Air pollutants from a pulmonologist's perspective

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Seminar overview

- Introduction
- Global burden of air pollution
- Health outcomes of air pollution
- Lung and air pollution
- Classification of air pollutants
- Composition and sources
- Air Quality Guidelines – Global Update 2005
- Revised National Ambient Air Quality Standards 2009
- Detrimental mechanisms of air pollutants
- Literatures on deleterious effects of air pollutants on the lung

Introduction

- Air pollution is an alteration of the levels of quality and purity of the air due to natural or anthropogenic emissions of chemical and biological substances
- Increasing evidence shows that air pollution is associated with adverse health outcomes, particularly respiratory diseases
- Rapid global urbanization and increased energy consumption have exposed the human body to not only an increased quantity of ambient air pollution, but also a greater variety of pollutants

Introduction

- Increased concentrations of greenhouse gases, and especially CO_2, in the earth's atmosphere have already substantially warmed up the planet, affecting biosphere and biodiversity and determining more severe and prolonged heat waves, temperature variability, air pollution, forest fires, droughts, and floods
- These changes in climate and air quality have a quantifiable impact for both morbidity and mortality of asthma and other respiratory diseases

Eur Respir J 2009;34:295-302

Annu Rev Public Health 2008;29:41-55

World Allergy Organ J 2015;8(1):25

Respirology 2006;11(5):523-32

Global burden of air pollution : WHO report

- **2008** : 1.3 million deaths were estimated to be related to ambient air pollution; 2 million deaths were attributable to the effects of household air pollution
- **2012** : deaths due to ambient air pollution went up to 3.7 million (tripled); deaths attributable to household air pollution went up to 4.3 million (doubled)
- More than 2 million premature deaths each year were related to air pollution
- Globally, 7 million deaths were attributable to the joint effects of household and ambient air pollution in 2012

Global burden of air pollution…..

- The 2015 WHO European Region document estimated economic costs for 2010 : “The annual economic cost of premature deaths from air pollution across the countries on the WHO European region stood at US$ 1.431 trillion and the overall annual economic cost of health impacts and mortality from air pollution, including estimates for morbidity costs, stood at US$ 1.575 trillion.”

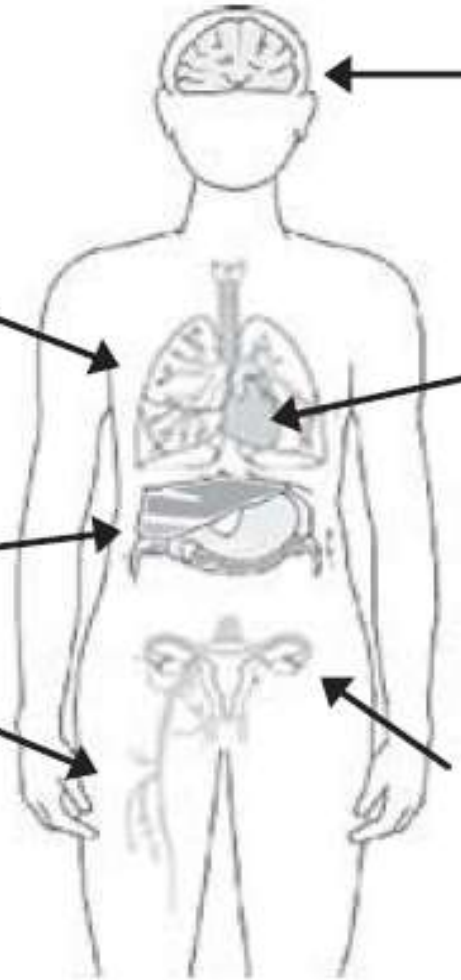
WHO Document. Regional office for Europe. Economic cost of health impact of air pollution in Europe. Clean air, health and wealth. (Marmorvej 51 - DK -2100. Copenhagen, Denmark) 2015

Health outcomes related to air pollution

- Respiratory mortality
- Respiratory symptoms
- Rhinitis/Pneumonia
- Airway inflammation
- Decreased lung function
- Lung cancer

- Metabolic disorders
- Diabetes

- Changes in blood pressure
- Increased blood coagulation
- Systemic inflammation



- Stroke
- Central nervous system diseases

- Cardiovascular mortality
- Cardiovascular hospital admission
- Changes in heart rate variability
- ST-segment depression

- Premature birth
- Decreased birth weight
- Decreased foetal weight

- Air pollution has impact on most of the organs and systems of human body
- The lung is one of the major sites of interaction with environmental particulates
- Cause and aggravating factor of many respiratory diseases like COPD, asthma, and lung cancer

Components and sources of air pollutants

- **Classification** : A). Outdoor and Indoor pollutants B). Primary and secondary pollutants
- **Outdoor pollutants** : major pollutants are particulate matter (PM), ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and lead (Pb)
- **Sources of outdoor pollutants** : industrial production, forest and brush fire, garbage burning, and emission of transport

Components and sources of air pollutants

- **Indoor pollutants** : Indoor air contains almost all the same pollutants as in the outdoor air, but the concentrations are different, usually lower
- **Sources of indoor pollutants** : Besides the same pollutants in outdoor air, the major sources of indoor pollutants include combustion of solid fuels indoors, tobacco smoking, emissions from construction materials and furnishings, and poor ventilation

Principal outdoor and indoor air pollutants of concern

Asia Pac Allergy 2013;3:145-154

Pollutant		Sources
Outdoor	PM	Fuel combustion (vehicles, power plants)
	O_3	Fuel combustion (cars, power plants, gasoline dispensing facilities)
	NO_2	High temperature combustion
	SO_2	Industrial processes Coal combustion Petroleum combustion
	CO	Vehicular exhaust Incomplete combustion of fuel (natural gas, coal, wood)
Indoor	Second-hand smoke	
	Radon	Rock formations beneath buildings
	CO	Fuel combustion
	CO_2	Human metabolic activity
	VOCs	Gases from certain solids or liquids (paints and lacquers, paint strippers, cleaning supplies, pesticides)

