[천식연구회 Workshop]

Air Pollution and Asthma

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Contents

- **Physiology**
- **Pollutants**
  - Particulate Matter (PM): PM 2.5 & 10
  - Gases
  - Traffic-related Air Pollution (TRAP)
- **Policy Issues and Future studies**

Introduction

- Urbanization – Air pollution

- Cause exacerbations or symptoms of pre-existing asthma
  - Adverse associations of PM10 with asthma symptoms (OR 1.03, 95% CI 1.01-1.05)
  - Significant positive associations with symptoms but not school absence

Environ Health Perspect 2010; 118: 449–57.
J Allergy Clin Immunol. 2008 May;121(5):1133-1139

- Childhood asthma
  - (10 European cities) 14% of the cases of incident asthma in children and 15% of all exacerbations of childhood asthma <- exposure to pollutants related to road traffic.

Eur Respir J 2013; **42:** 594–605

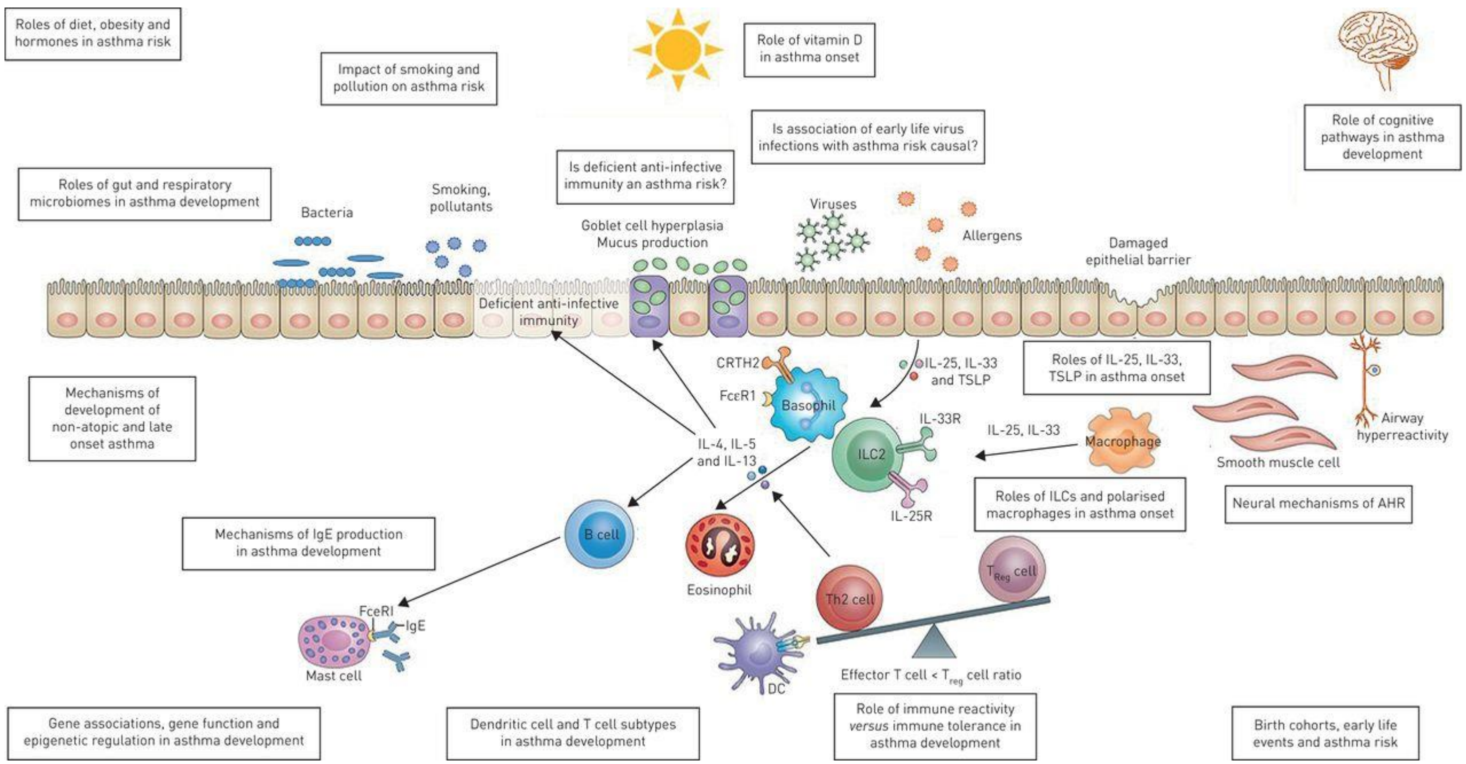
- Can air pollution cause new-onset asthma?
  - The incidence of asthma: a change in PM10 per 1 mg/m3 change (HR 1.30 (1.05 -1.61))
    -> not sensitive to further adjustments
  - Asthma onset (OR per 10 mg/m3: 1.46 (1.07-1.99) and incident asthma (OR 1.54 (1.00– 2.36)) and the levels of nitrogen dioxide (NO2)
    -> remained statistically significant after adjusting for potential confounders

Thorax 2009; 64: 664–70.
Eur Respir J 2009; 33: 1261–1267

Lung Physiology in Asthma

Edward MR, et al. *Eur Respir J* 2017; 49: 1602448

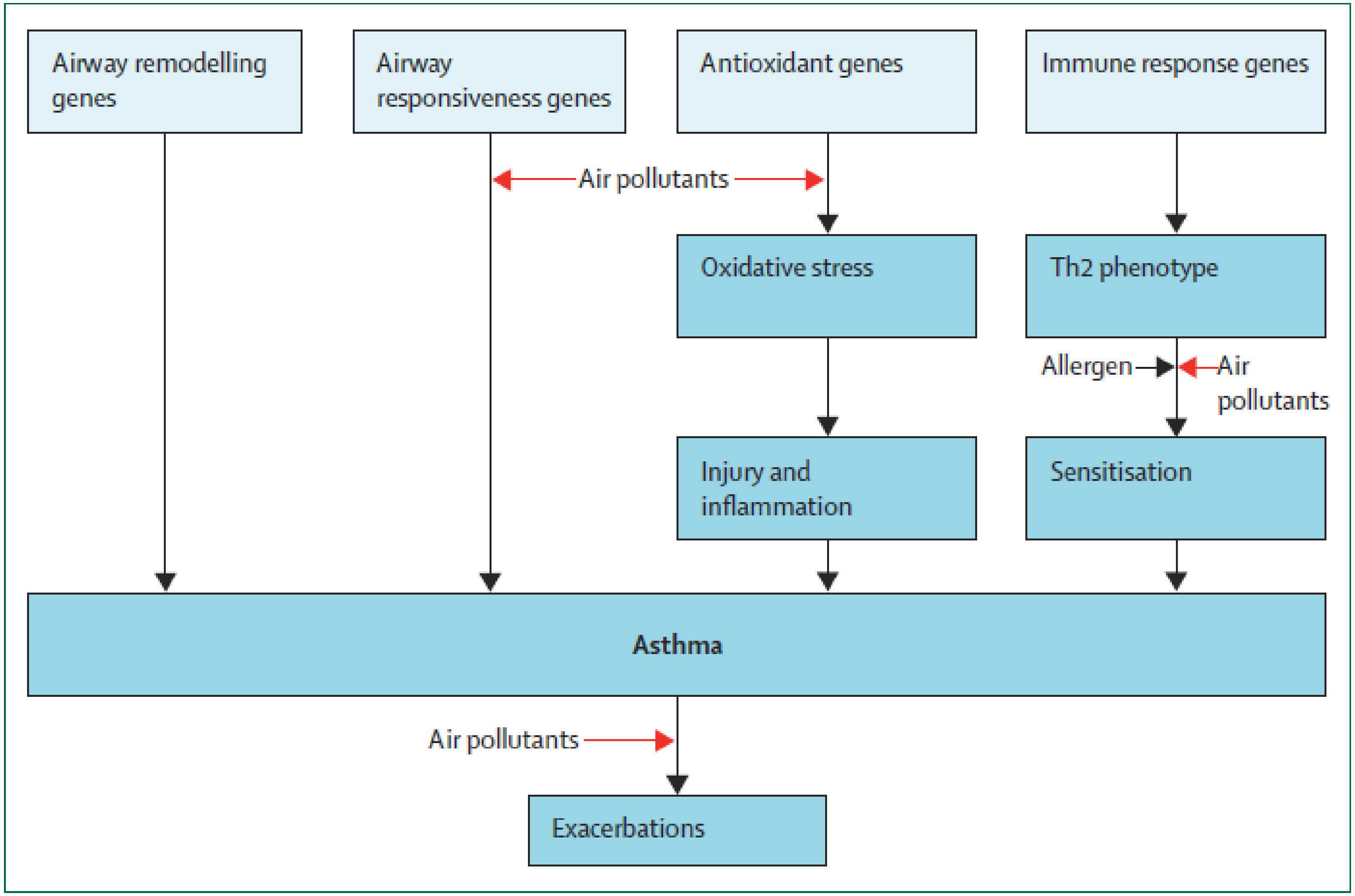
- Airway inflammation & hyper-responsiveness



-> Oxidative stress and damage
Airway remodeling
Inflammatory pathways and immunological responses
Enhancement of respiratory sensitization to aeroallergens

