

Supplemental Material

Prenatal and early-life exposure to air pollution and risk of severe lower respiratory tract infections during early childhood: the Espoo Cohort Study

Appendix 1: A systematic review of literature on the effects of perinatal exposure to air pollution and the risk of LRTIs during early childhood.

We conducted a systematic literature search on PubMed from inception to March 12, 2023, aiming to identify previous epidemiologic studies that assessed early-life air pollution exposures and the risk of respiratory tract infections during early childhood. We developed a query with keywords and search terms related to air pollution, early childhood, and respiratory tract infections. The query was made using Boolean logic (AND/OR/NOT) as ((air pollution) OR (air pollutants) OR (traffic-related pollution)) AND ((intrauterine) OR (pregnant) OR (maternal-fetal exchange) OR (prenatal) OR (antenatal) OR (maternal exposure) OR (early childhood) OR (infant) OR (postnatal)) AND ((respiratory tract infections) OR (lower respiratory tract infection) OR (pneumonia) OR (bronchitis) OR (bronchiolitis)) NOT ((asthma[Mesh])) NOT ((COVID-19[Mesh])) AND (humans[Filter]). The search identified, altogether, 740 journal articles. The inclusion criteria were the following: i) an original study of any epidemiologic design; ii) estimation of the risk of LRTIs; iii) in early childhood; iv) in relation to ambient air pollution exposure; v) during the perinatal period (pregnancy and first year of life). Based on the inclusion criteria, we excluded 674 irrelevant articles during the title and abstract screening. We found 67 studies that were eligible for a full-text review. More than half of these studies (n = 36) assessed only the effects of short-term exposure to ambient air pollution. Further 10 studies were excluded due to the following reasons: i) did not provide estimates for exposure-outcome association (n = 5); ii) used respiratory symptoms only as the outcome (n = 3), iii) used distance to traffic or traffic density as the exposure (n = 1), and iv) did not use an eligible study design (n = 1). One article was found after reviewing the references of the eligible studies. We updated our search on October 9, 2023, and we found two more articles. Finally, 24 original studies that assessed prenatal and/or first-year exposure to ambient air pollution and the risk of early childhood respiratory tract infections were identified. However, only 13 of them were cohort studies. The number of studies that assessed the effects of prenatal, postnatal, and both exposures on RTIs were five, three, and five, respectively.

Table S1: Previous cohort studies that assessed the effect of prenatal and first-year exposure to ambient air pollution on the risk of lower respiratory tract infections.

First Author, Year	Location, climatic zone ^a	Study population, age	Method of exposure assessment	Studied exposures	Exposure time periods	Outcome	Effect estimate, 95% CI	Remarks: Modifications
Lu 2023[1]	Changsha, China; Cfa	Children, 3-6 years	Individual-level exposure, using inverse distance weighting	PM _{2.5} , PM ₁₀ , SO ₂ , NO ₂ , and CO	Prenatal and Postnatal (first year)	Pneumonia, parental report	Prenatal: PM _{2.5} – 1.17, 1.04, 1.30 PM ₁₀ – 1.07, 1.00, 1.14 NO ₂ – 1.10, 1.00, 1.22 Postnatal: PM ₁₀ – 1.11, 1.03, 1.21	effect estimates are per interquartile range (IQR) increment of exposure
Goshen 2020[2]	Beer-Sheva, Southern Israel; BSh	n= 57,331, infants (Arab-Bedouin, Jewish ethnicity)	Individual-level exposure	PM _{2.5} : quartiles <u>Mean(range): Jewish</u> 22.3(13.0–60.4) µg/m ³ Q ₄ – 23.7–60.4 µg/m ³ <u>Arab-Bedouin</u> 22.0(13.5–77.0) µg/m ³ Q ₄ – 23.1–77.0 µg/m ³	Prenatal	First time hospitalization for bronchitis or pneumonia, ICD-9	<u>Arab-Bedouin</u> 1 st trimester Q ₄ – 1.31, 1.08–1.60 2 nd trimester Q ₄ – 1.34, 1.09–1.66	The association was not statistically significant for the Jewish population
Yang 2020[3]	Seoul, South Korea; Dfa	n = 930, from birth to 3 years	Individual-level exposure, IDW	PM _{2.5} , Highest tertile	Prenatal	Doctor-diagnosed LRTIs, parental report	at 2 years: Middle vs low tertile – 0.98, 0.91, 1.05 High vs low tertile – 0.98, 0.91-1.06	Similar result at 1 st and third years. But 3 rd trimester exposure showed significant effect
Liu 2020[4]	Shanghai, China; Cfa	n = 3,177, 4–6 years	Residence-district period average concentrations	IQR increase Mean (Range): <u>Prenatal</u> SO ₂ - 45.7 (22.6–71.1) µg/m ³ NO ₂ – 56.0 (33.6–74.1) µg/m ³ PM ₁₀ – 83.1 (51.9–118.9) µg/m ³ <u>Postnatal</u> SO ₂ – 44.9 (27.2–57.9) µg/m ³ . NO ₂ – 55.4 (36.0–67.1) µg/m ³ . PM ₁₀ – 82.9 (69.2–96.6) µg/m ³ .	Prenatal Postnatal (infancy)	Ever had pneumonia, parent reported	<u>Prenatal:</u> SO ₂ – 1.04, 0.80-1.34 NO ₂ - 1.24, 0.90-1.68 PM ₁₀ – 1.04, 0.84–1.31 <u>Postnatal:</u> SO ₂ – 1.00, 0.79–1.27 NO ₂ – 1.56, 1.14–2.20 PM ₁₀ – 0.99, 0.73–1.37	All estimates were from multipollutant exposure.
Gutiérrez 2018[5]	Valencia, Spain; BSk	n =624, 2 years	Individual-level exposure	NO ₂ per 10 µg/m ³ increase Mean (range): <u>Prenatal</u> 37.74 (7.10 – 62.83) µg/m ³ <u>Postnatal</u>	Prenatal Postnatal (infancy)	Medical diagnosis of bronchiolitis, bronchitis, or pneumonia, parental report at 2 years of age	<u>Prenatal:</u> 0.96, 0.82 – 1.12 <u>Postnatal:</u> 1.04, 0.89 – 1.22	