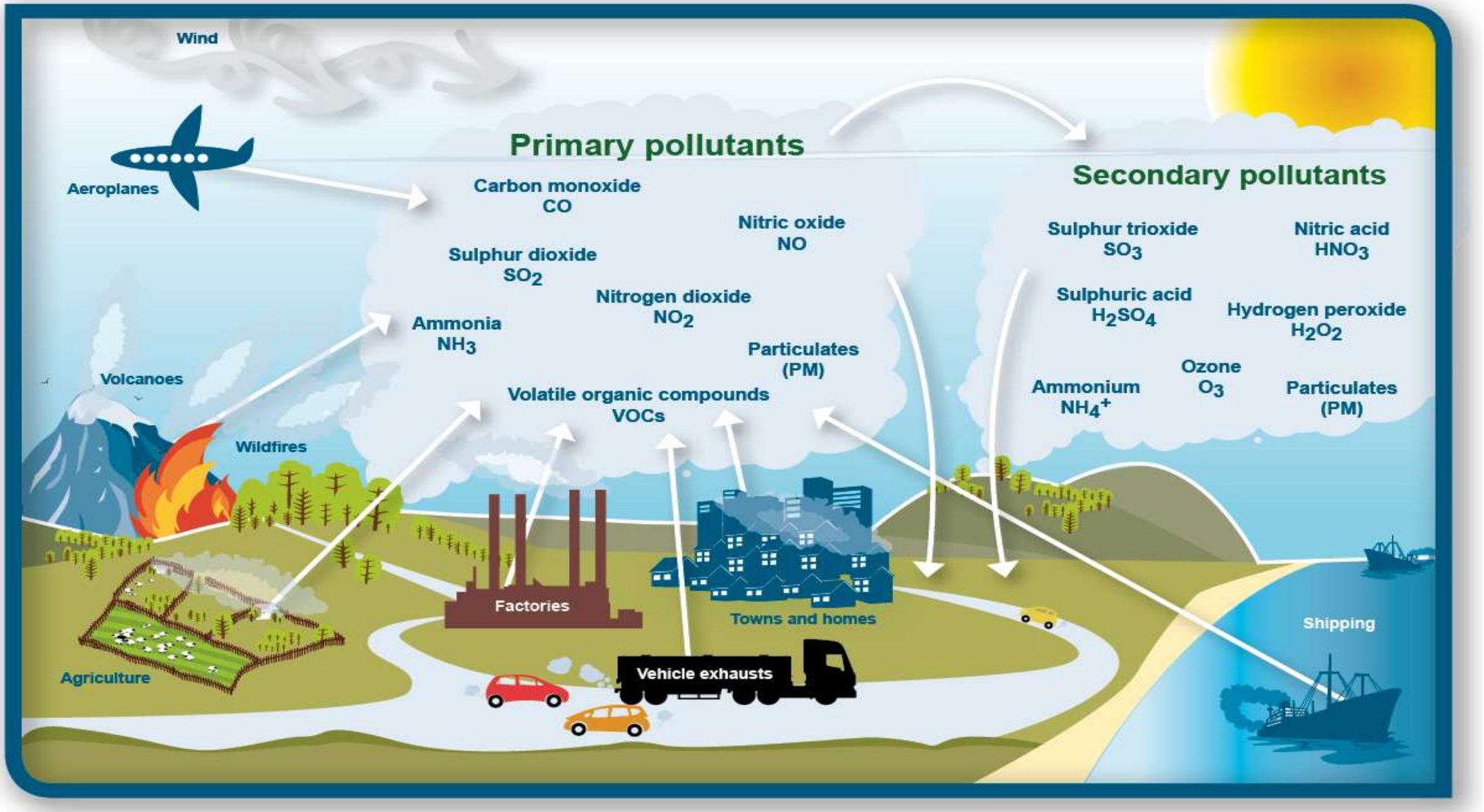
PM, particulate matter; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; VOCs, volatile organic compounds.

Major health-damaging pollutants generated from indoor sources

J Thorac Dis 2016;8(1):E31-E40

Pollutant	Major indoor sources
Fine particle	Fuel/tobacco combustion, cleaning operations, cooking
Carbon monoxide	Fuel/tobacco combustion
Polycyclic aromatic hydrocarbons	Fuel/tobacco combustion, cooking
Nitrogen oxides	Fuel combustion
Sulfur oxides	Coal combustion
Arsenic and fluorine	Coal combustion
Volatile and semi-volatile organic compounds	Fuel/tobacco combustion, consumer products, furnishings, construction materials, cooking
Aldehydes	Furnishings, construction materials, cooking
Pesticides	Consumer products, dust from outside
Asbestos	Remodelling/demolition of construction materials
Lead	Remodelling/demolition of painted surfaces
Biological pollutants	Damp materials/furnishings, components of climate control systems, occupants, outdoor air, pets
Radon	Soil under buildings, construction materials
Free radicals and other short-lived, highly reactive compounds	Indoor chemistry

Primary and secondary air pollutants



Particulate matters (PM)

- PM is a general term that refers to tiny fragments of solid or liquid matter associated with the atmosphere, which vary in number, size, shape, chemical composition, and origin; usually carbon particles with other chemical components, microbes, and heavy metal deposits on their surface
- **Sources of PM** : motor vehicles, power plants, residential wood burning, forest fires, agricultural burning, some industrial processes, other combustion processes
- **Particulate matters (PM) consist of 3 fractions** :

  1). a coarse fraction, $PM_{2.5\text{-}10}$ (2.5-10 µm)

  2). a fine fraction, $PM_{0.1\text{-}2.5}$ (0.1-2.5 µm) and

  3). ultrafine nanosize fraction, $PM_{0.1}$ (≤0.1 µm)

Particulate matters….

- **Coarse fraction** : mostly deposited along the large airway due to gravity and is relatively easy to be cleaned by mucociliary clearance
- **Fine fraction** : more potent; small enough to be aspirated into alveoli, absorbed into lung vascular endothelial cells, and transported into the systemic circulation
- **Nanosize particles** : can penetrate through the air-blood tissue barrier into the capillaries after being deposited on the alveolar wall, and thereby translocate to all other organs

Am J Physiol Lung Cell Mol Physiol 2003;285(3):L671-9

Respir Med 2015;109(9):1089-104

J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2008;26(4):339-62

PM2.5

- Contains a mixture of solid particles and liquid droplets, including black carbon, metals, nitrates, and sulfates
- Black carbon is formed by the incomplete combustion of fuels and biomass
- Common metal content of PM2.5 are iron, nickel, and vanadium
- PM2.5 can also be formed from chemical reactions of gases such as sulfur dioxide (SO_2) and nitrogen oxides (No_x) [nitric oxide (NO) and nitrogen dioxide (NO_2)]
- **Common outdoor sources of PM2.5** : industrial and vehicle emissions
- **Common indoor sources of PM2.5** : cigarette smoke, use of wood or non-smokeless fuels for cooking or heating

PM monitoring

- PM10 and PM2.5 are 2 frequently used indices for PM monitoring
- PM2.5 is now used as a main indicator of risk to health from particulate pollution in the air quality indices (AQIs) in many countries

Eur Respir J 2009;33:1261-7

Air Quality Guidelines (WHO) : Global Update 2005

- The guidelines relate to 4 common air pollutants : particulate matter, ozone, nitrogen dioxide, and sulfur dioxide
- Recommendations for individual pollutant :

Air pollutants	Maximum exposure levels
Particulate matters PM2.5 PM10	 10 µg/m^3 annual mean 25 µg/m^3 24-hour mean 20 µg/m^3 annual mean 50 µg/m^3 24-hour mean
Ozone (O_3)	100 µg/m^3 8-hour mean
Nitrogen dioxide (NO_2)	40 µg/m^3 annual mean 200 µg/m^3 1-hour mean
Sulfur dioxide (SO_2)	20 µg/m^3 24-hour mean 500 µg/m^3 10-minute mean

Ranking of countries and cities in the world by particulate pollution : WHO report 2014

Country PM $_{2.5}$	City PM $_{10}$
Pakistan	Delhi
Qatar	Karachi
Afghanistan	Dakar
Bangladesh	Dhaka
Iran	Abu Dhabi
Egypt	Doha
Mongolia	Ulan Bator
United Arab Emirates	Cairo
India	Amman
Bahrain	Beijing

Indian scenario : history

- Interest in air quality management policies began in India during the 1970s
- Following the 1972 Stockholm Conference on the Human Environment, it became obvious that India was in need of a uniform environmental law
- Hence, the Air (Prevention and Control of Pollution) Act was passed by Parliament in 1981
- With the goal of providing for the prevention, control, and abatement of air pollution, the first ambient air quality standards were adopted in 1982 by the Central Pollution Control Board (CPCB) and revised in 1994 and again in 2009

1972 Stockholm Conference on Human Environment : Local and national governments will bear the greatest burden for large-scale environmental policy and action within their jurisdictions. International cooperation is also needed in order to raise resources to support the developing countries in carrying out their responsibilities in this field.

Indian laws on air pollution

- Agencies responsible for air quality standard creation and monitoring include CPCB and several State Pollution Control Boards (SPCBs)
- All of these entities fall under the control of the Ministry of Environment and Forest (MoEF)
- The CPCB, working in collaboration with the SPCBs, provides technical advice to MoEF in order to fulfill the objectives outlined in the Air Act of 1981

Air Act of 1981

❑ The Air Act mandates the CPCB and SPCBs to :

- Establish national ambient air quality standards for criteria pollutants,
- Assist government in planning future environmental prevention and control strategies,
- Carry out research to better understand environmental issues,
- Undertake nationwide air sampling to ascertain the ambient air quality in India and identification of the problem areas,
- Conduct air quality inspections in areas of concern.