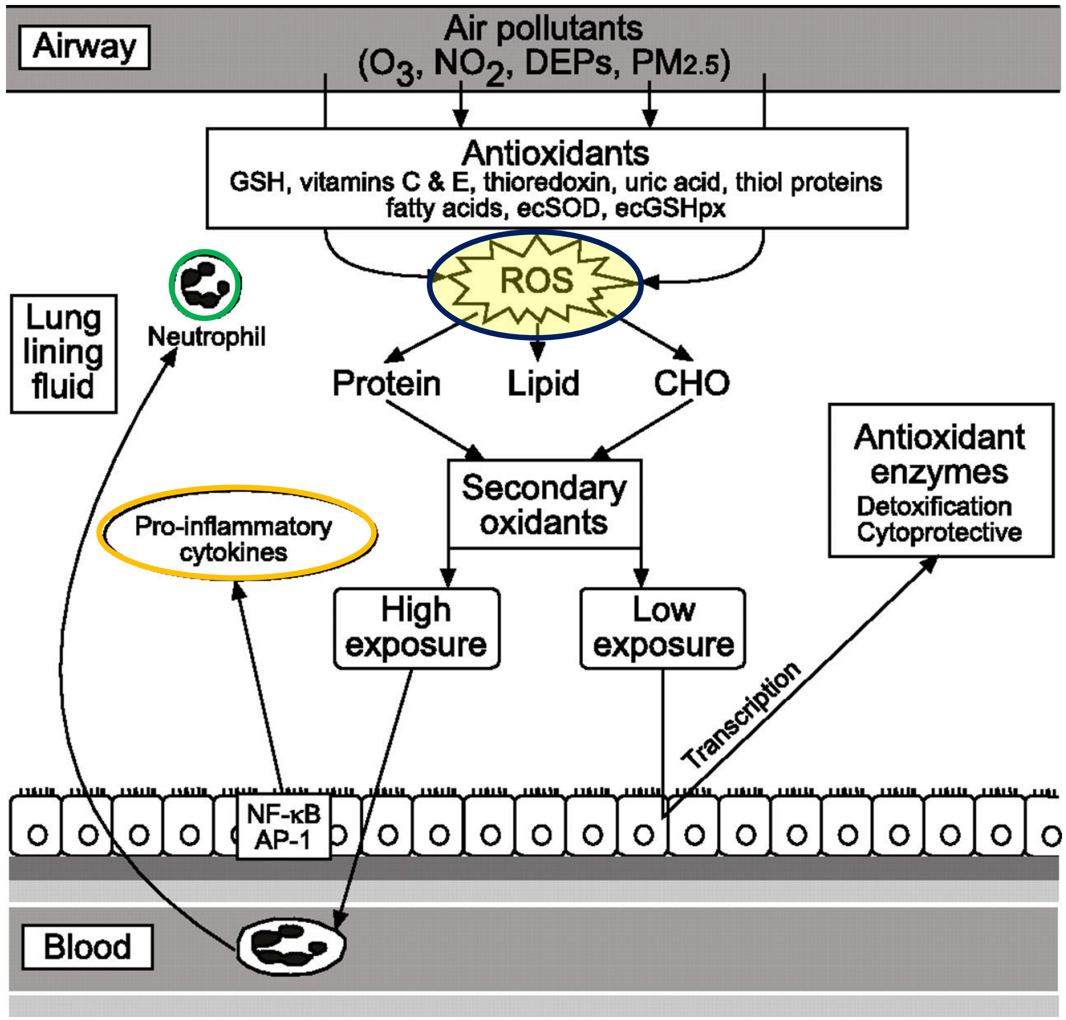
Air pollution effects in Asthma

Guanieri M. Lancet 2014; 383: 1581–92



Pollutant exposure

Bateman SS, et al. *Eur Respir J* 2008; 31: 179–196



Antioxidant actions

Sierra-Vargas MP, et al. *J Occup Med Toxicol*. 2009 Jun 29;4:17

In Mexico
6 asthma pts vs. 11 healthy controls
Neutrophil, TBARS

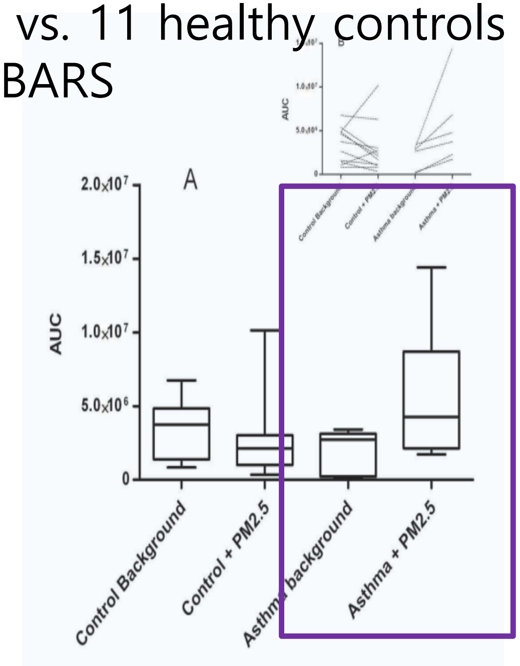


Figure 4
In vitro generation of reactive oxygen and nitrogen species by neutrophils in contact with $PM_{2.5}$. A. In vitro production of reactive oxygen and nitrogen species by neutrophils from healthy volunteers (NHV) compared with neutrophils from asthmatic patients (NAP), measured by luminol-enhanced chemiluminescence and expressed as the area under the curve (AUC). The graph represents the mean of AUC for each group. B. Each line represents the chemiluminescence response of each subject that participated in the study, before and after treatment with $PM_{2.5}$. The pattern shows a general increase in this response in the NAP group.

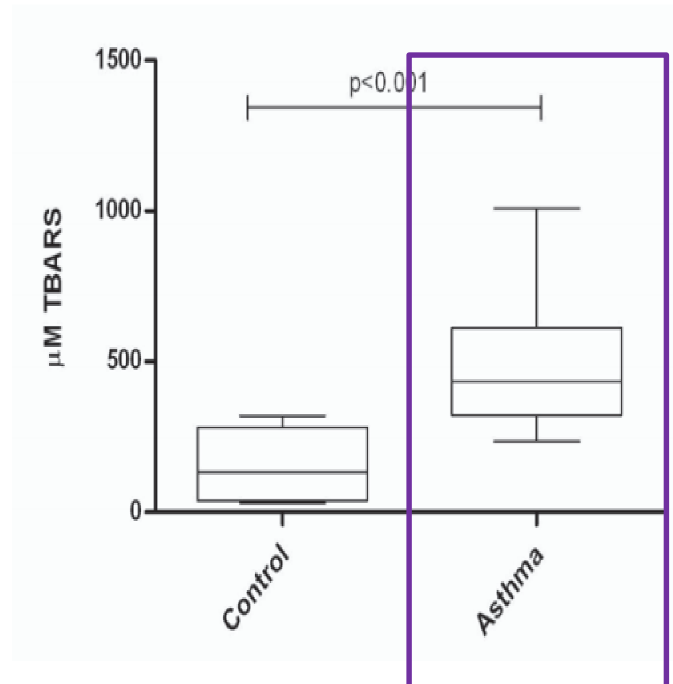


Figure 7
Susceptibility of lipids to oxidation. The graph shows a higher susceptibility of lipids from the asthmatic group to damage as a consequence of oxidative stress.

Antioxidant actions

Canova C, et al. Epidemiology. 2012 Jul;23(4):607-15.

In UK
209 admitted asthma patients
PM10- Acute exacerbation

TABLE 5. Adjusted[a] Association of COPD/Asthma Exacerbations for Each 10-$\mu g/m^3$ Increase in PM_{10} at Lag 0–3, by Individual Antioxidant Capacity, for 158 Chelsea and Westminster Hospital Admissions, 2008–2010

Effect Modifier	OR (95% CI)	Test for Interaction
Vitamin C		P = 0.007
<13 μmol/L	2.17 (1.38–3.43)	
≥13 μmol/L	0.90 (0.56–1.46)	
Uric acid		P = 0.238
<236 μmol/L	1.83 (1.18–2.84)	
≥236 μmol/L	1.13 (0.72–1.77)	
Vitamin A		P = 0.697
<2.2 μmol/L	1.37 (0.90–2.07)	
≥2.2 μmol/L	1.69 (1.04–2.75)	
Vitamin A (corrected for cholesterol)		P = 0.153
<0.5 μmol/L	1.18 (0.78–1.78)	
≥0.5 μmol/L	2.02 (1.22–3.36)	
Vitamin E		P = 0.062
<23.7 μmol/L	1.79 (1.19–2.68)	
≥23.7 μmol/L	1.12 (0.66–1.90)	
Vitamin E (corrected for cholesterol)		P = 0.256
<5.5 μmol/L	1.64 (1.09–2.47)	
≥5.5 μmol/L	1.37 (0.83–2.26)	

[a]Models adjusted for temperature and humidity.

Antioxidant actions

Reddy P, et al. *Am J Ind Med.* 2012 Dec;55(12):1078-86.

In South Africa
GSTM1
AP-FEV1 variability

TABLE V. Effect of Pollutant Exposure by *GSTM1* Genotype (Percent Change[a] in Intraday Variability[b] of FEV_1 Associated With Ambient Levels[c] of Pollutants From Single Pollutant Linear Regression Models Using Generalized Estimating Equations (GEE))

		PM_{10}		SO_2		NO_2		NO	
GSTM1		**Est**	**CI**	**Est**	**CI**	**Est**	**CI**	**Est**	**CI**
Pos	Lag 1	−2.03	−6.95, 2.88	0.31	−0.31, 0.93	1.40	−0.36, 3.17	1.34	−2.63, 5.31
Null		−1.38	−7.52, 4.75	0.44	−0.78, 1.66	−0.17	−0.29, 2.62	−2.19	−5.93, 1.55
Pos	Lag 2	−2.57	−8.60, 3.47	0.09	−0.44, 0.61	1.17	−0.69, 3.03	0.85	−3.47, 5.17
Null		0.36	−7.17, 7.89	1.06	−0.36, 2.48	−0.04	−2.97, 2.89	−1.56	−5.38, 2.26
Pos	Lag 3	−0.52	−5.78, 4.74	−0.56	−1.44, 0.32	1.68	−0.58, 3.95	1.52*	−2.11, 5.16 (* **0.05**)
Null		−5.66	−14.45, 3.14	1.46	−0.75, 3.66	−0.73	−3.77, 2.32	−3.06	−6.61, 0.49
Pos	Lag 4	0.17	−2.05, 2.38	6.28	−2.04, 14.60	0.7	−1.22, 2.61	1.34	−0.67, 3.36
Null		−0.12	−3.26, 3.02	−4.10	−13.84, 5.64	1.82	−1.82, 5.46	0.30	−3.32, 2.92
Pos	Lag 5	1.83	−0.22, 3.88	−0.23	−7.15, 6.67	1.39	−0.98, 3.75	−0.69	−3.26, 1.89
Null		−1.04	−4.49, 2.40	−2.47	−14.07, 9.12	1.88	−2.53, 6.34	0.34	−2.41, 3.10
Pos	5-day average	−0.98†	−1.56, −0.41 († ‹**0.00**)	1.08*	0.44, 2.60 (* ‹**0.00**)	−5.75*	−11.63, 0.12 (* **0.01**)	1.27	−1.03, 3.58
Null		−0.15	−1.50, 1.20	−1.18	−2.89, 0.53	1.63	−5.14, 8.40	0.51	−3.68, 4.70

Covariates in each model: race, school, caregiver smoking, caregiver education, household income, season, interaction between genotype and pollutants. Bold denotes significant *P*-value.

[a]The percent change value shown is for an increase of one interquartile range in each respective pollutant: NO_2: 8.19 ppb; NO: 29.7 ppb, PM_{10}: 29.4 μg m^{-3}; SO_2: 9.8 ppb.

[b]Intraday variability for FEV_1 is defined as: 100 (maximum best FEV_1-minimum best FEV_1)/maximum best FEV1; where the "best FEV_1" is the highest valid, error-free value for the specific time of day (08:00 hr, 09:45 hr, 11:30 hr, and 13:20 hr). An increase in the estimate for intraday FEV_1 is indicative of a negative impact on lung function.