Kennedy 2018[6]	Metropolitan Atlanta, Georgia, U.S.; Cfa	n=22,441, 29–24 months	Estimated using air pollutants from traffic in the vicinity of a roadway	37.01 (8.70 – 62.28) $\mu\text{g}/\text{m}^3$ Log-transformed: Median (range): PM _{2.5} – 1.41 (0.06 – 13.76) $\mu\text{g}/\text{m}^3$ NOx – 0.06 (0.01 – 0.59) ppm CO – 0.59 (0.10 – 5.13) ppm	Postnatal (infancy)	Pneumonia and bronchiolitis (time to first diagnosis), register-based data	<u>Pneumonia:</u> PM _{2.5} – 1.04, 0.89 – 1.23 NOx – 1.04, 0.90 – 1.21 CO – (1.03, 0.87 – 1.21) <u>Bronchiolitis:</u> PM _{2.5} – 1.23, 1.15 – 1.32 NOx – 1.19, 1.12 – 1.27 CO – 1.16, 1.08, 1.25 <u>Bronchitis</u> Q ₂ – 0.76, 0.51–1.14 Q ₃ – 1.13 0.78–1.63 Q ₄ – 1.28, 0.88–1.84 <u>Pneumonia</u> Q ₂ – 0.98, 0.61–1.56 Q ₃ – (0.90, 0.56–1.43) Q ₄ – (0.93, 0.50–1.74) <u>0–6 months</u> 0.99, 0.84 – 1.17 <u>6–18 months</u> 1.05, 0.94 – 1.16	Data is from subjects with health insurance, only a few were insured
Soh 2018[7]	Singapore; Af	n = 953, 0–2 years	Nationwide average, not individual level exposure	PM _{2.5} , quartiles Median (IQR) – 17.59 (16.84 – 19.07) $\mu\text{g}/\text{m}^3$	Prenatal	Doctor-diagnosed bronchitis and pneumonia ever, parental report	<u>Prenatal:</u> 1.05, 0.98 – 1.12 <u>Postnatal:</u> 1.03, 0.95 – 1.11	No adjustments were made for the other pollutants due to high collinearity.
Madsen 2017[8]	Norway; Cfb, Cfc, Dfb, Dfc (main type), Dsb, Dsc, ET	n= 17, 533, 0–18 months	Individual-level exposure	NO ₂ , per 10 $\mu\text{g}/\text{m}^3$ Mean (SD) -13.6(6.9) $\mu\text{g}/\text{m}^3$	Prenatal	LRTIs, parental report at 6- and 18-months age	<u>0–6 months</u> 0.99, 0.84 – 1.17 <u>6–18 months</u> 1.05, 0.94 – 1.16	
Aguilera, 2013[9]	Asturias, Gipuzkoa, Sabadell, and Valencia, Spain; Cfb, Cfa, BSk	n = 2199, 12–18 months	Individual-level exposure	NO ₂ , 10- $\mu\text{g}/\text{m}^3$ increase	Prenatal Postnatal (infancy)	Doctor-diagnosed LRTIs, parental report	<u>Prenatal:</u> 1.05, 0.98 – 1.12 <u>Postnatal:</u> 1.03, 0.95 – 1.11	No adjustments were made for the other pollutants due to high collinearity.
Jedrychowski 2013[10]	Krakow, Poland; Dfb	n=214, 0–7 years	Personal monitoring of two-day measurements, during 2 nd trimester.	PM _{2.5} (ln transformed) Mean (SD) - 42.37(27.55) $\mu\text{g}/\text{m}^3$	Prenatal	Recurrent episodes of bronchitis and pneumonia, parental report	2.05, 1.05–3.99	

Esplugues 2011 [11]	Valencia, Spain; BSk	n= 352, 12 months	Individual level exposure - prenatal (LUR) and postnatal (passive sampler at home address)	NO ₂ , 10 µg/m ³ increase Median (IQR): <u>Prenatal</u> 39.4 (31.6 – 48.6) µg/m ³ <u>Postnatal</u> 26.1 (18.4 - 37.1) µg/m ³	Prenatal Postnatal (infancy)	any episode of LRTI during the child's first year of life diagnosed by a doctor (bronchitis, bronchiolitis, or pneumonia), parental report	<u>Prenatal:</u> LRTIs – 1.18, 0.92 - 1.53 Bronchiolitis – 1.23, 0.93 – 1.62 bronchitis – 1.39, 0.94 – 2.05 <u>Postnatal:</u> LRTIs – 0.94, 0.78 - 1.15 Bronchiolitis – 0.96, 0.78 – 1.19 bronchitis – 1.00, 0.76 – 1.32)	But postnatal NO ₂ associated with persistent cough (more than 3 weeks) as of parents' report
Brauer 2007[12]	Several communities in the Netherlands; Cfb	4 th year (n= 2807) ever had outcome (n=2543), birth - 4 years	Individual-level exposure	IQR increase: Median (range) - <u>PM_{2.5}</u> 17.3(13.5 - 25.2) µg/m ³ <u>NO₂</u> 26.0(12.6 - 58.4) µg/m ³	Postnatal (lifetime)	Doctor-diagnosed bronchitis, parental report: at 4 th year and ever	at 4th year: PM _{2.5} – 0.86, 0.66– 1.11 NO ₂ – 0.89, 0.71– 1.12 Ever: PM _{2.5} – 0.96, 0.81– 1.13 NO ₂ – 0.94, 0.82– 1.08	
Brauer 2002[13]	Northern, western, and central parts of the Netherlands; Cfb	n=2986, birth - 2 years	Individual-level exposure	IQR increase: Median (range) - <u>PM_{2.5}</u> 17.3(13.5 - 25.2) µg/m ³ <u>NO₂</u> 26.0(12.6 - 58.4) µg/m ³	Postnatal (lifetime)	Doctor-diagnosed bronchitis, parental report: at 2 nd year	PM _{2.5} – 1.04, 0.85– 1.26 NO ₂ – 0.99, 0.84– 1.17	