National Ambient Air Quality Monitoring Programme (NAAQM), Bangalore City

- **The Board is monitoring ambient air quality of Bangalore city at 10 locations using manual equipments under National Ambient Air Quality Monitoring Programme (NAMP) covering Industrial Area, Mixed Urban Area and Sensitive Area**
- **The Board has established 2 continuous ambient air quality monitoring stations (CAAQMS) one at City Railway station and other at Regional Office complex at S.G Halli**
- **Monitoring is being carried out on 24 hourly basis for RSPM, SO_2, NO_2 and CO**

Revised National Ambient Air Quality Standards 2009

❑ **Following are the major changes :**

- As against previous 3 areas [(i) Industrial area, (ii) Residential, rural, and other areas, (iii) Sensitive area], the new standards is applicable for only 2 areas, viz. (i) Industrial, residential, rural, and other areas (ii) Ecologically sensitive area (notified by Central Government)
- The new parameters included are PM2.5, ozone, ammonia (NH_3), benzene, benzo(a)pyrene (BaP), arsenic (As), and nickel (Ni)

Maximum exposure limits of individual pollutants (Indian set-up) : based on Revised National Ambient Air Quality Standards 2009

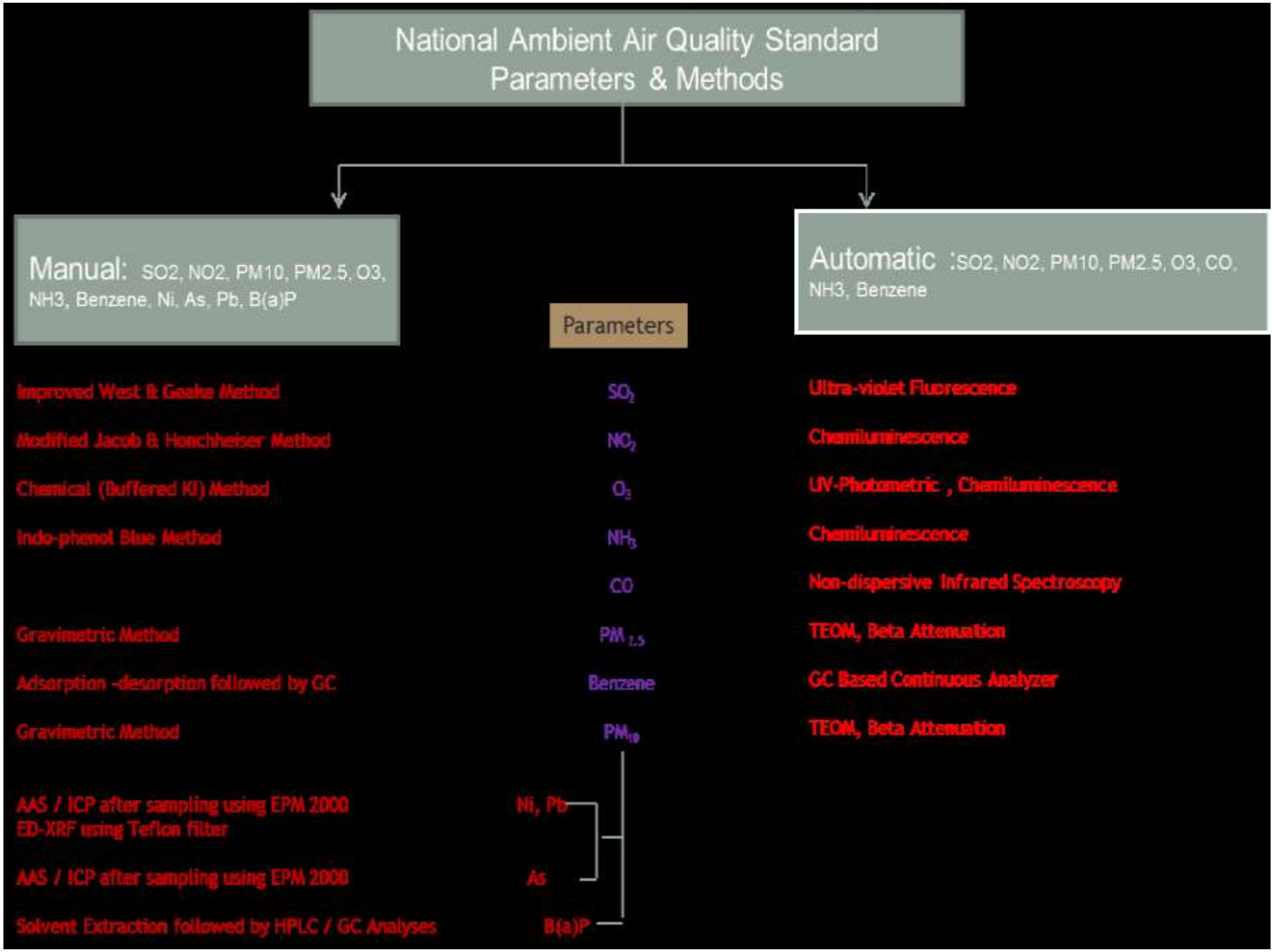
Sl. No	Pollutant	Time Weighted Average	New Standards (Schedule VII, Rule 3 (3B) 16th Nov 2009		Methods of measurement
			Concentration in ambient air		
			Industrial Area Residential, Rural & other Areas	Ecologically sensitive area (Notified by Central Govt)	
1	Sulphur Dioxide(SO2)	Annual Avg*	50.0 µg/m3	20.0 µg/m3	-Improved West and Gaeke method -Ultraviolet fluorescence
		24 hours**	80.0 µg/m3	80.0 µg/m3	
2	Oxides of Nitrogen as NO2	Annual Avg*	40.0 µg/m3	30.0 µg/m3	-Modified Jocob and Hochheise (Sodium Arsenite) -Chemiluminescence
		24 hours**	80.0 µg/m3	80.0 µg/m3	
3	Particulate matter (size less than 10µm)	Annual Avg*	60.0 µg/m3	60.0 µg/m3	-Gravimetric -TOEM -Beta attenuation
		24 hours**	100.0 µg/m3	100.0 µg/m3	
4	Particulate matter (size less than 2.5 µm	Annual Avg*	40.0 µg/m3	40.0 µg/m3	-Gravimetric -TOEM -Beta attenuation
		24 hours**	60.0 µg/m3	60.0 µg/m3	
5	Lead (Pb)	Annual Avg*	0.50 µg/m3	0.50 µg/m3	-AAS/ICP method for sampling on EPM2000 or Equivalent Filter paper -ED-XRF using Teflon filter paper
		24 hours**	1.0 µg/m3	1.0 µg/m3	

Maximum exposure limits of individual pollutants (Indian set-up).....contd

6	Carbon Monoxide (CO)	8 hours** 1 hour	2.0 mg/m3 4.0 mg/m3	2.0 mg/m3 4.0 mg/m3	-Non Dispersive Infra Red (NDIR) spectroscopy
7	Ozone	8 hours**	100.0 µg/m3	100.0 µg/m3	-Photometric -Chemiluminescence -Chemical method
		1 hour	180.0 µg/m3	180.0 µg/m3	
		24 hours**	60.0 µg/m3	60.0 µg/m3	
8	Ammonia (NH3)	Annual Avg*	100.0 µg/m3	100.0 µg/m3	-Chemiluminescence -Indo-Phenol Blue method
		24 hours**	400.0µg/m3	400.0 µg/m3	
9	Benzene	Annual Avg*	5.0 µg/m3	5.0 µg/m3	-GC based continuous analyzer -Adsorption/desorption followed by GC analysis
10	Benzo(a) pyrene	Annual Avg*	1.0 ng/m3	1.0 ng/m3	-Solvent extraction followed by GC/HPLC extraction
11	Arsenic	Annual Avg*	6.0 ng/m3	6.0 ng/m3	AAS/ICP method for sampling on EPM2000 OR Equivalent Filter paper
12	Nickel		20.0 ng/m3	20.0 ng/m3	-AAS/ICP method for sampling on EPM2000 OR Equivalent Filter paper