[c]Pollution levels used in regression models combine measured and imputed values.

*P-value for genotype–pollutant interaction term ≤ 0.05.

†P-value for the change in estimate ≤ 0.05.

Antioxidant actions

Reddy P, et al. *Am J Ind Med.* 2012 Dec;55(12):1078-86.

In South Africa
GSTP1
AP-FEV1 variability

TABLE VI. Effect of Pollutant Exposure by *GSTP1* Genotype (Percent Change[a] in Intraday Variability[b] of FEV_1 Associated With Ambient Levels[c] of Pollutants From Single Pollutant Linear Regression Models Using Generalized Estimating Equations (GEE))

		PM_{10}		SO_2		NO_2		NO	
GSTP1		**Est**	**CI**	**Est**	**CI**	**Est**	**CI**	**Est**	**CI**
AA	Lag1	−0.14	−5.31, 5.0	−0.11	−0.62, 0.39	1.86*	−0.14, 3.87 (* **0.04**)	0.58	−4.00, 5.17
AG + GG		0.50	5.35, 6.34	1.17†	0.16, 2.18 († **0.03**)	−3.40	−5.95, −8.85	−1.56	−5.53, 2.41
AA	Lag2	−4.47*	−10.70, 1.18 (* **0.01**)	0.22	−0.34, 0.77	2.29†,*	0.01, 4.56 (* **<0.00**; † **0.04**)	−0.15	−4.94, 4.64
AG + GG		9.0	−0.83, 18.84	0.32	−1.13, 1.78	−3.82†	−6.53, −1.11 († **0.01**)	−0.78	−4.92, 3.37
AA	Lag3	−2.52*	−10.23, 5.20 (* **0.02**)	−0.72*	−2.14, 0.69 (* **0.03**)	2.33	−0.36, 5.02	−0.77	−5.32, 3.78
AG + GG		7.98†	1.14, 14.78 († **0.02**)	3.05†	1.53, 4.56 († **<0.00**)	−3.05†	−6.02, −0.08 († **0.04**)	−0.32	−4.37, 3.74
AA	Lag4	0.35	−1.55, 2.24	−4.06	−13.87, 5.34	−0.41	−2.91, 2.09	−1.40	−3.55, 0.78
AG + GG		−0.86	−3.73, 2.02	4.37	−3.06, 11.81	2.04	−1.36, 5.45	0.73	−1.51, 2.96
AA	Lag5	−0.18	2.37, 2.02	−0.09	−7.81, 7.63	−0.46	−3.25, 2.33	−1.43	−4.00, 1.14
AG + GG		1.08	−2.62, 4.77	−1.03	−8.29, 6.25	2.66	−0.93, 2.63	2.04	−1.01, 5.09
AA	5-day average	−0.40	−1.42, 0.62	0.63	−1.01, 2.26	−3.52	−11.45, 4.40	1.91	−0.85, 4.67
AG + GG		0.20	−1.18, 1.63	−1.80	−3.87, 0.26	4.42	−3.27, 12.11	0.63	−2.09, 3.36

Covariates in each model: race, school, caregiver smoking, caregiver education, household income, season, interaction between genotype and pollutants. Bold denotes significant *P*-value.

[a]The percent change value shown is for an increase of one interquartile range in each respective pollutant: NO_2: 8.19 ppb; NO: 29.7 ppb, PM_{10}: 29.4 $\mu g\ m^{-3}$; SO_2: 9.8 ppb.

[b]Intraday variability for FEV_1 is defined as: 100 (maximum best FEV_1-minimum best FEV_1)/maximum best FEV1; where the "best FEV_1" is the highest valid, error-free value for the specific time of day (08:00 hr, 09:45 hr, 11:30 hr, and 13:20 hr). An increase in the estimate for intraday FEV_1 is indicative of a negative impact on lung function.

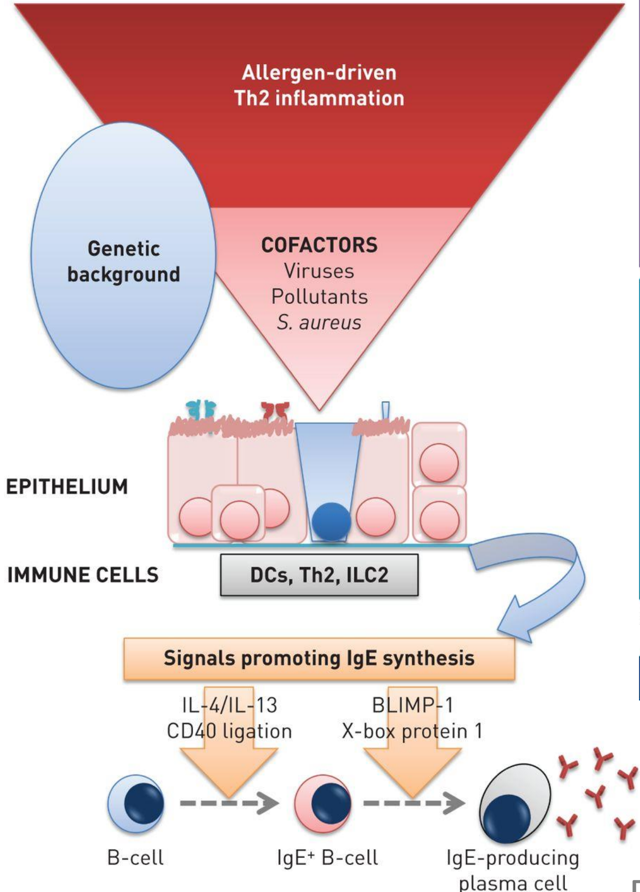
[c]Pollution levels used in regression models combine measured and imputed values.

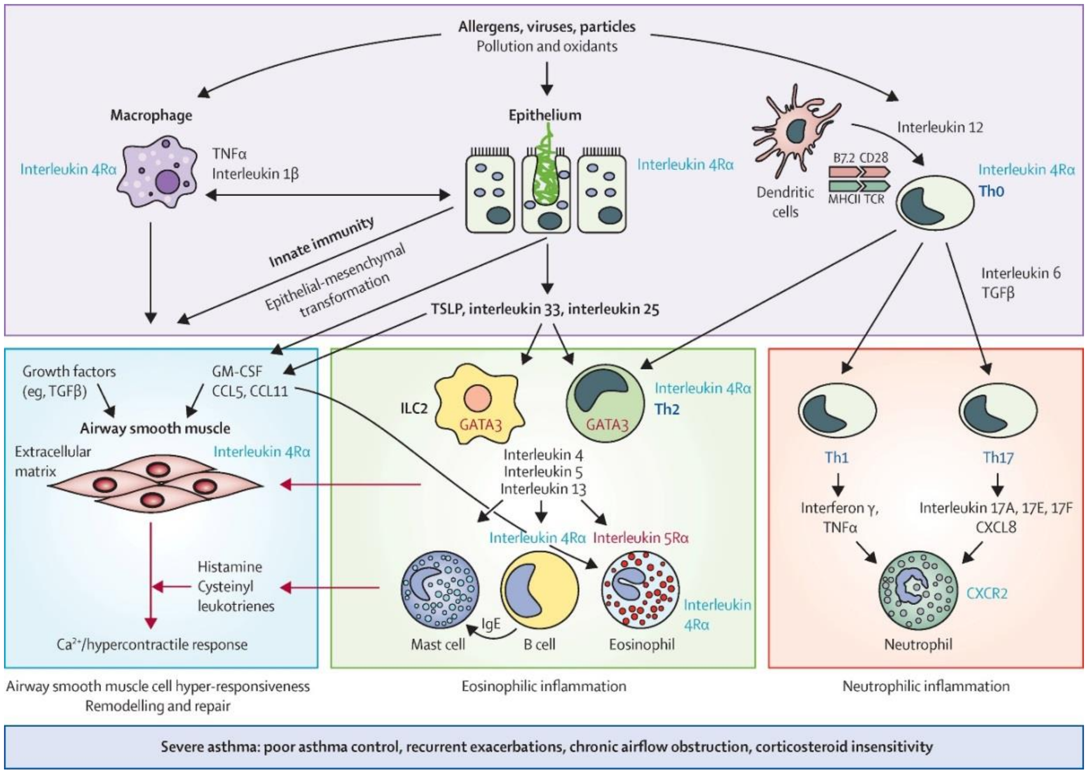
* *P*-value for genotype–pollutant interaction term ≤ 0.05.

† *P*-value for the change in estimate ≤ 0.05.

Immune-response

- Enhanced pulmonary neutrophilic inflammation and the promotion of a **Th2/Th17 phenotype**





Chung KF. Lancet. 2015 Sep 12;386(9998):1086-96.

Froidure A, et al. *Eur Respir J* 2016; 47: 304–319

Allergen sensitization

Bowatte G, et al. Allergy. 2015 Mar;70(3):245-56.