^a Climatic zone classification was based on Köppen-Geiger classification-based open data from the Climate Data website (<https://en.climate-data.org/>); The climate zone codes in the table mean the following: Cfb - Temperate oceanic climate, Cfc - Subpolar oceanic climate, Dfb - Warm-summer humid continental climate, Dfc – Subarctic climate, Dsb - Warm, dry-summer continental climate, Dsc - Dry-summer subarctic climate, ET - Tundra, Cfa - Humid subtropical climate, BSk - Cold semi-arid (steppe) climate, BSh - Hot semi-arid (steppe) climate, , Dfa - Hot-summer humid continental climate, Af - Tropical rainforest climate, Csa - Hot-summer Mediterranean climate, Csb - Warm-summer Mediterranean climate

Table S2. ICD Codes and the corresponding Diagnoses

Diagnosis	ICD-8	ICD-9
Acute bronchitis		466.0A, 466.1A, 466.99
Viral pneumonia		480.1A, 480.8X, 480.9X
Pneumococcal pneumonia		481.0A
Other bacterial pneumonia	482.98	
Pneumonia due to another specified organism		483.0A, 483.0X
Unspecified pneumonia	486.09	485.09, 485.9X, 486.11

ICD – International Classification of Diseases

Table S3. Correlation matrix between the two air pollutant exposure periods, pregnancy and the first year of life

Exposure period		First year of life						Pregnancy					
		PM _{2.5}	PM ₁₀	CO	SO ₂	NO ₂	O ₃	PM _{2.5}	PM ₁₀	CO	SO ₂	NO ₂	O ₃
First year of life	PM _{2.5}	1.0000											
	PM ₁₀	0.9966	1.0000										
	CO	0.8767	0.8941	1.0000									
	SO ₂	0.9297	0.9496	0.8662	1.0000								
	NO ₂	0.9182	0.9357	0.9843	0.9062	1.0000							
	O ₃	-0.7440	-0.7290	-0.6535	-0.7265	-0.6752	1.0000						
		PM _{2.5}	0.6023	0.6184	0.6364	0.6319	0.6690	-0.3421	1.0000				
Pregnancy	PM ₁₀	0.6074	0.6277	0.6484	0.6496	0.6820	-0.3441	0.9969	1.0000				
	CO	0.5382	0.5623	0.6714	0.5717	0.6776	-0.3435	0.8978	0.9067	1.0000			
	SO ₂	0.6600	0.6874	0.6664	0.7560	0.7036	-0.4408	0.9028	0.9251	0.8485	1.0000		
	NO ₂	0.5783	0.6060	0.6981	0.6181	0.7161	-0.3246	0.9202	0.9353	0.9725	0.8960	1.0000	
	O ₃	-0.3342	-0.3271	-0.3176	-0.3284	-0.3117	0.2392	-0.2848	-0.2729	-0.2656	-0.3775	-0.3148	1.0000

Table S4. Average concentrations ($\mu\text{g}/\text{m}^3$) of exposures by quartiles during pregnancy and first year period ^a

Pollutants	<Q ₁	Q ₁ -Q ₂	Q ₂ -Q ₃	>Q ₃
During entire pregnancy				
PM _{2.5}	14.27 (2.84)	18.19 (0.72)	20.82 (0.70)	25.19 (2.98)
PM ₁₀	15.39 (3.18)	19.74 (0.77)	22.59 (0.76)	27.69 (3.69)
NO ₂	5.53 (1.69)	8.12 (0.44)	9.57 (0.37)	11.66 (1.28)
CO	282.3 (37.93)	345.5 (10.69)	385.4 (11.26)	441.9 (29.79)
SO ₂	5.53 (1.73)	8.95 (0.91)	11.75 (0.71)	18.14 (5.53)
O ₃	42.43 (2.42)	48.35 (1.37)	52.67 (1.23)	57.64 (2.31)
First year of life				
PM _{2.5}	14.72 (2.44)	18.01 (0.55)	20.22 (0.61)	23.90 (2.71)
PM ₁₀	15.93 (2.74)	19.60 (0.57)	22.01 (0.67)	26.26 (3.33)
NO ₂	5.85 (1.52)	8.08 (0.45)	9.49 (0.33)	11.20 (1.19)
CO	291.4 (34.59)	346.9 (13.49)	383.7 (8.35)	427.4 (26.68)
SO ₂	5.52 (1.48)	8.54 (0.55)	11.21 (0.76)	16.44 (4.82)
O ₃	47.67 (1.32)	49.94 (0.54)	51.92 (0.62)	54.68 (1.88)

^a Mean (Standard deviation); Q₁, Q₂ and Q₃ represent quartiles 1, 2 and 3, respectively (the corresponding values are presented in Table 2).