* Annual arithmetic mean of minimum 104 measurements in a year taken twice a week 24 hourly at uniform interval

** 24-hourly/8-hourly/1-hourly monitored values as applicable shall be complied with 98% of the time in a year; 2% of the time they may exceed the limits but not on 2 consecutive days of monitoring



- **GC : gas chromatography**
- **AAS/ICP : Atomic absorption spectrometry/Inductively coupled plasma**
- **ED-XRF : energy dispersive X-ray fluorescence**
- **HPLC : high performance liquid chromatography**
- **TEOM : tapered element oscillating microbalance**

Deleterious mechanisms of air pollutants on the human lungs

1. Inflammation

- The studies of ozone (O_3), nitrogen dioxide (NO_2), and diesel exhaust particles (DEP) have demonstrated that these pollutants induce permeability of human bronchial epithelial cell cultures while inhibiting ciliary beat frequency
- O_3, NO_2, and DEP can induce the release of inflammatory mediators such as hyaluron, platelet activating factor (PAF), interleukin IL-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, granulocyte macrophage-colony stimulating factor (GM-CSF), leukotriene (LT) C_4, regulated on activation normal T-cell expressed and secreted (RANTES), and soluble intercellular adhesion molecule (sICAM)-1 from human bronchial epithelial cells (HBEC)

Arsalane K et al. Am J Respir Cell Mol Biol. 1995;13:60-8

Rusznak C et al. Eur Respir J. 1996;9:2296-305

Devalia JL et al. Allergy. 1997; 52 suppl 38:45-51

Inflammation……

- Studies of human B cells demonstrated that diesel exhaust particles (DEP) and polyaromatic hydrocarbons (PAH) derived from DEP can induce the synthesis of IgE in the presence of IL-4 and CD40 monoclonal antibodies

Diaz-Sanchez D et al. Allergy. 1997;52 suppl 38:52-6

Bayram H et al. Am J Respir Cell Mol Biol. 1998;18:441-8

Inflammation……

- Studies of asthmatic patients have suggested that their airway epithelial cells are more susceptible to deleterious effects of air pollutants
- Under standard culture conditions, asthmatic bronchial epithelial cells produced greater amounts of IL-8, GM-CSF, sICAM-1, and RANTES as compared to non-asthmatic cells
- When these cultures were exposed to O_3, NO_2, and DEP, the release by asthmatic cells was higher than cells of non-asthmatic subjects

Bayram H et al. J Allergy Clin Immunol. 1998;102:771-82

Bayram H et al. J Allergy Clin Immunol. 2001;107:287-94

Bayram H et al. Clin Exp Allergy. 2002;32:1285-92

2. Oxidative stress

- Reports indicate that the oxidative stress is increased and the oxidant-antioxidant balance is tilted toward a pro-inflammatory state in chronic airway diseases such as asthma and COPD
- Air pollutants lead to oxidative and nitrosative stress in cell systems that activate stress activating signaling pathways in epithelial cells and resident alveolar inflammatory cells
- This mechanism involves activation of the transcription factor nuclear factor (NF)-κβ and its translocation to nucleus where it binds to DNA consensus sequences in the promoters of pro-inflammatory genes that code for inflammatory cytokines and chemokines, which attract neutrophils and adhesion molecules

Ercan H et al. J Allergy Clin Immunol. 2006;118:1097-104

Manzo ND et al. Part Fibre Toxicol. 2012;15:9-43

3. Cell cycle and death

- Studies have suggested that air pollutants cause cell toxicity and modify the cell death and cell cycle of lung cells

Mayer D et al. J Toxicol Environ Health. 1992;35:235-46

Bayram H et al. Toxicol Lett. 2013;218:215-23

To summarize……

❑ Air pollutants exert their detrimental effects on airways and lungs by :

- Attenuating ciliary activity of airway epithelial cells
- Increasing permeability of airway epithelium that leads to
- Inflammatory changes in cells of airways and lung parenchyma
- Triggering oxidative pathway
- Modulating cell cycle and cell death of respiratory system

Adverse respiratory health effects of air pollution

J Thorac Dis 2016;8(1):E31-E40

Increased mortality
Increased incidence of cancer
Increased frequency of symptomatic asthmatic attacks
Increased incidence of lower respiratory tract infections
Increased exacerbations of chronic cardiopulmonary or other disease
Reduction in FEV_1 or FVC associated with clinical symptoms
Increased prevalence of wheezing
Increased prevalence or incidence of chest tightness
Increased prevalence or incidence of cough/phlegm production requiring medical attention
Increased incidence of acute upper respiratory infections that interfere with normal activity
Acute upper respiratory tract infections that do not interfere with normal activity
Eye, nose, and throat irritation that may interfere with normal activity
Odors

Diesel exhaust particles (DEPs)

- These account for most airborne PM (90%) in the world's largest cities because of the increasing number of new cars with diesel engines in industrialized countries
- Diesel fuel combustion results in up to 100 times more particles than gasoline : significant contributor to increases in the prevalence of allergic diseases

Environ Sci Technol 2004;38:2544-50

J Allergy Clin Immunol 2005;115:221-8

- Human data show that DEP exposure increases interleukin (IL)-4, IL-5, IL-6, and IL-10 mRNA levels and reduces interferon (IFN)-γ levels

J Allergy Clin Immunol 1996;98:114-23

Int Arch Allergy Immunol 2009;148:239-50

The role of diesel exhaust particles and their associated polyaromatic hydrocarbons in the induction of allergic airway disease

Diaz-Sanchez D et al. Allergy 1997; 52 (Suppl 38): 52-56

- **In vitro studies demonstrated that PAH-DEP enhanced IgE production by tonsillar B-cells in the presence of IL-4 and CD40 monoclonal antibody, and altered the nature of the IgE produced**
- **In vivo nasal provocation studies using 0.30 mg DEP in saline also showed enhanced IgE production in the human upper respiratory mucosa, accompanied by a reduced CH4'-CHe5 mRNA splice variant (feature characteristic of IgE-producing B-cells that have undergone differentiation)**
- **Nasal challenge with DEP also influenced cytokine production**

1. In *vitro* studies : enhanced IgE production by PAH-DEP

Takenaka H et al. J Allergy Clin Immunol 1995;95:103-15

- Tested the ability of extracts of PAH from DEP to enhance human IgE production from either purified blood or tonsillar B-cells
- In the absence of co-stimulants, PAH-DEP could not induce *de novo* production of IgE from B-cells
- Addition of PAH-DEP to purified B-cell cultures simultaneously stimulated with interleukin-4 (IL-4) and CD40 monoclonal antibody, resulted in enhanced IgE production (20-360%)
- PAH-DEP could not increase production of either IgG or IgM