Meta-analysis of birth cohorts

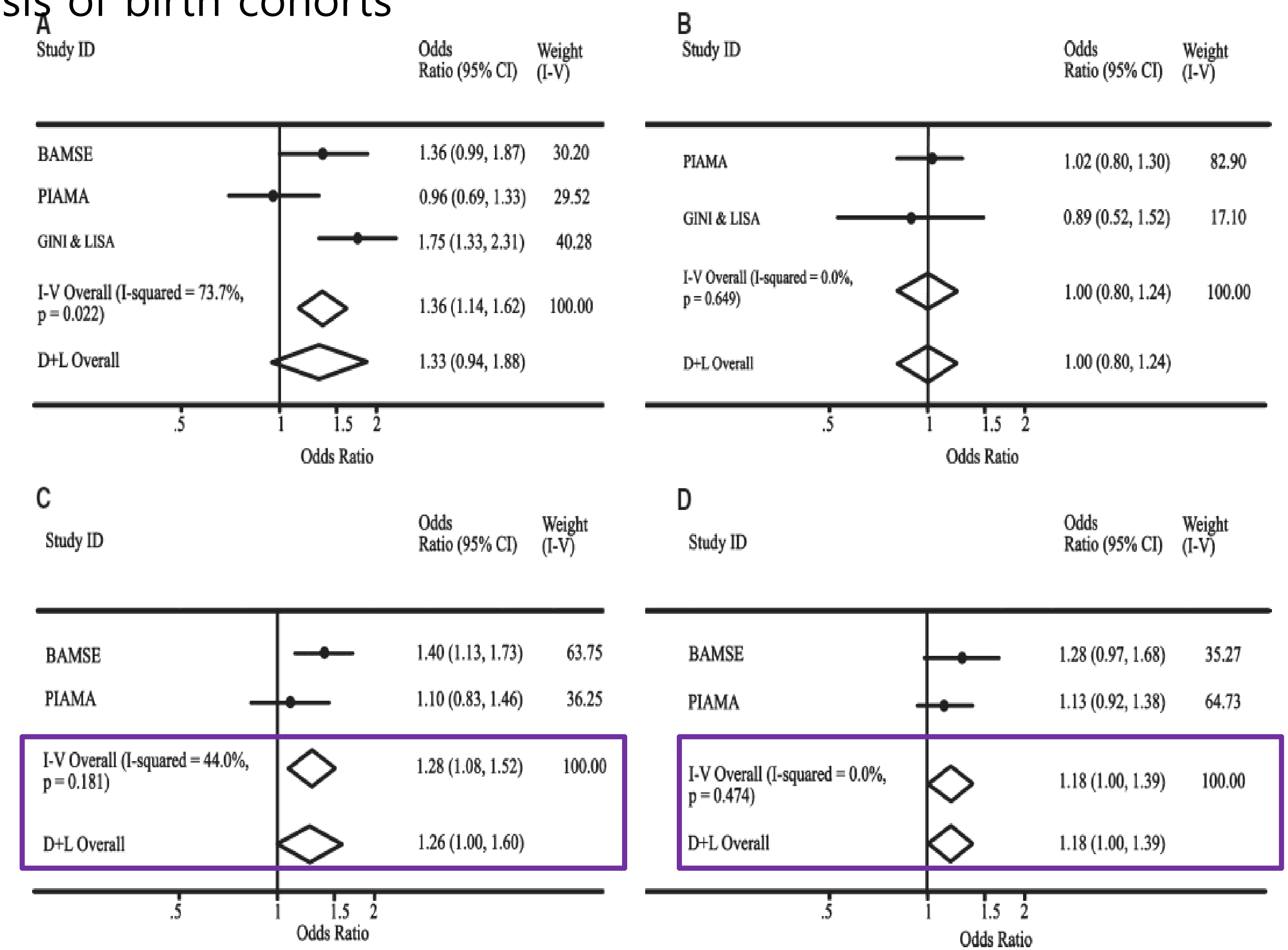
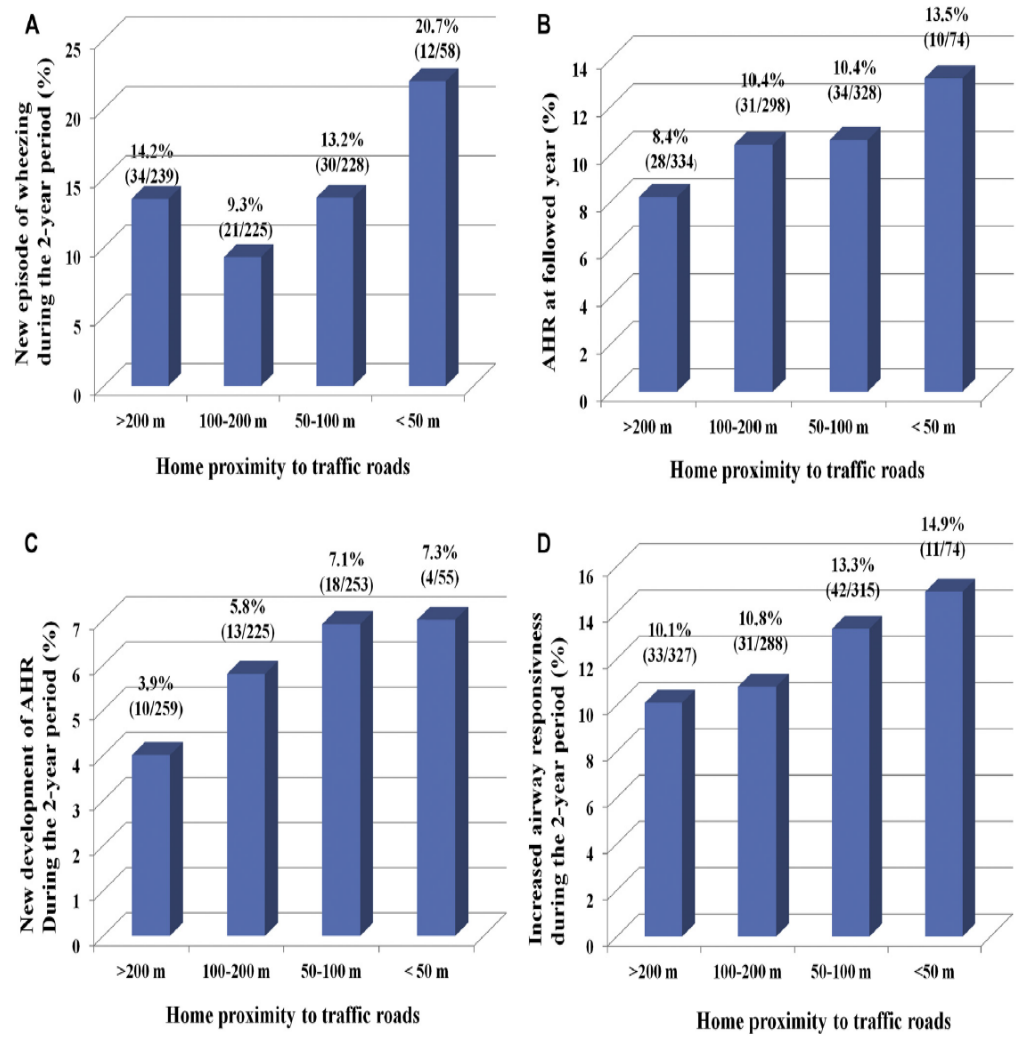


Figure 4 Early childhood exposure per 2 μg/m^3 increase in $PM_{2.5}$ and sensitization to (A) outdoor allergens, (B) indoor allergens, (C) food allergens at the age of 4 years and (D) food allergens at the age of 8 years.

Airway hyperresponsiveness

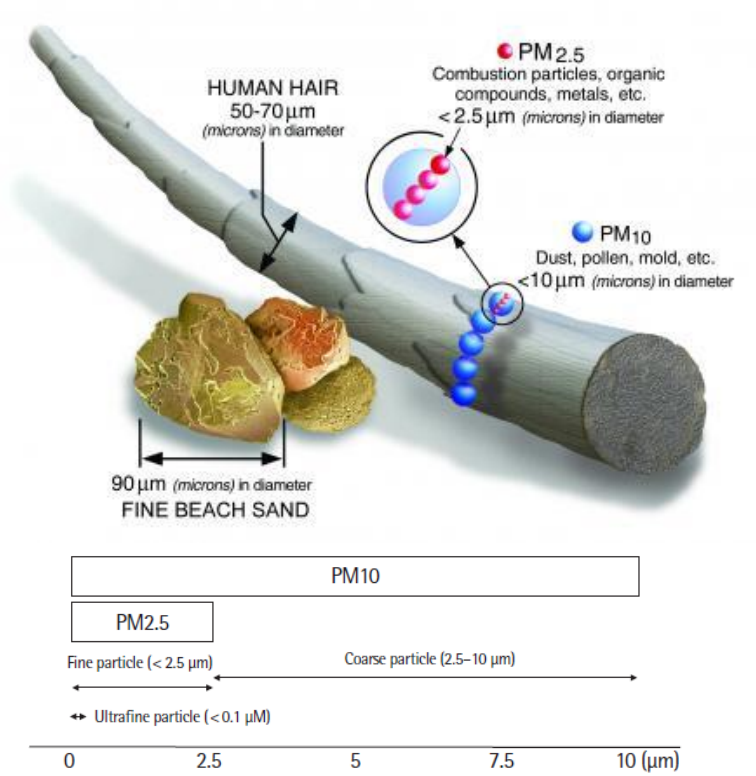
Kim BJ, et al. *J Allergy Clin Immunol*. 2014 Jun;133(6):1763-5.

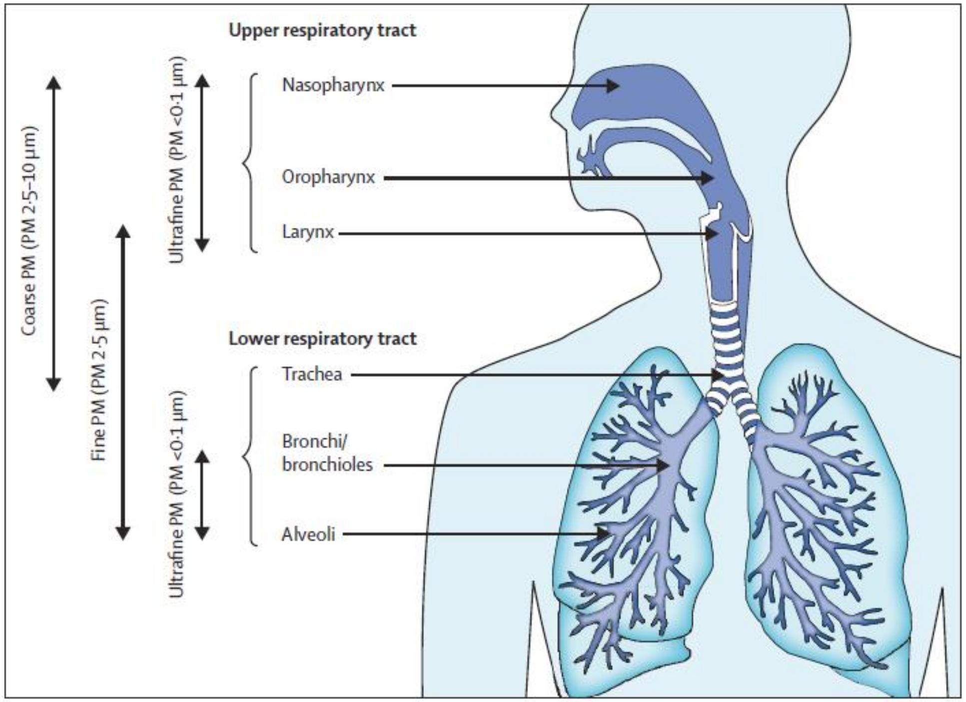
N=1,340
2-year prospective survey



Compartmental deposition of PM

the US Environmental Protection Agency





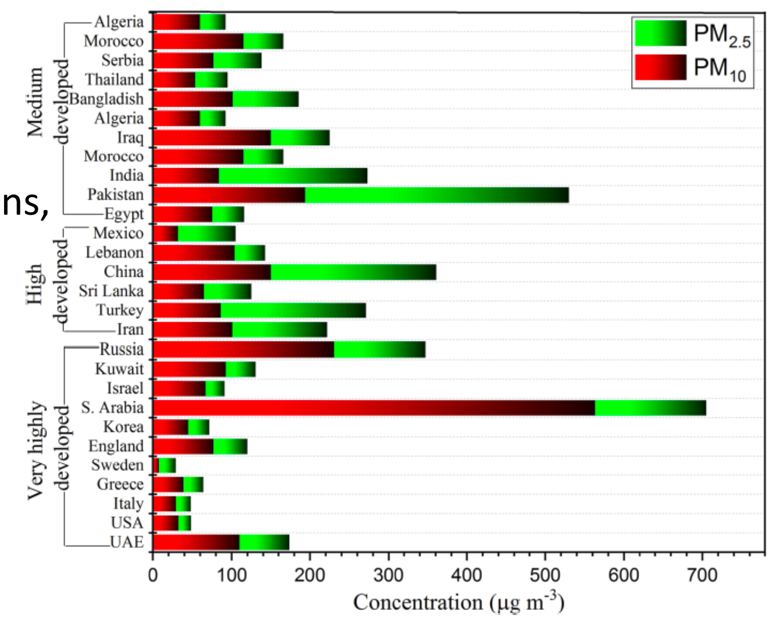
PM 10 & 2.5

Ubiquitous atmospheric aerosol
with both anthropogenic and natural sources

- **Composition**
  - Combustion or not
  - Transition metals, polycyclic aromatic hydrocarbons, and environmentally persistent free radicals