Table S5: Incidence rates of lower respiratory tract infections during the first two-years of life by sex, the Espoo Cohort Study, 1991 – 2011.^a

Infections	Sex	n	IR (95% CI)	IRR (95% CI)
0–1 year				
LRTIs	Girl	8	0.64 (0.27, 1.25)	1.00
	Boy	18	1.37 (0.81, 2.17)	2.16 (0.89, 5.73)
	Total	26	1.01 (0.66, 1.48)	-
Acute bronchitis	Girl	3	0.24 (0.05, 0.70)	1.00
	Boy	8	0.61 (0.26, 1.20)	2.56 (0.61, 14.96)
	Total	11	0.43 (0.21, 0.77)	-
Pneumonia	Girl	5	0.40 (0.13, 0.93)	1.00
	Boy	10	0.76 (0.37, 1.40)	1.29 (0.78, 2.16)
	Total	15	0.58 (0.32, 0.96)	-
1–2 years				
LRTIs	Girl	29	2.31 (1.55, 3.31)	1.00
	Boy	34	2.59 (1.79, 3.62)	1.12 (0.66, 1.91)
	Total	63	2.45 (1.89, 3.14)	-
Acute bronchitis	Girl	5	0.40 (0.13, 0.93)	1.00
	Boy	5	0.38 (0.12, 0.89)	0.96 (0.22, 4.17)
	Total	10	0.39 (0.19, 0.72)	-
Pneumonia	Girl	24	1.91 (1.22, 2.84)	1.00
	Boy	29	2.21 (1.48, 3.18)	1.16 (0.65, 2.08)
	Total	53	2.06 (1.55, 2.70)	-
0–2 years				
LRTIs	Girl	37	1.47 (1.04, 2.6)	1.00
	Boy	52	1.98 (1.48, 2.60)	1.35 (0.87, 2.11)
	Total	89	1.73 (1.39, 2.13)	-
Acute bronchitis	Girl	8	0.32 (0.14, 0.63)	1.00
	Boy	13	0.50 (0.26, 0.85)	1.56 (0.60, 4.34)
	Total	21	0.41 (0.25, 0.63)	-
Pneumonia ^b	Girl	29	1.15 (0.77, 1.66)	1.00
	Boy	39	1.49 (1.06, 2.03)	1.29 (0.78, 2.16)
	Total	68	1.32 (1.03, 1.68)	-

n – episodes of infections; IR – Incidence rate per 100 person-years; CI – Confidence interval; IRR – Incidence rate ratio. LRTIs – Lower Respiratory Tract Infections.

^a Incidence rate ratios (IRRs) were calculated based on IR among men divided by IR among women.

^b Pneumonias included i) viral pneumonia (n = 5), ii) bacterial pneumonia (n = 1), iii) pneumonia by other specified organism (n = 1), and unspecified pneumonia (n = 46).

Table S6. Association between exposure to air pollution during the entire pregnancy and lower respiratory tract infections during the first two years of life