In *vitro* studies : enhanced IgE production by PAH-DEP

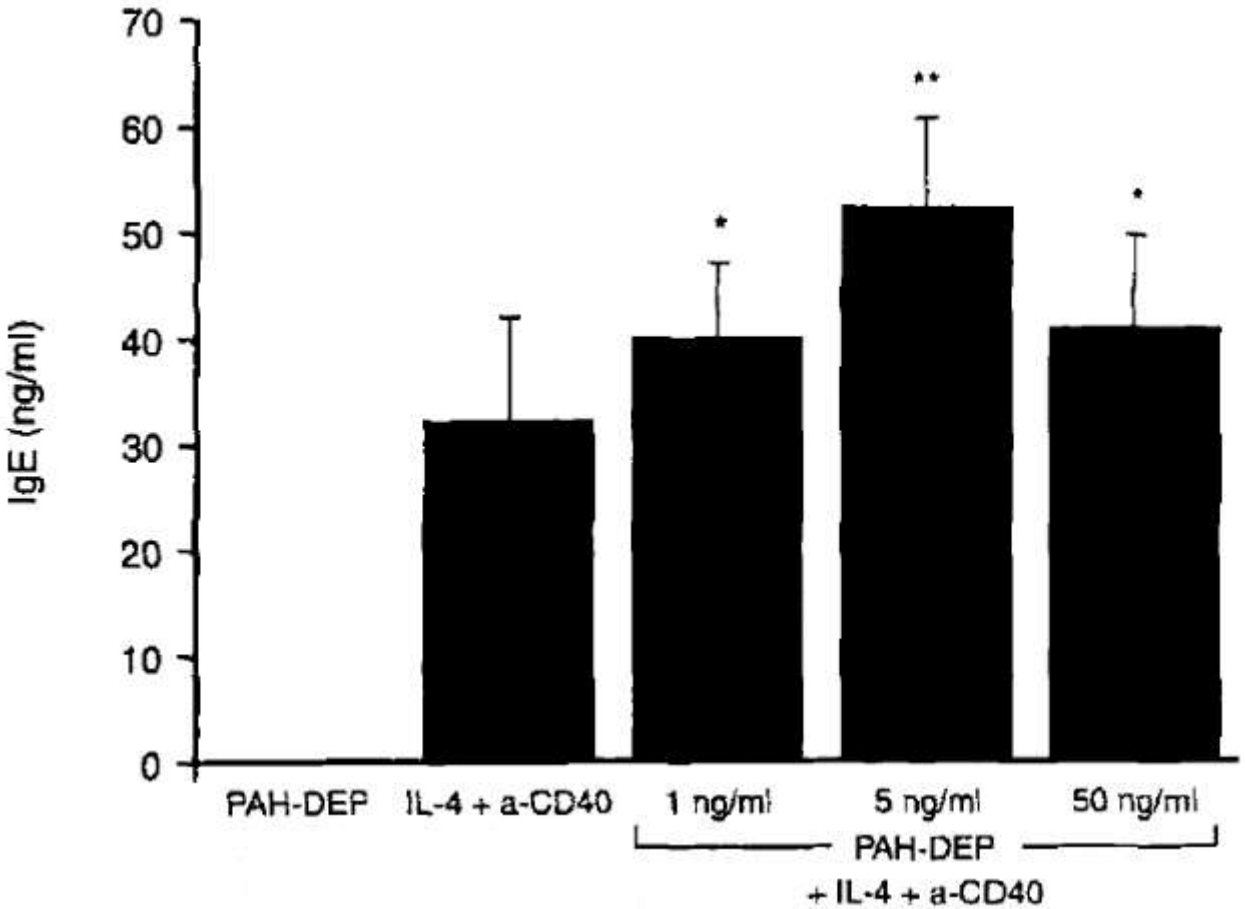


Fig. 1. Enhancing effect of PAH-DEP on IL-4 plus CD40 monoclonal antibody-driven IgE production. PBL (2×10^5 cells/well) were cultured for 14 days in the presence of IL-4 (200 U/ml) plus CD40 monoclonal antibody (0.1 μg/ml) plus different combinations of PAH-DEP. The mean of five experiments is shown. $^*P<0.05$ and $^{**}P<0.01$ compared with IL-4 plus a-CD40 only (Mann-Whitney).

In *vitro* studies : enhanced IgE production by PAH-DEP

- PAH-DEP also qualitatively altered the nature of the IgE produced
- Alternative 3’ splicing of the epsilon heavy-chain gene results in different splice variants for epsilon mRNA, and these variants code for IgE proteins of different lengths
- Addition of PAH-DEP to IL-4 plus CD40-stimulated B-cells induced a selective 200-fold increase in the production of one particular variant (M2’) and a marked selection against another variant (CH4’-CHe5)
- The relative decrease in the CH4’-CHe5 mRNA splice variant seems to be a marker for differentiation of IgE-producing B-cells

Diaz-Sanchez D et al. J Immunol 1995;155:1930-41

2. In *vivo* studies : DEP induces local IgE production

Diaz-Sanchez D et al. J Clin Invest 1994;94:1417-25

- Nasal challenge was performed by spraying either saline or 0.30 mg of DEP in saline into the nostrils of subjects
- Immunoglobulin levels were measured in the supernatants of nasal lavages performed prior to and at several timepoints after nasal challenge
- Albumin levels in the lavage fluids were also determined, which served as a control for protein derived from vascular leakage
- **Results** : no change in IgE was seen after saline challenge but DEP induced a significant increase in IgE production; enhanced nasal IgE levels could be observed after as little as 24 hours in some individuals, though generally, peak production was observed 4 days after DEP challenge

In *vivo* studies : DEP induces local IgE production

- By day 7, IgE levels had returned to baseline values
- The increase in protein levels after DEP challenge was reflected by a 25-fold increase in the levels of epsilon mRNA from cells recovered in the nasal lavage fluid at day 4; this was accompanied by a qualitative change in the nature of the IgE produced
- By day 4, there was a marked relative decrease in the CH4'-CHe5 mRNA splice variant (feature characteristic of IgE-producing B-cells that have undergone differentiation)