- Oxidative stress
- Phenotype change in asthma
- Exacerbation of symptoms

Fig. 3 PM_{10} and $PM_{2.5}$ concentrations (μm^{-3}) in medium-developed, high-developed and very highly developed countries of world



Environ Geochem Health. 2018 Oct 8. doi: 10.1007

PM: Allergic sensitization

Mann JK, et al. *Environ Health Perspect*. 2010 Oct;118(10):1497-502

Table 4. Association between air pollution at "representative lag" and wheeze in selected subgroups of the FACES cohort.

"in a few days"

In California
A cohort of 315 children with asthma
AP-wheeze

Subgroup/pollutant	Lag	OR (95% CI)
Allergy to cat dander (*n* = 49 children, 2,869 panel-days)		
NO_2 (ppb)	2	1.27 (1.06–1.51)*
$PM_{10-2.5}$ (µg/m³)	3	1.28 (1.09–1.51)*
NO_3 (µg/m³)	5	1.21 (1.01–1.45)*
EC (µg/m³)	6	1.33 (1.04–1.71)*
$PM_{2.5}$ (µg/m³)	5	1.23 (0.94–1.62)
O_3 (ppb)	1	0.93 (0.73–1.19)
Allergy to fungi (*n* = 85 children, 4,943 panel-days)		
NO_2 (ppb)	2	1.23 (1.10–1.39)*
$PM_{10-2.5}$ (µg/m³)	3	1.16 (1.02–1.33)*
NO_3 (µg/m³)	5	1.12 (0.97–1.29)
EC (µg/m³)	6	1.30 (1.06–1.59)*
$PM_{2.5}$ (µg/m³)	5	1.16 (0.94–1.44)
O_3 (ppb)	1	1.06 (0.92–1.23)
Boys with mild asthma (*n* = 47 children, 2,901 panel-days)		
NO_2 (ppb)	2	1.51 (1.23–1.85)*
$PM_{10-2.5}$ (µg/m³)	3	1.35 (1.10–1.65)*
NO_3 (µg/m³)	5	1.25 (1.03–1.52)*
EC (µg/m³)	6	1.70 (1.37–2.12)*
$PM_{2.5}$ (µg/m³)	5	1.41 (1.12–1.77)*
O_3 (ppb)	1	0.86 (0.65–1.13)

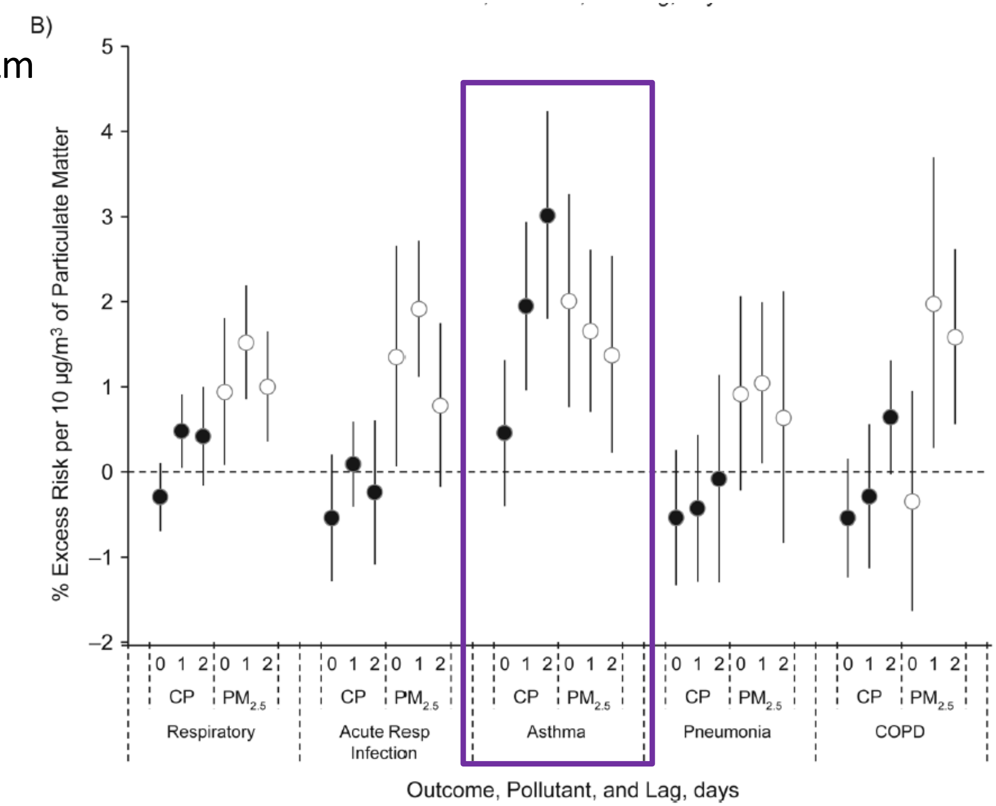
"Representative lag" is the one associated with the largest coefficient in the first 7 days.
*$p < 0.05$.

PM 10 & 2.5

Malig BJ, et al. *Am J Epidemiol*. 2013;178(1):58–69

- **Coarse particle**
  - Short or long-term exposure : symptom increase, poorly controlled asthma
    -> Increased health-care use
  - Particulate matter from 2.5 to 10 µm

In 35 California counties
487,068 cases
74,978 asthma cases
Coarse particle
ER visit for pulmonary diseases



PM: Symptom & Hospitalization

Meng Y-Y, et al. *J Epidemiol Community Health*. 2010 Feb;64(2):142-7.

In California
1,502 diagnosed asthma
Sx., ER visit, hospitalization

Table 3 Association (OR (95% CI)) between annual average air pollution concentrations and asthma outcomes for California Health Interview Survey 2001 respondents residing in the San Joaquin Valley, California (all ages)

		Daily/weekly symptoms*		Emergency department visits/hospitalisation	
		Crude	Adjusted†	Crude	Adjusted†
Ozone		(193 yes, 559 no)		(78 yes, 681 no)	
	Continuous (per 10 ppb)	1.13 (0.88 1.46)	1.23 (0.94 to 1.60)	1.47 (1.05 to 2.07)	1.49 (1.05 to 2.11)
	Quartile				
	<27.0	1.00	1.00	1.00	1.00
	27.1 to 30.2	1.68 (1.01 to 2.79)	1.54 (0.91 to 2.61)	2.44 (1.18 to 5.07)	2.35 (1.12 to 4.95)
	30.3 to 33.9	1.97 (1.19 to 3.26)	2.18 (1.30 to 3.68)	1.75 (0.81 to 3.79)	1.80 (0.82 to 3.95)
	34.0+	1.44 (0.86 to 2.42)	1.62 (0.95 to 2.61)	2.63 (1.27 to 5.43)	2.65 (1.26 to 5.57)
PM_{10}		(198 yes, 569 no)		(79 yes, 695 no)	
	Continuous (per 10 μg/m^3)	1.31 (1.08 to 1.60)	1.29 (1.05 to 1.57)	1.32 (1.01 to 1.73)	1.29 (0.99 to 1.69)
	Quartile				
	<31.71	1.00	1.00	1.00	1.00
	31.72 to 42.66	1.68 (0.99 to 2.85)	1.73 (1.00 to 2.98)	1.78 (0.87 to 3.67)	2.00 (0.95 to 4.20)
	42.67 to 44.33	1.96 (1.17 to 3.30)	1.89 (1.11 to 3.22)	1.42 (0.67 to 3.01)	1.45 (0.67 to 3.11)
	44.34+	2.64 (1.60 to 4.37)	2.51 (1.49 to 4.21)	2.17 (1.08 to 4.36)	2.03 (1.00 to 4.13)
$PM_{2.5}$		(152 yes, 459 no)		(58 yes, 559 no)	
	Continuous (per 10 μg/m^3)	1.86 (1.15 to 2.99)	1.82 (1.11 to 2.98)	1.42 (0.74 to 2.71)	1.47 (0.76 to 2.84)
	Quartile				
	<17.89	1.00	1.00	1.00	1.00
	17.90 to 21.39	1.39 (0.76 to 2.51)	1.53 (0.83 to 2.84)	2.03 (0.85 to 4.86)	2.15 (0.87 to 5.29)
	21.40 to 23.49	2.03 (1.14 to 3.60)	1.82 (1.01 to 3.29)	2.53 (1.08 to 5.95)	2.33 (0.97 to 5.58)
	23.50+	2.39 (1.36 to 4.20)	2.46 (1.38 to 4.41)	2.23 (0.94 to 5.31)	2.30 (0.95 to 5.56)

*Participants were asked in a single question to report the frequency of asthma symptoms, such as coughing, wheezing, shortness of breath, chest tightness, and phlegm production.
†Adjusted for age, gender, race/ethnicity, poverty and insurance status.
O_3, ozone; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter.

PM: Symptom & Hospitalization

Meng Y-Y, et al. *J Epidemiol Community Health*. 2010 Feb;64(2):142-7.