Exposure	Effect estimates compared to the first quartile, IRR (95% CI)			Per 10 µg/m ³ of air pollutant exposure IRR (95% CI)
	Quartile 2	Quartile 3	Quartile 4	
PM _{2.5} ^a	1.48 (0.79, 2.76)	0.87 (0.44, 1.72)	0.87 (0.43, 1.73)	0.93 (0.52, 1.66)
PM _{2.5} ^b	1.58 (0.83, 2.98)	0.87 (0.43, 1.76)	0.61 (0.28, 1.31)	0.53 (0.28, 0.99)
+SO ₂	1.51 (0.78, 2.93)	0.77 (0.32, 1.85)	0.51 (0.17, 1.53)	0.54 (0.17, 1.71)
+O ₃	1.64 (0.87, 3.10)	0.87 (0.43, 1.76)	0.58 (0.27, 1.25)	0.50 (0.27, 0.93)
+SO ₂ +O ₃	1.67 (0.85, 3.28)	0.91 (0.37, 2.20)	0.62 (0.20, 1.90)	0.68 (0.21, 2.22)
NO ₂ ^a	1.28 (0.70, 2.35)	0.45 (0.21, 0.97)	0.68 (0.33, 1.37)	0.76 (0.23, 2.52)
NO ₂ ^b	1.42 (0.76, 2.64)	0.45 (0.20, 0.98)	0.46 (0.21, 1.01)	0.31 (0.08, 1.13)
+ PM ₁₀	1.44 (0.72, 2.90)	0.46 (0.16, 1.33)	0.48 (0.13, 1.79)	1.33 (0.09, 20.34)
+ O ₃	1.32 (0.71, 2.46)	0.43 (0.20, 0.93)	0.42 (0.20, 0.91)	0.27 (0.07, 0.96)
+ PM ₁₀ + O ₃	1.33 (0.66, 2.67)	0.43 (0.15, 1.23)	0.42 (0.11, 1.56)	0.97 (0.06, 15.77)
CO ^a	0.89 (0.47, 1.69)	0.69 (0.34, 1.38)	0.75 (0.37, 1.52)	1.00 (0.95, 1.04)
CO ^b	0.92 (0.48, 1.77)	0.59 (0.28, 1.23)	0.49 (0.23, 1.05)	0.96 (0.91, 1.01)
+ PM ₁₀	1.06 (0.52, 2.18)	0.82 (0.30, 2.27)	0.78 (0.22, 2.77)	1.01 (0.92, 1.10)
+ O ₃	0.90 (0.47, 1.71)	0.56 (0.27, 1.17)	0.46 (0.21, 0.99)	0.96 (0.91, 1.00)
+ SO ₂	0.83 (0.40, 1.74)	0.47 (0.17, 1.32)	0.36 (0.10, 1.28)	0.97 (0.91, 1.05)
+ SO ₂ + O ₃	0.91 (0.43, 1.91)	0.58 (0.20, 1.68)	0.48 (0.13, 1.82)	0.99 (0.92, 1.07)
+ PM ₁₀ + O ₃	1.05 (0.51, 2.16)	0.81 (0.29, 2.26)	0.77 (0.21, 2.81)	1.01 (0.92, 1.11)
PM ₁₀ ^a	1.18 (0.64, 2.18)	0.79 (0.41, 1.51)	0.71 (0.36, 1.40)	0.93 (0.55, 1.56)
PM ₁₀ ^b	1.29 (0.69, 2.41)	0.79 (0.40, 1.55)	0.48 (0.22, 1.03)	0.55 (0.31, 0.98)
+ CO	1.32 (0.66, 2.63)	0.83 (0.32, 2.16)	0.51 (0.15, 1.74)	0.41 (0.12, 1.34)
+ NO ₂	1.47 (0.74, 2.93)	1.05 (0.41, 2.67)	0.73 (0.21, 2.59)	0.40 (0.10, 1.51)
+ CO + O ₃	1.39 (0.69, 2.77)	0.83 (0.32, 2.15)	0.50 (0.14, 1.71)	0.41 (0.12, 1.34)
+ NO ₂ + O ₃	1.63 (0.81, 3.28)	1.15 (0.45, 2.89)	0.83 (0.23, 2.94)	0.46 (0.12, 1.75)
SO ₂ ^a	2.43 (1.21, 4.88)	1.21 (0.55, 2.69)	0.92 (0.40, 2.09)	0.80 (0.44, 1.45)
SO ₂ ^b	2.70 (1.32, 5.52)	1.09 (0.47, 2.53)	0.72 (0.30, 1.74)	0.50 (0.24, 1.01)
+ CO	3.08 (1.42, 6.71)	1.52 (0.49, 4.71)	1.16 (0.28, 4.73)	0.50 (0.24, 1.01)
+ NO ₂	3.66 (1.66, 8.07)	2.21 (0.69, 7.04)	2.13 (0.47, 9.68)	0.49 (0.12, 1.92)
+ O ₃	2.39 (1.16, 4.96)	0.98 (0.42, 2.29)	0.60 (0.24, 1.49)	0.42 (0.20, 0.87)
+ CO + O ₃	2.60 (1.16, 5.84)	1.18 (0.36, 3.86)	0.79 (0.18, 3.58)	0.32 (0.08, 1.25)
+ NO ₂ + O ₃	3.19 (1.41, 7.22)	1.85 (0.57, 6.07)	1.62 (0.33, 7.85)	0.34 (0.08, 1.54)
O ₃ ^a	0.79 (0.45, 1.39)	0.46 (0.23, 0.90)	1.11 (0.63, 1.95)	1.00 (0.69, 1.44)
O ₃ ^b	0.69 (0.38, 1.25)	0.46 (0.23, 0.90)	0.75 (0.40, 1.40)	0.75 (0.50, 1.11)
+ SO ₂	0.68 (0.38, 1.23)	0.43 (0.21, 0.85)	0.65 (0.34, 1.24)	0.64 (0.42, 0.97)
+ NO ₂	0.69 (0.38, 1.24)	0.43 (0.22, 0.85)	0.64 (0.34, 1.21)	0.68 (0.45, 1.02)
+ CO	0.71 (0.39, 1.28)	0.45 (0.23, 0.89)	0.69 (0.37, 1.30)	0.70 (0.47, 1.05)
+ PM _{2.5}	0.68 (0.38, 1.23)	0.44 (0.22, 0.87)	0.68 (0.36, 1.29)	0.69 (0.46, 1.03)
+ SO ₂ + CO	0.71 (0.39, 1.29)	0.45 (0.23, 0.91)	0.70 (0.36, 1.36)	0.64 (0.42, 0.97)
+ PM ₁₀ + NO ₂	0.69 (0.38, 1.24)	0.43 (0.22, 0.85)	0.64 (0.34, 1.22)	0.70 (0.46, 1.05)
+ PM _{2.5} + SO ₂	0.68 (0.38, 1.23)	0.44 (0.22, 0.87)	0.68 (0.35, 1.31)	0.65 (0.42, 0.99)
+ NO ₂ + SO ₂	0.70 (0.39, 1.27)	0.45 (0.23, 0.90)	0.69 (0.36, 1.33)	0.63 (0.42, 0.97)

a – single pollutant models, adjusted for prenatal exposure only

b – adjusted for prenatal exposure of the respective pollutant and for sex, breastfeeding duration, maternal smoking during pregnancy, family socioeconomic status, child atopy, and parental atopy.

Table S7. Association between exposure to air pollution during the first year of life and incidence rate of lower respiratory tract infections during the second (1-2) year of life