In *vivo* studies : DEP induces local IgE production

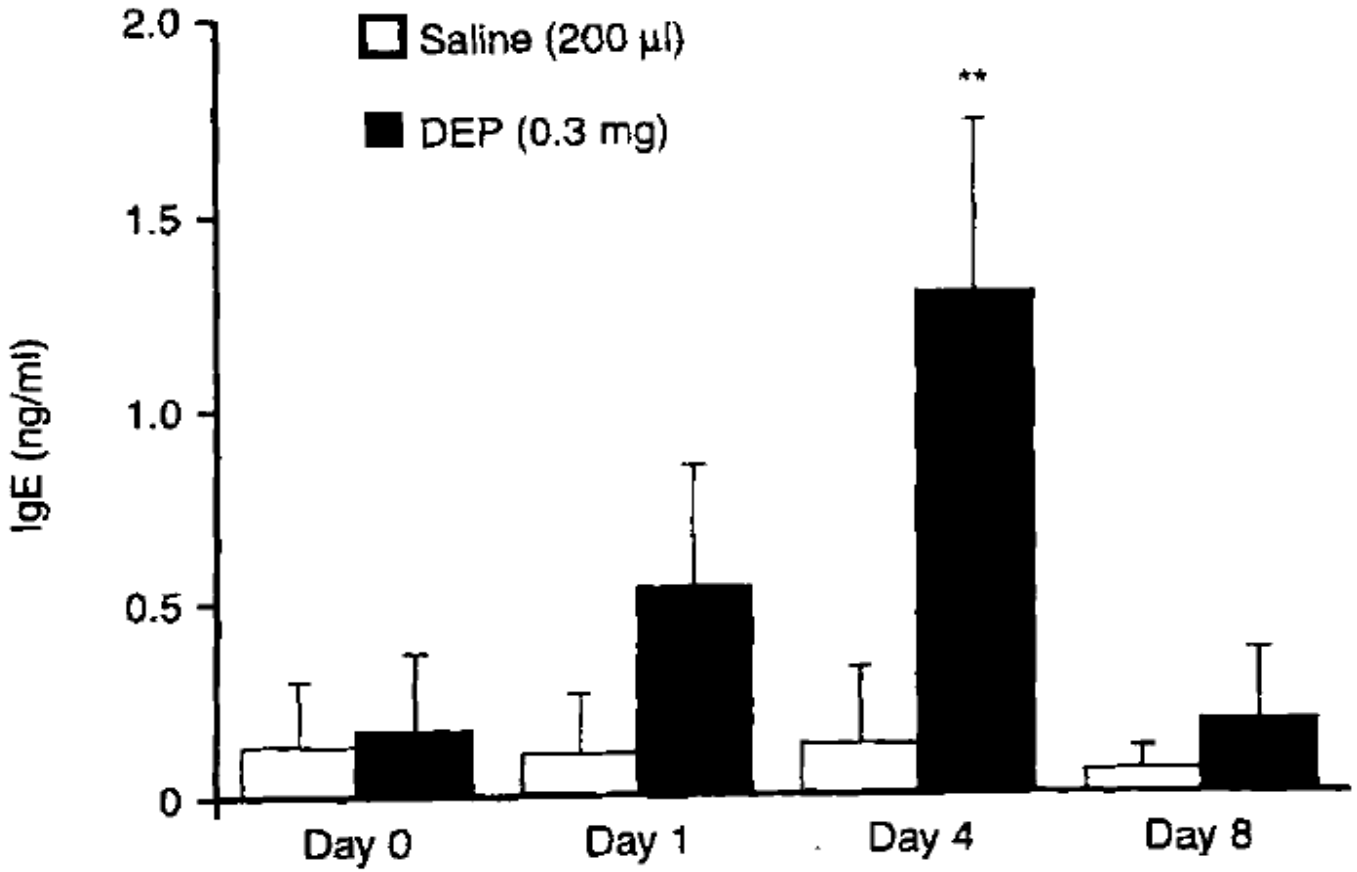


Fig. 2. DEP enhances *in vivo* nasal IgE responses. Mean levels of IgE in 12 subjects in nasal washes performed immediately before or 1, 4 or 8 days following nasal challenge with 0.3 mg DEP or 200 µl saline. $^{**}P<0.01$ compared with saline challenge (paired *t*-test).

3. DEP influences the cytokine environment

Diaz-Sanchez D et al. J Allergy Clin Immunol 1996;98:114-23

- Examined whether DEP could alter the production of cytokines by cells residing in the nasal mucosa
- Cytokine mRNA was measured by a reverse transcriptase PCR technique from cells obtained both before and 18 hours after intranasal challenge of ragweed-allergic subjects with either saline, DEP, ragweed antigen, or a combination of ragweed and DEP
- Prior to challenge, mRNA was readily detectable in most subjects for interferon-γ (IFN-γ), IL-2 and IL-13; mRNA for IL-4, IL-5, IL-6, IL-10, and lymphotoxin could not be detected in the majority of subjects

DEP influences the cytokine environment

- Following challenge with ragweed, no consistent pattern of cytokine alteration was observed between subjects and no significant elevation of any cytokine mRNA
- After DEP challenge there was a significant increase in both the number of subjects from whom various cytokine mRNAs could be detected and in the levels of mRNAs for all of the cytokines studied; this enhancement was far greater than that observed following challenge with ragweed alone in allergic subjects
- Increased IL-4 protein was detectable in the post-DEP challenge lavage fluid
- Peripheral blood mononuclear cells from the same subjects, cultured alone or in the presence of the organic extract of DEP showed no significant increase in the production of mRNA for any of the cytokines measured, which implies that the enhanced cytokine production by nasal mucosal cells following DEP challenge was due to interaction with cells in the mucosal tissue

DEP influences the cytokine environment

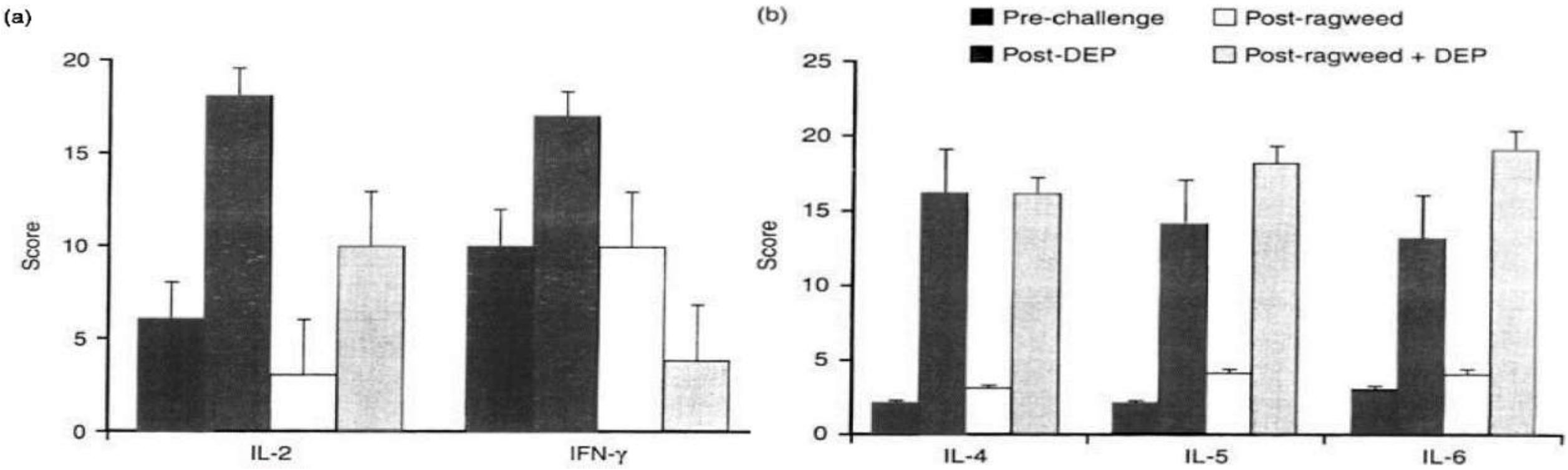


Fig. 4. DEP enhances cytokine mRNA levels. The levels of cytokine mRNA were measured by reverse transcriptase PCR from mRNA recovered from nasal washes performed either on day 0 (pre-challenge), or 18 h after challenge with either 0.3 mg DEP, up to 1,000 U/ml ragweed, or both ragweed and DEP. The levels were scored according to the number of subjects from whom message could be detected and the levels of mRNA detected. The mean scores are shown for six subjects for IL-1 and IFN-γ (a) and for IL-4, IL-5, and IL-6 (b).

DEP influences the cytokine environment

- Nasal provocation challenge with combined allergen plus DEP resulted in a strong increase in specific cytokines
- In almost all subjects, expression of mRNA for TH_1 and TH_2-type cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13) was significantly enhanced
- Ragweed challenge alone did not cause any change in IFN-γ gene expression but challenge with ragweed plus DEP had a pronounced inhibitory effect; IFN-γ expression could be detected in 85% of subjects after allergen challenge, but this fell to 38% if DEP was also present
- Similar results were seen with lymphotoxin mRNA expression and to a lesser extent IL-2
- DEP alone induces a non-TH_1, non-TH_2 specific pattern of cytokine production but DEP plus ragweed selects against TH_1-type cytokines

Conclusion

- Diesel exhaust particles are a major source of air-borne pollution
- They have the ability to induce IgE responses by acting directly on B-cells and indirectly by enhancing cytokine production
- In conjunction with allergen, they can generate a TH_2-type cytokine environment and favour the generation of allergen-specific IgE
- DEP can enhance B-cell differentiation, and by initiating and enhancing IgE production, may play an important role in the increased incidence of allergic airway disease