In California
1,502 diagnosed asthma
Sx., ER visit, hospitalization

Table 4 Association (OR (95% CI)) between annual average air pollution concentrations and asthma outcomes for California Health Interview Survey 2001 respondents residing in the San Joaquin Valley, California by age group*

		Children (ages 1–17)		Adults (ages 18+)	
		Daily/weekly symptoms†	Emergency department/ hospitalisation	Daily/weekly symptoms†	Emergency department/ hospitalisation
Ozone		(32 yes, 215 no)	(29 yes, 221 no)	(161 yes, 344 no)	(49 yes, 460 no)
	Continuous (per 10 ppb)	0.76 (0.42 to 1.38)	1.63 (0.95 to 2.81)	1.40 (1.02 to 1.91)	1.43 (0.87 to 2.34)
PM_{10}		(36 yes, 222 no)	(31 yes, 230 no)	(162 yes, 347 no)	(48 yes, 465 no)
	Continuous (per 10 $\mu g/m^3$)	0.90 (0.60 to 1.37)	1.31 (0.89 to 1.93)	1.43 (1.13 to 1.82)	1.29 (0.87 to 1.92)
$PM_{2.5}$		(25 yes, 173 no)	(21 yes, 179 no)	(127 yes, 286 no)	(37 yes, 380 no)
	Continuous (per 10 $\mu g/m^3$)	0.64 (0.27 to 1.50)	1.48 (0.62 to 3.50)	2.96 (1.60 to 5.50)	1.58 (0.56 to 4.43)

*Adjusted for gender, race/ethnicity, poverty and insurance status.
†Participants were asked in a single question to report the frequency of asthma symptoms, such as coughing, wheezing, shortness of breath, chest tightness and phlegm production
O_3, ozone; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter.

PM: Hospital admission in Korea

Lee JT, et al. Epidemiology. 2002 Jul;13(4):481-4.

TABLE 4. Asthma-Related Hospital Admissions by Interquartile Increase in Daily Concentration of Five Pollution Variables, Using One- or Two-Pollutant Models*

	RR 95% CI				
Pollutant	Baseline + PM_{10}	Baseline + SO_2	Baseline + NO_2	Baseline + O_3	Baseline + CO
PM_{10}	**1.07†** **1.04–1.11**	1.05 1.01–1.09	1.03 0.99–1.07	1.06 1.03–1.10	1.04 1.00–1.08
SO_2	1.08 1.02–1.14	**1.11†** **1.06–1.17**	0.95 0.88–1.03	1.12 1.06–1.17	0.99 0.92–1.07
NO_2	1.13 1.07–1.19	1.20 1.11–1.29	**1.15†** **1.10–1.20**	1.14 1.09–1.20	1.12 1.03–1.22
O_3	1.10 1.05–1.15	1.12 1.07–1.17	1.11 1.06–1.16	**1.12†** **1.07–1.16**	1.12 1.07–1.17
CO	1.13 1.07–1.20	1.17 1.08–1.27	1.04 0.95–1.14	1.16 1.11–1.22	**1.16†** **1.10–1.22**

* The baseline model includes the following variables: an intercept, indicator variables for day of week, and smooth spline functions of date, temperature, and humidity. Values for two-pollutant models indicate the effect of the row pollutant, after adjustment for the baseline variables and the column pollutant.
† From one-pollutant model.

Gases

Oxidative stress in asthma

- Ground level Ozone: Photochemical reactions
  - sunlight and pollutant precursor: nitrogen oxide, volatile compounds
- Nitrogen oxide: reaction of ozone with nitric oxide emitted during fossil fuel combustion
- Indoor exposure to nitrogen oxide: burn natural gas
- Sulphur dioxide: energy production or industrial processes

	Ozone	Nitrogen dioxide	Sulphur dioxide
Bronchoconstriction	+/–	–	+
Decreased FEV1 and FVC	+	–	–
Increased airway responsiveness	+	+	–
Airway inflammation	+	+	–
Enhanced responses to inhaled allergen	+	+	+

FEV1=forced expiratory volume in 1 s. FVC=forced vital capacity.

Table 1: **Acute effects of short-term exposures to pollutant gases in asthmatic adults**

Guarnieri M, Balmes JR. Lancet 2014; 383: 1581–92

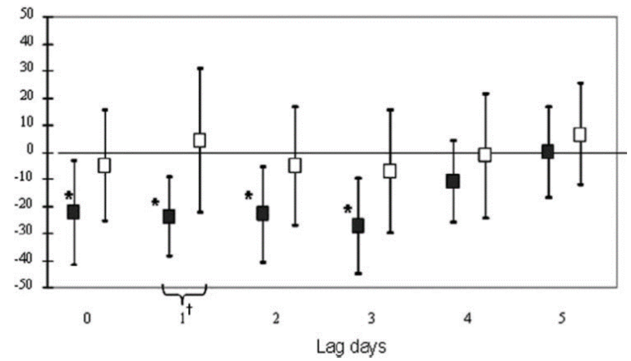
Gases

Nitrogen oxide (NO, NO2)

- Experimental data : inconsistent or unclear

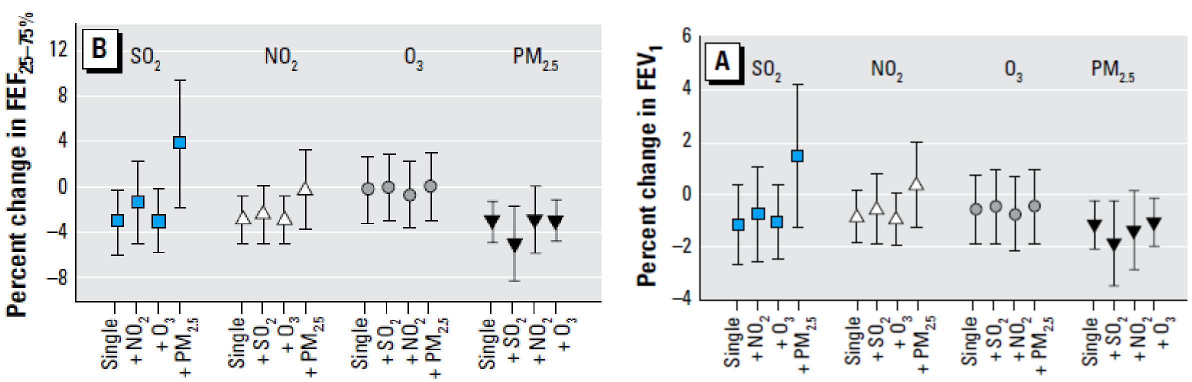
- Observational data
  - Reduced response to bronchodilators

    In Mexico
    N=85
    NO2-BD response



Cadena L, et al. Chest. 2009 Dec;136(6):1529-1536

  - Decrements in lung function



Liu L, et al. *Environ Health Perspect.* 2009 Apr;117(4):668-74

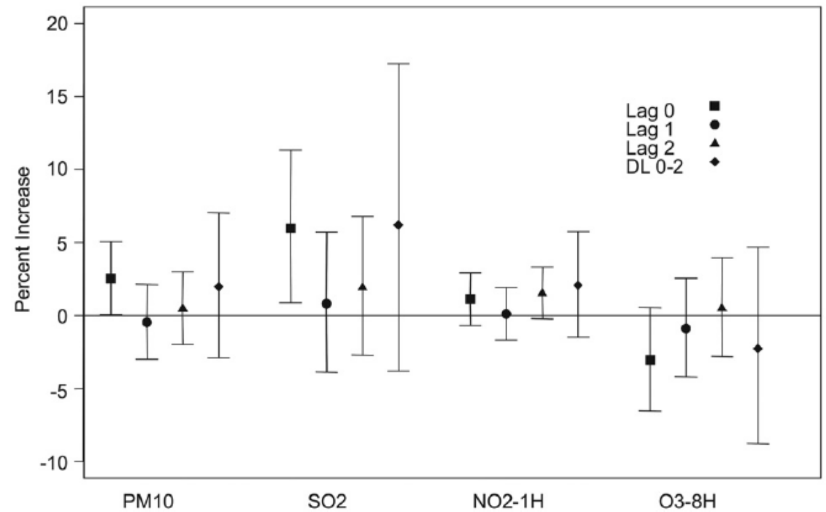
Gases

Nitrogen oxide (NO, NO2)

- Exacerbation of asthma

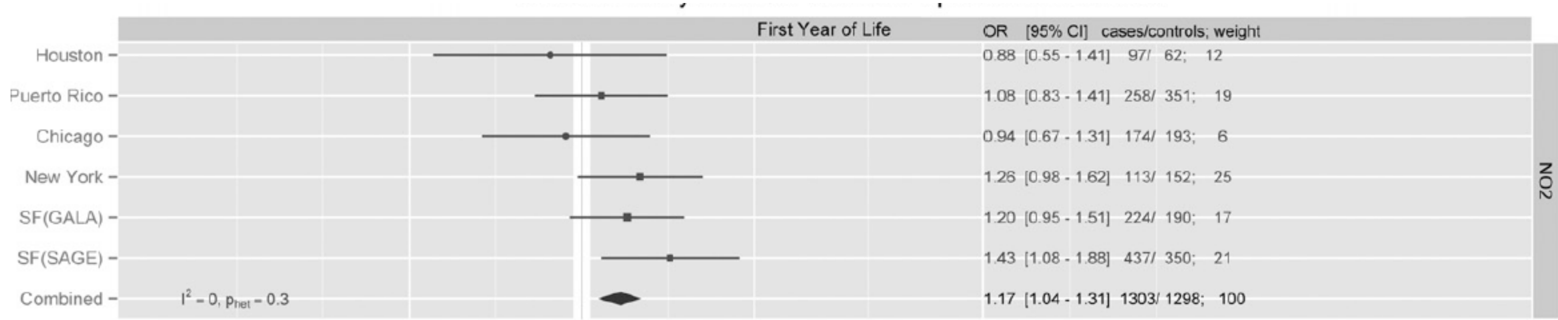
  In Athens, Greece
  3 representative hospitals
  AP- Admission for AE

  Samoli E, et al. Environ Res 2011; 111: 418–24



- Increase in adulthood asthma?

In the US and Puerto Rico
4,329 (2,291 cases), case-control



Early-life air pollution and asthma risk in minority children: **Not** NOx, O3, PM2.5, PM10

Nishimura K, et al. *Am J Respir Crit Care Med* 2013; 188: 309–18.

Gases

Nitrogen oxide (NO, NO2)

Table 3 Studies evaluating adult onset asthma on exposure to air pollution

Castro-Giner et al. [43]	Sweden, UK, Spain Barcelona, Germany, France, Paris, Belgium	Exposures to NO_2 at each of the participants' addresses were determined using air pollution maps using focal sum techniques in a global information system model.	20–44 years	NO_2	No significant association between NO_2 exposure and development of asthma. Significant association between development of asthma and NO_2 exposure in those carrying NQO1 rs2917666 genotype.
Lindgren et al. [44]	Sweden	Self-reported exposure to traffic, traffic intensity within 100 m, modeled exposure to NO_x using modified Gaussian dispersion model.	18–77 years	NO_x	Asthma diagnosis was associated with living within 100 m of a road with greater than 10 cars/min. Participants with high exposure to NO_x (> 19 $\mu g/m^3$) had increased odds ratio for asthma symptoms but not diagnosi
Lindgren et al. [45]	Sweden	Self-reported exposure to traffic, traffic intensity within 100 m, modeled exposure to NO_x using modified Gaussian dispersion model.	18–77 years	NO_x	Increased prevalence of allergic asthma was seen for participants living within 100 m of a road with greater than 10 cars/min but not for non-allergic asthma. No statistical significance of allergic and non-allergic asthma prevalence on exposure to NO_x at various concentrations.