Exposure	Effect estimates, IRR (95% CI), relative to the first quartile			Per 10 µg/ increase IRR (95% CI)
	Quartile 2	Quartile 3	Quartile 4	
PM _{2.5} ^a	0.82(0.34, 1.98)	1.50 (0.66, 3.45)	2.49 (1.16, 5.34)	1.30 (0.59, 2.86)
PM _{2.5} ^b	0.94 (0.38, 2.32)	1.46 (0.60, 3.58)	2.95 (1.32, 6.56)	1.95 (0.86, 4.44)
+SO ₂	1.59 (0.50, 5.05)	1.96 (0.44, 8.72)	2.09 (0.40, 10.89)	1.65 (0.26, 10.40)
+O ₃	0.94 (0.33, 2.66)	1.22 (0.36, 4.11)	2.22 (0.63, 7.88)	0.75 (0.25, 2.24)
+SO ₂ +O ₃	1.59 (0.44, 5.79)	1.68 (0.31, 9.10)	1.77 (0.27, 11.44)	0.97 (0.17, 5.48)
PM ₁₀ ^a	0.68 (0.28, 1.68)	1.62 (0.73, 3.58)	2.25 (1.05, 4.83)	1.24 (0.61, 2.52)
PM ₁₀ ^b	0.76 (0.30, 1.91)	1.56 (0.67, 3.64)	2.62 (1.18, 5.83)	1.80 (0.86, 3.77)
+ CO	1.26 (0.44, 3.64)	3.33 (0.97, 11.42)	5.76 (1.46, 22.69)	2.43 (0.66, 8.89)
+ NO ₂	1.46 (0.48, 4.38)	4.33 (1.14, 16.42)	5.86 (1.22, 28.22)	3.04 (0.57, 16.19)
+ CO + O ₃	1.09 (0.32, 3.74)	2.38 (0.51, 11.15)	3.41 (0.59, 19.70)	1.16 (0.28, 4.77)
+ NO ₂ + O ₃	1.23 (0.35, 4.40)	3.08 (0.61, 15.56)	3.35 (0.49, 22.83)	1.48 (0.25, 8.74)
NO ₂ ^a	0.72 (0.32, 1.66)	1.67 (0.73, 3.81)	2.41 (1.12, 5.19)	1.63 (0.33, 8.10)
NO ₂ ^b	0.79 (0.34, 1.86)	1.54 (0.63, 3.77)	3.03 (1.37, 6.73)	3.18 (0.57, 17.71)
+ PM ₁₀	0.42 (0.13, 1.31)	0.42 (0.09, 1.84)	0.68 (0.13, 3.62)	0.56 (0.01, 33.06)
+ O ₃	0.74 (0.30, 1.82)	1.03 (0.36, 2.97)	1.71 (0.54, 5.36)	0.43 (0.05, 3.91)
+ PM ₁₀ + O ₃	0.47 (0.14, 1.52)	0.45 (0.10, 2.10)	0.75 (0.13, 4.45)	0.26 (0.003, 18.53)
CO ^a	0.95 (0.44, 2.06)	1.22 (0.53, 2.80)	1.65 (0.73, 3.73)	1.00 (0.95, 1.07)
CO ^b	0.87 (0.37, 2.02)	1.52 (0.64, 3.61)	2.25 (0.97, 5.23)	1.04 (0.97, 1.11)
+ PM ₁₀	0.47 (0.16, 1.40)	0.48 (0.13, 1.76)	0.47 (0.11, 1.98)	0.99 (0.88, 1.11)
+ O ₃	0.73 (0.30, 1.75)	0.94 (0.35, 2.52)	1.08 (0.38, 3.08)	0.97 (0.89, 1.05)
+ SO ₂	0.48 (0.14, 1.61)	0.31 (0.07, 1.30)	0.17 (0.03, 0.85)	0.99 (0.90, 1.10)
+ SO ₂ + O ₃	0.53 (0.16, 1.78)	0.34 (0.08, 1.51)	0.18 (0.04, 0.95)	0.97 (0.87, 1.08)
+ PM ₁₀ + O ₃	0.51 (0.17, 1.57)	0.52 (0.13, 1.98)	0.51 (0.11, 2.28)	0.97 (0.86, 1.10)
SO ₂ ^a	0.44 (0.18, 1.11)	1.09 (0.46, 2.58)	2.31 (1.05, 5.07)	1.45 (0.68, 3.09)
SO ₂ ^b	0.47 (0.19, 1.22)	1.05 (0.42, 2.64)	2.66 (1.17, 6.05)	2.12 (0.92, 4.92)
+ CO	0.91 (0.27, 3.05)	3.18 (0.79, 12.85)	13.85 (2.89, 66.35)	3.02 (1.03, 8.88)
+ NO ₂	0.96 (0.28, 3.28)	5.17 (1.30, 20.59)	23.21 (4.21, 128.02)	3.42 (1.04, 11.29)
+ O ₃	0.47 (0.18, 1.24)	0.93 (0.31, 2.78)	2.27 (0.71, 7.26)	0.89 (0.28, 2.84)
+ CO + O ₃	0.78 (0.22, 2.72)	2.49 (0.52, 11.88)	10.73 (1.76, 65.39)	1.49 (0.40, 5.57)
+NO ₂ + O ₃	0.85 (0.24, 2.93)	4.05 (0.90, 18.12)	16.65 (2.56, 108.26)	1.69 (0.41, 7.01)
O ₃ ^a	0.79 (0.43, 1.46)	0.41 (0.19, 0.91)	0.49 (0.23, 1.02)	0.42 (0.16, 1.09)
O ₃ ^b	0.78 (0.41, 1.49)	0.47 (0.20, 1.09)	0.54 (0.25, 1.16)	0.48 (0.17, 1.32)
+ SO ₂	1.13 (0.53, 2.39)	0.72 (0.25, 2.07)	0.73 (0.23, 2.31)	0.18 (0.04, 0.85)
+ NO ₂	0.80 (0.36, 1.78)	0.44 (0.16, 1.24)	0.42 (0.14, 1.24)	0.18 (0.05, 0.69)
+ CO	0.69 (0.33, 1.45)	0.40 (0.16, 1.05)	0.39 (0.14, 1.06)	0.18(0.05, 0.69)
+ PM _{2.5}	1.06 (0.50, 2.25)	0.71 (0.23, 2.14)	0.72 (0.21, 2.52)	0.20 (0.05, 0.82)
+ SO ₂ + CO	1.08 (0.50, 2.30)	0.80 (0.28, 2.24)	0.79 (0.25, 2.47)	0.18 (0.04, 0.77)
+ PM ₁₀ + NO ₂	0.87 (0.38, 1.97)	0.61 (0.20, 1.83)	0.59 (0.16, 2.10)	0.19 (0.05, 0.81)
+ PM _{2.5} + SO ₂	1.21 (0.55, 2.65)	0.77 (0.25, 2.40)	0.78 (0.22, 2.84)	0.17 (0.04, 0.79)
+ NO ₂ + SO ₂	0.96 (0.44, 2.10)	0.72 (0.25, 2.10)	0.71 (0.22, 2.28)	0.18 (0.04, 0.80)

IRR – Incidence rate ratio; CI – confidence interval; PM_{2.5} – particulate matter with a diameter of 2.5 µm; NO₂ – nitrogen dioxide; CO – carbon monoxide; PM₁₀ – particulate matter with a diameter of 10 µm; SO₂ – sulfur dioxide; O₃ – ozone.

a – single pollutant models, adjusted only for prenatal exposure of respective pollutant

b – adjusted for prenatal exposure of respective pollutants and sex, breastfeeding duration, maternal smoking during pregnancy, family socioeconomic status, child atopy and parental atopy.