Traffic-related exposure studies on the respiratory diseases

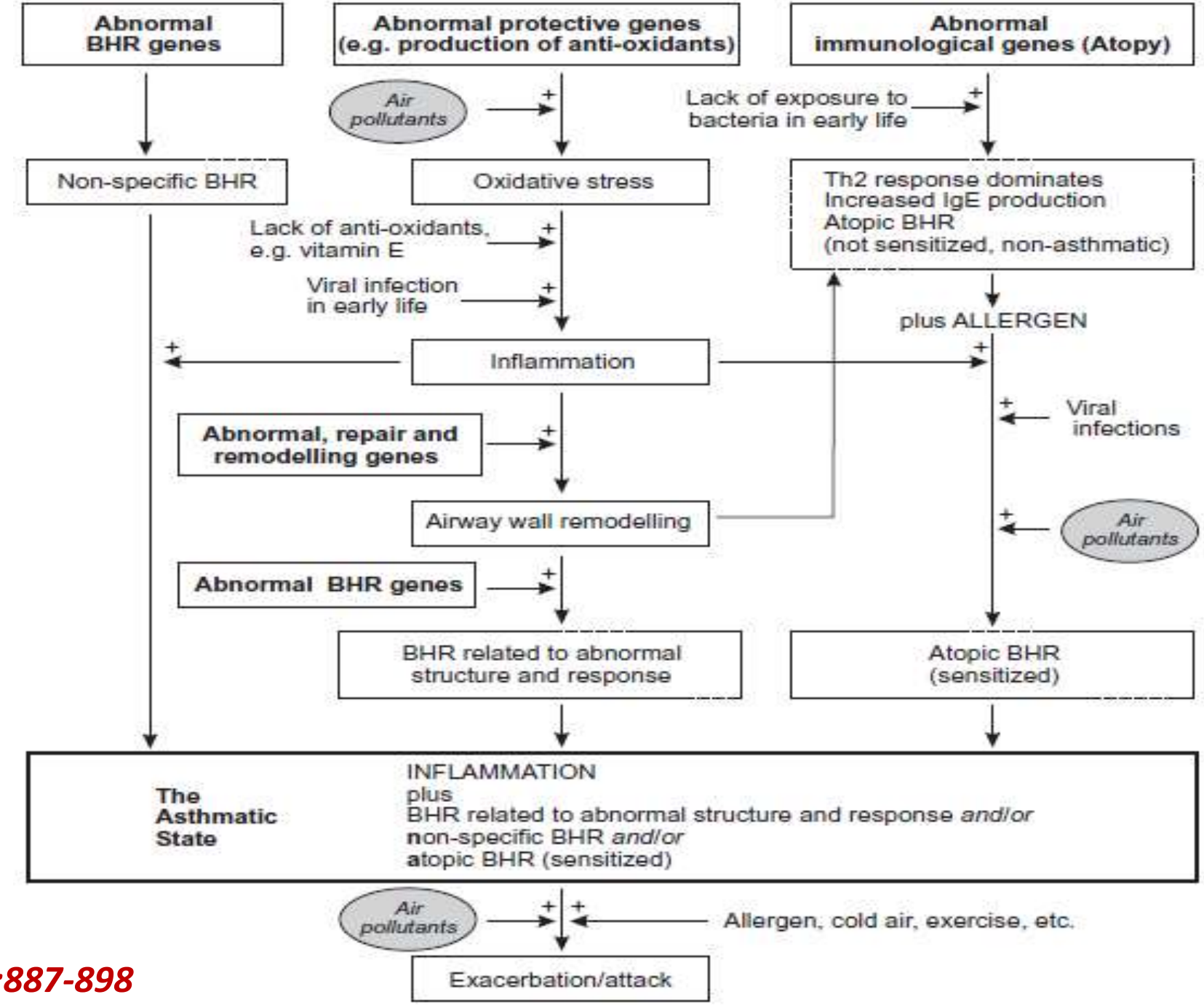
Association with asthma and other allergic airway diseases

- Exposure to ambient air pollution can cause short-term exacerbations in those who already have respiratory allergies (i.e. asthma and rhinitis)
- Asthma exacerbations (measured as visits to emergency departments) have been frequently reported on days with higher levels of O_3 and other pollutants

Weisel C et al. Environ Health Perspect. 1995;103(suppl 2):97-102

- Whether air pollutants play a role in the initiation of new cases of asthma in those previously free from the condition is less clear

Hypothetical network of causation of asthma in relation to air pollution exposure



Gowers A et al. Respirology. 2012;17:887-898

Marino E et al. Ther Adv Chronic Dis. 2015;6(5):286-298

Study	Date	Location	Pollutants	Subject/location	Results
Gehring *et al.* [2010], McConnell *et al.* [2010]	1996–1997	Netherlands	PM2.5	3863 yearly from birth until age 8 years	significant increase in incidence and prevalence of asthma
Penard-Morand *et al.* [2010]	1998–2000	6 French cities	benzene, SO_2, PM10, NOx, and CO	6683 children (9–11 years)	increased risk of asthma and allergic rhinitis
Yamazaki *et al.* [2014]		Japan	elemental carbon	10,069 school children 6–9-year old	increased risk of asthma incidence
Kunzli *et al.* [2009]	1991–2002	Switzerland	PM10	adult aged 18–60 years	increased risk of asthma incidence
Young *et al.* [2014]		U.S.	PM2.5	50,884 women	increased risk of asthma incidence

Association with COPD

- It is important to distinguish 2 features of COPD in the assessment of evidence related to air pollution : the long-term development of chronic obstructive pathology and the superimposed acute exacerbations
- In air pollution research, most studies have focused on the role of air pollution in triggering symptoms and exacerbations, i.e. the short-term (acute or subacute) effects of air pollution
- Like in asthma, the role of air pollution in the long-term development of the pathophysiological changes that characterize COPD are far less clear

Reviews from ATS and HEI

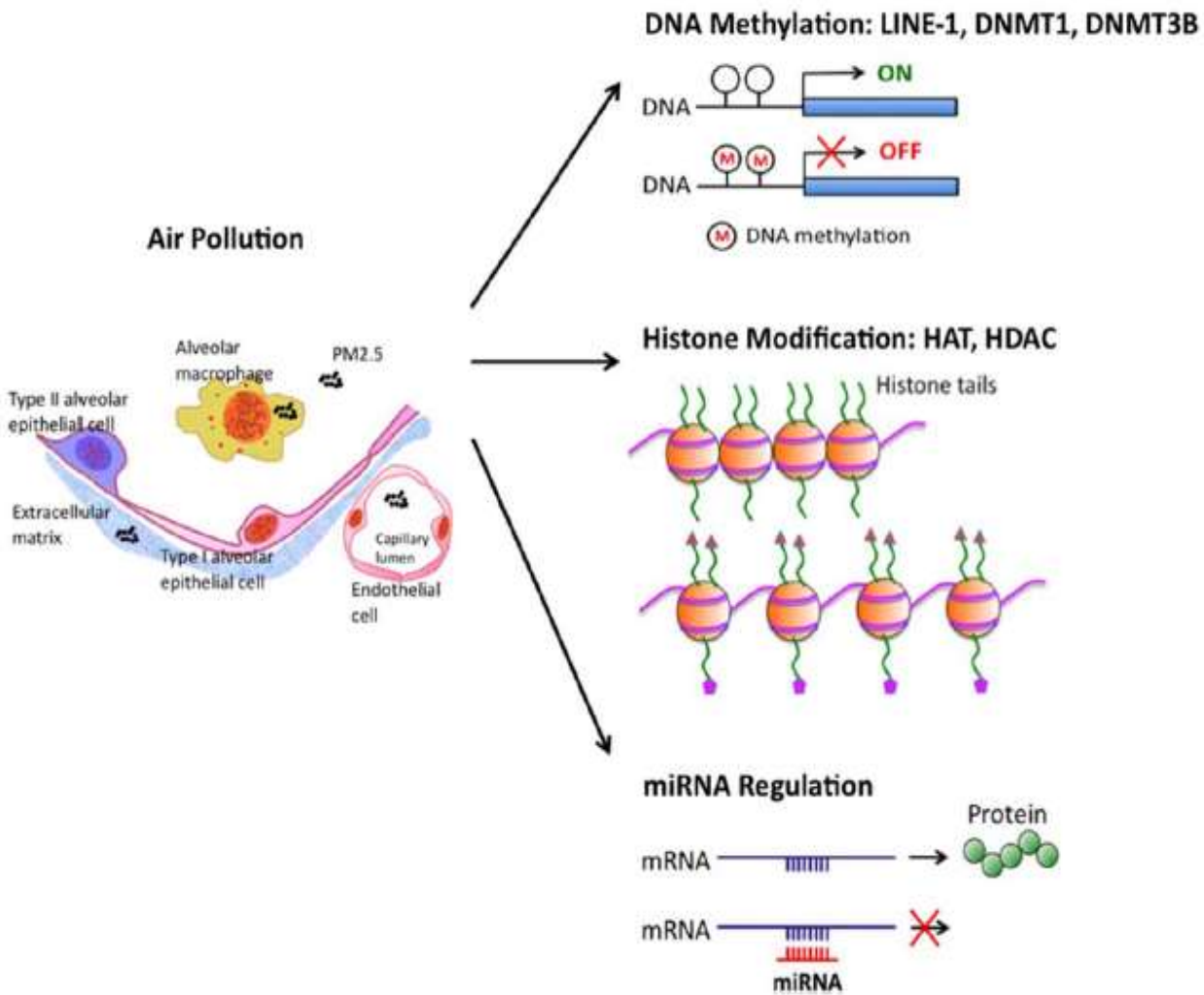
- **American Thoracic Society (ATS) review upto May 2008, Health Effects Institute (HEI) review upto October 2008** : both addressed the role of ambient air pollution in the development of COPD (long-term effects)
- In the ATS review, which focused on the causes of COPD other than active smoking, the conclusion was that there is limited/suggestive evidence for a role of ambient air pollution
- The HEI report focused exclusively on traffic-related near-road exposures; it concluded that there are inconsistencies in the existing data and that there is insufficient evidence of an association between local traffic-related pollution and COPD