Yasmin Hassoun, et al. *Clinic Rev Allerg Immunol* 2019 Feb 26. doi: 10.1007/s12016-019-08730-3

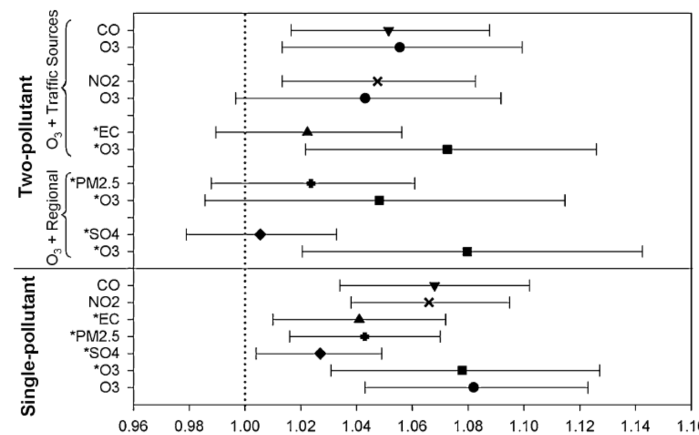
Gases

Ozone

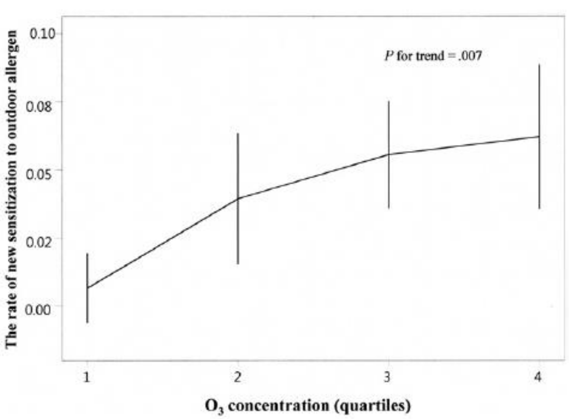
- Short-term exposure: Asthma exacerbation

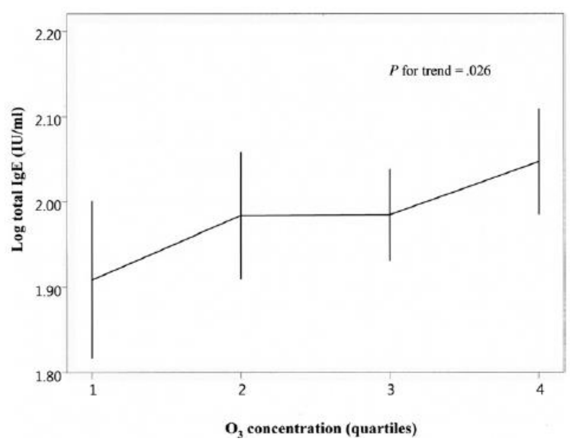
In Atlanta
N=591,386
Ozone-asthma AE

Strickland MJ, et al. *Am J Respir Crit Care Med* 2010; 182: 307–16.



- Long-term exposure: allergic sensitization, new-onset asthma





Kim BJ, et al. *Ann Allergy Asthma Immunol* 2011; 107: 214–19.

heavily exposed?

	Low ozone communities		High ozone communities	
	N (incidence)*	RR (95% CI)	N (incidence)*	RR (95% CI)
Number of sports played				
0	58 (0·027)	1·0	46 (0·018)	1·0
1	50 (0·033)	1·3 (0·9–1·9)	40 (0·021)	1·3 (0·8–2·0)
2	20 (0·023)	0·8 (0·5–1·4)	16 (0·020)	1·3 (0·7–2·3)
⩾3	9 (0·019)	0·8 (0·4–1·6)	20 (0·050)	3·3 (1·9–5·8)

McConnell R, et al. Lancet 2002; 359: 386–91.

Gases

Sulphur dioxide: greatly reduced in the developed world

In China
30,139 (aged 3-12)
AP- asthmatic symptoms

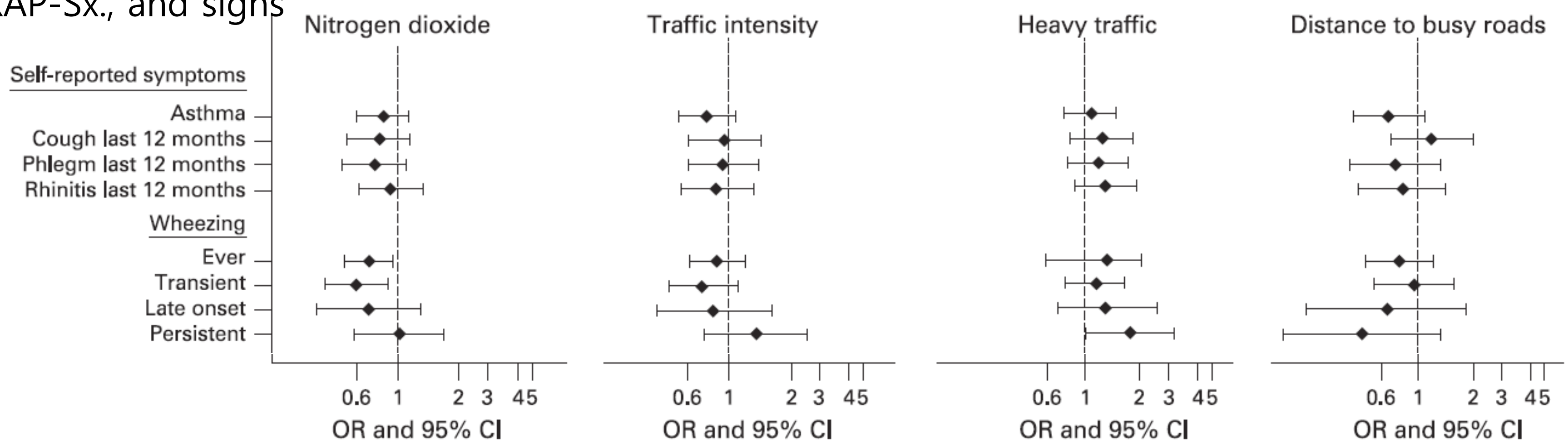
Pollutant		PM_{10}	SO_2	NO_2	O_3	CO
Multi-pollutant (five pollutants) model[*]						
Males	Persistent cough	0.92(0.64–1.34)	1.07(0.81–1.40)	1.18(0.90–1.56)	1.31(0.93–1.83)	0.99(0.75–1.31)
	Persistent phlegm	1.08(0.64–1.82)	1.05(0.73–1.52)	1.14(0.79–1.65)	1.11(0.71–1.72)	1.14(0.78–1.65)
	Doctor-diagnosed asthma	1.27(0.87–1.87)	0.88(0.66–1.16)	0.91(0.69–1.21)	**1.42(1.01–1.99)**	0.85(0.64–1.12)
	Current asthma	1.40(0.80–2.44)	1.05(0.71–1.54)	0.94(0.63–1.40)	1.28(0.79–2.07)	0.75(0.50–1.11)
	Current wheeze	1.39(0.93–2.08)	1.02(0.75–1.39)	1.07(0.79–1.46)	0.73(0.50–1.06)	0.95(0.70–1.29)
	Allergy rhinitis	1.17(0.73–1.86)	1.28(0.93–1.76)	1.16(0.84–1.58)	1.11(0.77–1.58)	070(0.51–0.96)
Females	Persistent cough	1.24(0.84–1.81)	1.08(0.82–1.42)	1.03(0.78–1.36)	1.04(0.74–1.46)	0.97(0.73–1.28)
	Persistent phlegm	0.96(0.58–1.61)	0.97(0.67–1.38)	0.79(0.54–1.14)	**1.98(1.25–3.13)**	1.22(0.84–1.77)
	Doctor-diagnosed asthma	**1.54(1.01–2.39)**	**1.45(1.06–1.98)**	0.97(0.72–1.33)	0.78(0.53–1.13)	0.69(0.51–0.95)
	Current asthma	**2.04(1.24–3.35)**	**1.91(1.00–3.67)**	1.34(0.84–2.15)	0.33(0.19–0.60)	0.72(0.45–1.16)
	Current wheeze	1.13(0.77–1.67)	0.82(0.62–1.09)	0.73(0.54–0.97)	**1.66(1.16–2.38)**	0.97(0.73–1.30)
	Allergy rhinitis	**1.84(1.06–3.19)**	1.15(0.81–1.63)	1.19(0.84–1.69)	0.99(0.67–1.45)	0.50(0.35–0.71)

Dong GH, et al. PLoS One 2011; 6: e22470.

TRAP (Traffic-related Air Pollution)

- A complex mixture of PM
  - **Combustion**: elemental or black carbon
  - **Non-combustion**: road dust, tyre wear, and brake wear
  - **Primary gaseous emissions**: nitrogen oxides
  - Specifically ambient polycyclic aromatic hydrocarbons and diesel-exhaust particles
  - Affect regulatory T cell (Treg) function through an epigenetic mechanism

In Rome
N=2,017, Cross-sectional survey
TRAP-Sx., and signs



Rosenlund M, et al. Thorax 2009;64:573–580.

TRAP (Traffic-related Air Pollution)

- Distances within 300–500 m of roadways
  - The most relevant for effects on human health.

Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. Boston, MA: Health Effects Institute, 2010.