Table S8. Relation between exposure to air pollution during the first year of life and lower respiratory tract infections during the first two years of life, in term-born babies (n = 2301)

Exposure	IRR (95% CI) of LRTI relative to the first quartile, in term born babies		
	Quartile 2	Quartile 3	Quartile 4
PM _{2.5} ^a	1.17 (0.55, 2.50)	1.64 (0.74, 3.60)	2.67 (1.31, 5.44)
PM _{2.5} ^b	1.33 (0.61, 2.89)	1.85 (0.82, 4.16)	3.10 (1.47, 6.52)
+SO ₂	1.93 (0.69, 5.38)	2.06 (0.56, 7.62)	1.53 (0.35, 6.69)
+O ₃	1.46 (0.60, 3.52)	1.76 (0.60, 5.20)	2.71 (0.87, 8.44)
+SO ₂ +O ₃	2.12 (0.68, 6.60)	1.97 (0.45, 8.68)	1.47 (0.28, 7.81)
NO ₂ ^a	0.71 (0.33, 1.51)	1.58 (0.74, 3.38)	2.38 (1.17, 4.85)
NO ₂ ^b	0.76 (0.35, 1.64)	1.73 (0.79, 3.77)	2.78 (1.33, 5.84)
+ PM ₁₀	0.37 (0.14, 0.96)	0.65 (0.20, 2.16)	0.98 (0.24, 4.04)
+ O ₃	0.76 (0.33, 1.75)	1.43 (0.56, 3.62)	2.15 (0.77, 6.04)
+ PM ₁₀ + O ₃	0.40 (0.15, 1.10)	0.70 (0.21, 2.40)	1.11 (0.25, 4.95)
CO ^a	0.78 (0.36, 1.66)	1.55 (0.73, 3.29)	1.97 (0.92, 4.20)
CO ^b	0.88 (0.41, 1.91)	1.76 (0.81, 3.82)	2.27 (1.02, 5.01)
+ PM ₁₀	0.46 (0.18, 1.18)	0.71 (0.24, 2.04)	0.67 (0.19, 2.32)
+ O ₃	0.80 (0.36, 1.79)	1.35 (0.57, 3.22)	1.45 (0.56, 3.77)
+ SO ₂	0.49 (0.17, 1.39)	0.54 (0.16, 1.83)	0.28 (0.07, 1.16)
+ SO ₂ + O ₃	0.55 (0.19, 1.60)	0.64 (0.18, 2.26)	0.32 (0.08, 1.37)
+ PM ₁₀ + O ₃	0.50 (0.19, 1.31)	0.76 (0.25, 2.31)	0.74 (0.20, 2.68)
PM ₁₀ ^a	1.23 (0.57, 2.66)	1.80 (0.83, 3.92)	2.80 (1.35, 5.81)
PM ₁₀ ^b	1.38 (0.63, 3.02)	1.96 (0.88, 4.35)	3.20 (1.50, 6.84)
+ CO	2.19 (0.87, 5.52)	3.32 (1.10, 10.01)	4.95 (1.49, 16.46)
+ NO ₂	2.69 (1.03, 6.99)	4.01 (1.21, 13.30)	4.63 (1.18, 18.25)
+ CO + O ₃	1.63 (0.59, 4.53)	1.96 (0.53, 7.27)	2.62 (0.60, 11.44)
+ NO ₂ + O ₃	2.78 (0.90, 8.56)	3.82 (0.88, 16.70)	3.89 (0.88, 21.62)
SO ₂ ^a	0.70 (0.32, 1.53)	1.00 (0.43, 2.33)	2.46 (1.16, 5.22)
SO ₂ ^b	0.74 (0.33, 1.63)	1.08 (0.45, 2.57)	2.97 (1.36, 6.45)
+ CO	1.29 (0.46, 3.67)	2.19 (0.60, 8.06)	8.64 (2.13, 34.96)
+ NO ₂	1.56 (0.54, 4.49)	3.08 (0.77, 12.37)	12.36 (2.53, 60.46)
+ O ₃	0.75 (0.33, 1.71)	1.05 (0.38, 2.92)	2.90 (0.98, 8.58)
+ CO + O ₃	1.12 (0.37, 3.42)	1.83 (0.41, 8.24)	7.61 (1.41, 41.09)
+ NO ₂ + O ₃	1.39 (0.45, 4.24)	2.63 (0.57, 12.23)	10.36 (1.72, 62.47)
O ₃ ^a	0.86 (0.48, 1.54)	0.45 (0.22, 0.95)	0.59 (0.30, 1.15)
O ₃ ^b	0.89 (0.48, 1.62)	0.51 (0.24, 1.08)	0.59 (0.29, 1.18)
+ SO ₂	1.29 (0.64, 2.58)	0.80 (0.32, 2.04)	0.88 (0.32, 2.44)
+ NO ₂	1.00 (0.49, 2.02)	0.58 (0.24, 1.41)	0.59 (0.23, 1.52)
+ CO	0.88 (0.45, 1.71)	0.51 (0.22, 1.18)	0.54 (0.23, 1.31)
+ PM _{2.5}	1.09 (0.55, 2.16)	0.69 (0.26, 1.77)	0.86 (0.30, 2.48)
+ SO ₂ + CO	1.26 (0.62, 2.55)	0.85 (0.34, 2.13)	0.95 (0.35, 2.63)
+ PM ₁₀ + NO ₂	1.01 (0.49, 2.09)	0.68 (0.26, 1.73)	0.92 (0.32, 2.64)
+ PM _{2.5} + SO ₂	1.26 (0.61, 2.60)	0.76 (0.28, 2.03)	0.93 (0.31, 2.77)
+ NO ₂ + SO ₂	1.15 (0.56, 2.34)	0.82 (0.32, 2.09)	0.89 (0.32, 2.48)

a – single pollutant models, adjusted only for prenatal exposure

b – adjusted for prenatal exposure of respective pollutant and sex, breastfeeding duration, maternal smoking during pregnancy, family socioeconomic status, child atopy and parental atopy.

