997 Rosenlund et al. 2009 Cakmak et al. 2016 Random effects model Heterogeneity: / ² = 65%,	SAVIAH ISAAC Rome Windsor Children's Health 05 $\tau^2 = 0.0129, p = 0.06$	0.75 1 1.5 Peletice Bick per 10 up/m ³	0.94 0.78 1.05 0.93	[0.82; 1.07] [0.63; 0.96] [0.92; 1.19] [0.65; 1.33]

NO₂ – Prevalence of wheeze ever – Children

Sensitivity analysis - reverse selection

NO₂ - Prevalence of wheeze ever - Children (<18 years)



Recent years > cumulative average > first year of life > at birth > pregnancy

Distance measures - Prevalence of wheeze ever - Children

Reference	Study Name	Categories	RR	95% CI
Rosenlund et al. 2009	ISAAC Rome	<100 vs. >100 m	0.80	[0.50, 1.20]
Skrzypek et al. 2013	ISAAC Bytom	<100 vs. >100 m	1.09	[0.79, 1.51]
Dell et al. 2014	T-CHEQ	• <100 vs. >100 m	0.75	[0.23, 2.44]
Ranzi et al. 2014	GASPI	<86.1 vs. >86.1 m	0.98	[0.73, 1.32]
Jung et al. 2015	CHEER	<75 vs. >225 m	1.17	[0.99, 1.38]
Jung et al. 2015	CHEER	■ 75-150 vs. >225 m	1.04	[0.89, 1.21]
Jung et al. 2015	CHEER	■ 150-225 vs. >225 m	1.09	[0.88, 1.35]
Lee et al. 2018	CHEER	■ <75 vs. >700 m	1.29	[0.90, 1.85]
Lee et al. 2018	CHEER	■ 75-700 vs. >700 m	1.03	[0.74, 1.43]
	0	1 1 2 Relative Risk		

Distance measures - Prevalence of wheeze ever - Children (<18 years)

Density measures - Prevalence of wheeze ever – Adults





Density measures - Prevalence of wheeze ever - Children

Density measures - Prevalence of wheeze ever - Chidlren (<18 years)