- Diesel-exhaust particles
  - In isolation, have inconsistent effects in animals and in vitro
  - Exposure to such pollutants concomitant with or after sensitisation to variety of allergen

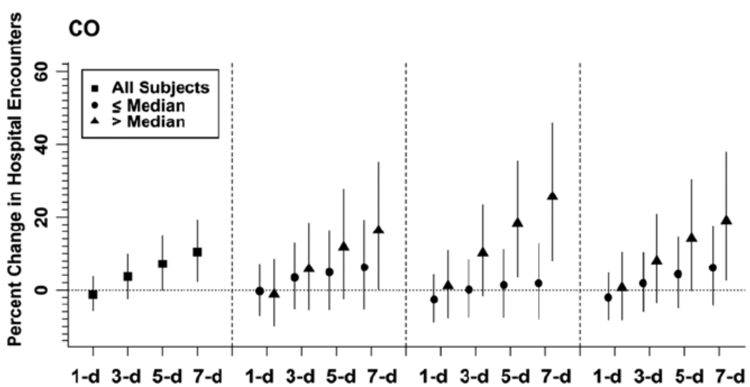
  => Results in oxidative stress, airway hyper-responsiveness, enhanced neutrophilic and eosinophilic airway inflammation

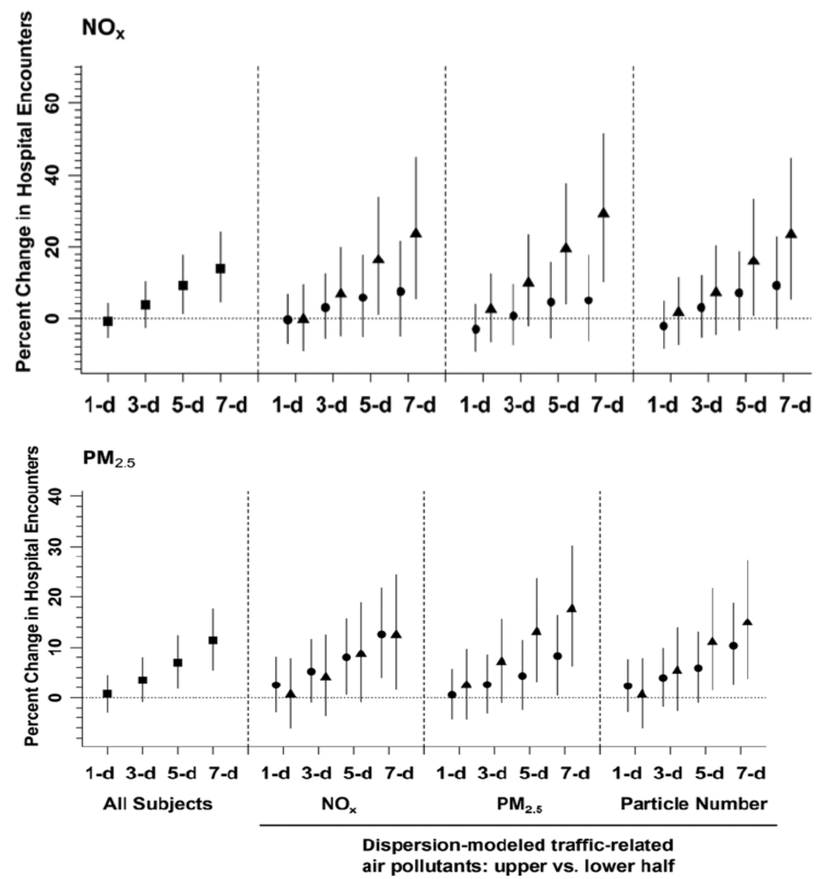
  => Switch to Th2/Th17 phenotypes

TRAP (Traffic-related Air Pollution)

- Regional air pollution + long-term TRAP exposure

In California
N=7,492
11,390 asthma-related hospital encounter
TRAP-AP-hospital encounter





Delfino RJ, et al. Epidemiology 2014; 25: 48–57.

TRAP (Traffic-related Air Pollution)

- Phase 3 ISAAC study
  - Representing over 500 000 children and adolescents across five continents
  - Identified a dose-response association between symptoms of asthma

Table 4. Association between self-reported truck traffic on the street of residence and symptoms in 6- to 7-year-old children.

	No.			OR (95% confidence interval)		
Group/symptom	Country	Center	Total	High vs. never	Medium vs. never	Low vs. never
All study participants[a]						
Current wheeze	29	70	197,515	1.46 (1.36–1.56)	1.31 (1.24–1.39)	1.09 (1.03–1.15)
Asthma ever	29	70	197,515	1.32 (1.23–1.42)	1.21 (1.14–1.28)	1.04 (0.98–1.10)
Severe asthma symptoms	29	69	194,932	1.64 (1.49–1.80)	1.33 (1.22–1.45)	1.08 (1.00–1.17)
Rhinoconjunctivitis	29	70	197,515	1.44 (1.34–1.54)	1.24 (1.17–1.32)	1.07 (1.01–1.13)
Eczema	28	69	194,622	1.37 (1.28–1.48)	1.20 (1.13–1.28)	1.08 (1.02–1.14)

Table 3. Association between self-reported truck traffic on the street of residence and symptoms in 13- to 14-year-old children.

	No.			OR (95% confidence interval)		
Group/symptom	Country	Center	Total	High vs. never	Medium vs. never	Low vs. never
All study participants[a]						
Current wheeze	46	110	315,572	1.46 (1.36–1.56)	1.33 (1.25–1.41)	1.13 (1.07–1.19)
Asthma ever	46	110	315,572	1.23 (1.16–1.30)	1.11 (1.05–1.17)	1.04 (0.99–1.09)
Current wheeze–video	35	86	246,658	1.53 (1.40–1.67)	1.35 (1.25–1.47)	1.13 (1.04–1.22)
Severe asthma symptoms	46	108	310,808	1.65 (1.53–1.79)	1.35 (1.26–1.46)	1.10 (1.03–1.18)
Rhinoconjunctivitis	46	110	315,572	1.49 (1.41–1.59)	1.28 (1.21–1.35)	1.09 (1.03–1.14)
Eczema	45	109	313,085	1.59 (1.47–1.72)	1.35 (1.25–1.44)	1.09 (1.03–1.17)

Brunekreef B, et al. *Environ Health Perspect* 2009; 117: 1791–98.

Possible Risk Modifiers

Previous study Gap

- Young boys than in girls
- Ethnicity
- Socioeconomic status
- Secondhand tobacco smoking
- Neighborhood characteristics: crimes, and green spaces
- Stress
- Diet

Future Perspectives

Policy Issues

- **Alert In Korea**
  - Ozone alert
  - PM 10 & PM 2.5 alert

오존 예보 등급과 행동요령

예보구간		등급: 좋음	보통	나쁨	매우 나쁨
예측농도 (ppm)	O_3	0~0.030	0.031~0.090	0.091~0.150	0.151 이상
행동요령 (오존)	민감군*	-	실외활동시 특별히 행동에 제약을 받을 필요는 없지만 몸상태에 따라 유의하여 활동	장시간 또는 무리한 실외활동 제한	가급적 실내 활동
	일반인	-	-	장시간 또는 무리한 실외활동 제한 특히 눈이 아픈 증상이 있는 사람은 실외활동을 피해야 함	실외에서의 활동을 제한, 실내생활 권고

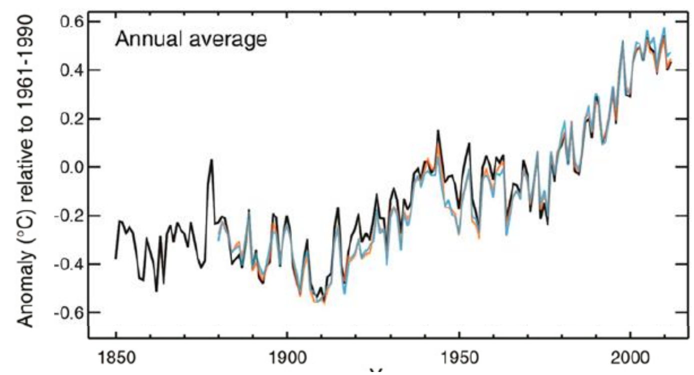
* 민감군 : 어린이, 노인, 천식 같은 폐질환 및 심장질환을 앓고 있는 어른

- **Considerations**
  - Residency : How far away from the traffic road for residency in Korea?
  - Indoor pollutant?
  - Change in treatment? **How to do clinicians :** Avoid outdoor activities **in asthma patients**..

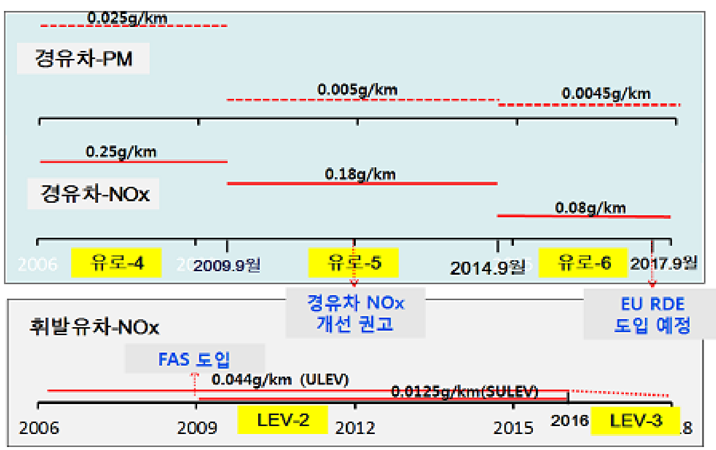
Future Perspectives

Policy Issues

- **Climate change & clean-air regulation**
  - Pollutants - climate change
    & Climate change - Pollutants



Vehicle registration for emissions



Am J Respir Crit Care Med 2014; 189: 512–19.

Future Perspectives

further studies

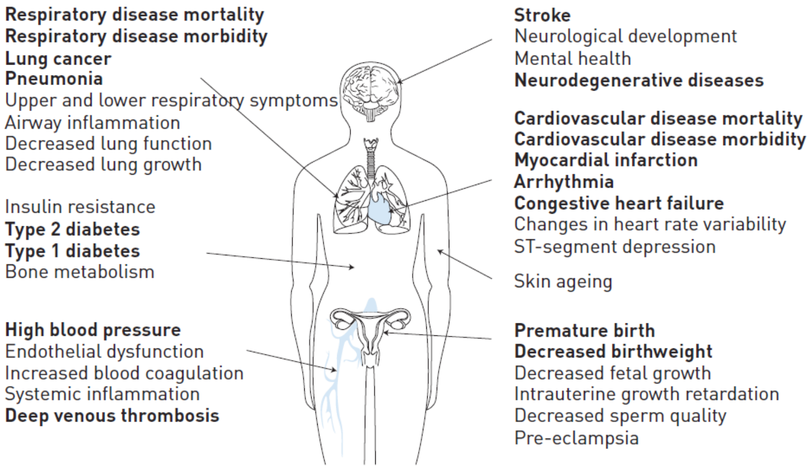
- **Air pollutants – climate change – health imperatives**

✓ The onset of asthma and lag time

✓ Methodology: how assuming pre-exposed pollutants?

✓ Further Cardiovascular clinical effects

✓ Treatment strategies – which level target ?



ERS/ATS STATEMENT. *Eur Respir J. 2017 Jan 11;49(1). pii: 1600419*

"Thanks for your attention."

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National Medical Center