Table S9. Incidence rate ratio for the relation between exposure to air pollution during the first year of life and lower respiratory tract infections during the first two years of life,

Exposure	Effect estimates relative to the first quartile, girls			Effect estimates relative to the first quartile, boys		
	Quartile 2	Quartile 3	Quartile 4	Quartile 2	Quartile 3	Quartile 4
PM_{2.5}^a	0.91 (0.31, 2.71)	1.10 (0.35, 3.48)	2.86 (1.10, 7.43)	1.54 (0.57, 4.15)	2.42 (0.93, 6.31)	2.26 (0.86, 5.89)
PM_{2.5}^b	1.05 (0.35, 3.12)	1.16 (0.35, 3.90)	3.71 (1.38, 9.98)	1.74 (0.62, 4.90)	2.13 (0.75, 6.09)	2.76 (1.01, 7.57)
NO₂^a	0.26 (0.07, 0.96)	1.12 (0.39, 3.20)	2.40 (0.98, 5.85)	1.63 (0.63, 4.24)	2.88 (1.07, 7.80)	2.46 (0.91, 6.70)
NO₂^b	0.28 (0.08, 1.01)	1.66 (0.57, 4.83)	2.78 (1.09, 7.09)	1.82 (0.67, 4.97)	2.32 (0.78, 6.82)	3.43 (1.20, 9.81)
CO^a	0.26 (0.07, 0.95)	1.10 (0.42, 2.85)	1.07 (0.38, 3.01)	2.12 (0.86, 5.25)	2.05 (0.73, 5.76)	2.83 (1.06, 7.57)
CO^b	0.30 (0.08, 1.09)	1.52 (0.58, 3.98)	1.11 (0.36, 3.42)	2.01 (0.75, 5.42)	2.17 (0.71, 6.65)	4.58 (1.64, 12.76)
PM₁₀^a	1.11 (0.37, 3.34)	1.44 (0.47, 4.38)	3.21 (1.20, 8.56)	1.12 (0.42, 2.97)	2.10 (0.84, 5.25)	1.91 (0.75, 4.84)
PM₁₀^b	1.24 (0.41, 3.75)	1.44 (0.46, 4.56)	3.88 (1.41, 10.69)	1.22 (0.44, 3.36)	1.74 (0.64, 4.75)	2.33 (0.88, 6.17)
SO₂^a	0.78 (0.25, 2.38)	1.03 (0.30, 3.53)	2.85 (0.97, 8.33)	0.74 (0.28, 1.97)	1.27 (0.48, 3.38)	2.22 (0.88, 5.61)
SO₂^b	0.84 (0.28, 2.54)	1.45 (0.42, 5.00)	3.64 (1.21, 10.98)	0.76 (0.28, 2.08)	1.04 (0.36, 3.00)	2.48 (0.94, 6.55)
O₃^a	0.78 (0.36, 1.72)	0.21 (0.06, 0.75)	0.44 (0.17, 1.14)	0.87 (0.43, 1.77)	0.79 (0.36, 1.73)	0.55 (0.23, 1.27)
O₃^b	1.04 (0.45, 2.40)	0.28 (0.08, 1.04)	0.52 (0.19, 1.41)	0.66 (0.31, 1.43)	0.76 (0.33, 1.72)	0.55 (0.23, 1.32)

a – single pollutant models, adjusted only for prenatal exposure

b – adjusted for prenatal exposure of the studied pollutant, duration of breastfeeding, maternal smoking during pregnancy, family socioeconomic status, child atopy, and parental atopy.

Appendix 2: Weighted Quantile Sum regression

Weighted Quantile Sum (WQS) regression analysis is a statistical method for estimating the effect of simultaneous exposure to multiple environmental pollutants on health. This analysis is conducted by splitting the data into training and validation data sets. It was conducted in two steps using the R package, “gWQS—generalized weighted quantile sum regression.” First, the model estimates the WQS index, a mixture variable, using the training data set (40% in our data) and bootstrap sampling ($n = 200$). The weighted quantile sum index is a weighted sum of each pollutant’s quantile (i.e., in this case, quartiles) based on each pollutant’s relevance to the outcome (i.e., the incidence of LRTIs) derived from bootstrap samples. In the second step, the model estimates the cumulative effect of the air pollutant mixture on the outcome. A positive relationship was detected between exposure to air pollutants and the incidence of LRTIs, as indicated in Figure 1. Therefore, we assumed a positive association between exposure to air pollutants and the incidence of LRTIs to estimate the effect of the mixture.

The effect of exposure to ambient air pollutant mixture during pregnancy and the first year of life on the incidence rate of LRTIs during the first two years of life was modeled using WQS regression as follows:

$$g(\mu) = \beta_0 + \beta_1 \left(\sum_{i=1}^C \omega_i q_i \right) + z' \varphi$$

g Poisson function with log link. μ represents the mean number LRTIs during the first two years of life. β_0 is the intercept. ω_i is the unknown weight for the i th exposure. q_i represents the quartile of exposure (e.g., $q_i = 0, 1, 2,$ or 3 for values in the 1st, 2nd, 3rd, or 4th quartile, respectively). C is the number of exposures. $\sum_{i=1}^C \omega_i q_i$ represents the weighted index for the set of c pollutants of interest,

where $\sum_{i=1}^C \omega_i = 1$ and $0 \leq \omega_i \leq 1$. β_1 is the regression coefficient of the weighted quantile sum. z is a vector of covariates. φ is a vector of regression coefficients for the covariates.

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