Marino E et al. Ther Adv Chronic Dis. 2015;6(5):286-298

Study	Date	Location	Pollutants	Subject/location	Results
Schikowski *et al.* [2005], Schikowski *et al.* [2010]	1985–1994	Rhine-Ruhr Basin (Germany)	PM10	4757 women living less than 100 m from a busy road	4.5% prevalence of COPD
Pujades-Rodriguez *et al.* [2009]	1991–2000	Nottingham (UK)	NO_2	2644 adults aged 18–70 living in close proximity to traffic	spirometry confirmed COPD
Andersen *et al.* [2011]	1993–2006	Denmark	NO_2/NOx	57,000 adults	incident COPD
Zanobetti *et al.* [2000]	1986–1994	10 US cities	PM10	adults aged >65 years living in a metropolitan county	2.5% increase in hospital admissions for AECOPD
Dominici *et al.* [2006]	1999–2002	204 US urban counties	PM2.5	11.5 million adults aged >65 years	risk of about 0.9% for COPD hospitalization
Medina-Ramon *et al.* [2006]	1986–1999	36 US cities	PM10	warm season	1.47% increase in hospital admissions for AECOPD
Fusco *et al.* [2001]	1995–1997	Rome (Italy)	NO_2 and O_3	residents of all ages and among children (0–14 years)	4.3% increase in hospital admissions for AECOPD
Tao *et al.* [2014]	2001–2005	Lanzhou, China	PM10, SO_2, NO_2	females and aged ⩾65 years	increases in hospital admissions for AECOPD

Association with lung cancer

- In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollutants and related PM (especially DEPs of size 0.1-0.25µm) as a class I human carcinogen



Jinghong Li et al. Clin Res J. 2015

LINE : long interspersed nucleotide element
DNMT : DNA methyltransferase
HAT : histone acetyltransferase
HDAC : histone deacetylase

Figure 1. Epigenetic changes associated with PM exposure. PM2.5 is small enough to be aspirated into alveoli, to be absorbed either by alveolar macrophage or direct translocation into extracellular matrix and vascular endothelial cells, and to be transported into the systemic circulation. The circulating PM2.5 may induce epigenetic changes and systemic inflammation. PM2.5 exposure decreases DNA methylation of LINE-1, decreases DNMT1 and increased DNMT3B expression. PM10 exposure increases HAT activity and cigarette smoke decreases HDAC2 activity. PM2.5 exposure is associated with miRNA changes related to multiple inflammatory pathways.

Marino E et al. Ther Adv Chronic Dis. 2015;6(5):286-298

Study	Date	Location	Pollutants	Subject/location	Results
Vineis *et al.* [2006]	1993–1998	10 European countries	NO_2	adults aged 35–74 residing near heavy traffic roads	46% increase in lung cancer
Chiu *et al.* [2006]	1994–2003	Taiwan	PM10, SO_2, NO_2	females	28% increased risk of lung cancer
Edwards *et al.* [2006]	2000–2004	Teesside, northeast England	PM10, SO_2, NO_2	women aged <80 years living for >25 years close to highly industrialized area	83% increased risk of lung cancer
Loomis *et al.* [2014]	2003–2012	31 provincial capital cities in China	PM2.5	71,000 adults	increased risk of lung cancer
Raaschou-Nielsen *et al.* [2013]	2008–2011	17 separate European cohorts	PM10	312,944 adults	increased risk of lung cancer

Association with Idiopathic pulmonary fibrosis (IPF)

Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure

Kerri A. Johannson[1,2,3], Eric Vittinghoff[4], Kiyoung Lee[5], John R. Balmes[1,2], Wonjun Ji[6], Gilaad G. Kaplan[3], Dong Soon Kim[6] and Harold R. Collard[1]

Eur Respir J. 2014;43:1124-1131

The Study investigates the relationship between ambient air pollution exposure (O_3, NO_2, PM10, SO_2, and CO) and acute exacerbations of IPF in a large, well-characterized cohort with contemporaneous clinical and ambient air pollution data

Materials and methodology

- **Case definition** : Acute exacerbations of IPF were defined by convention as a worsening of dyspnea within 30 days of presentation, the presence of new pulmonary opacities on high-resolution computed tomography of the lung, and the exclusion of known causes for respiratory worsening such as infection, pulmonary embolism, or congestive heart failure
- The diagnosis of all enrolled patients was reconfirmed as IPF according to American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association consensus criteria
- Patients with IPF were identified from an ongoing institutional review board-approved longitudinal cohort developed at Asan Medical Center in Seoul, South Korea

Materials and methodology

- Patients experiencing acute exacerbation during the follow-up period from January 1, 2001 to December 31, 2010 were considered cases
- Due to potential effect modification between past and future exacerbations, patients experiencing more than one exacerbation only had their first event included as a case in the primary analysis (**inclusion criterion**)
- For each case, a pooled control population was constructed using all remaining patients in the cohort at the date of the case event, provided they had not yet experienced an acute exacerbation and did not develop one within 6 weeks following the date of the case event
- **Exclusion criterion** : patients were excluded if the baseline forced vital capacity (FVC), smoking status, residential address or corresponding air pollution exposure data were unavailable

- Mean and maximum exposures were defined as the average or highest of all 1-hour (NO_2 and SO_2), 8-hour (O_3), or 24-hour (PM10 and CO) levels over the 42-day (6 week) period prior to acute exacerbation date (exposure period), respectively
- Follow-up for each patient began at the date of IPF diagnosis, and ended at lung transplantation, death or on December 31, 2010, whichever came first
- The average distance from the patient's residence to the geo-code-assigned TMS was 7.2 km

Patient population

- 505 patients with IPF were identified from the longitudinal cohort
- 69 were excluded for missing baseline data (n=22) or lack of air pollution exposure data (n=47)
- 436 patients were included in the final analysis, of which 75 experienced at least 1 acute exacerbation

Baseline patient characteristics

Characteristic	Acute exacerbation	No acute exacerbation	p-value[#]
Subjects n	75	361	
Age years	63.7±8.4	62.8±7.9	0.29
Females	17 (23)	74 (20)	0.67
Smoking status			
Never	26 (35)	89 (25)	
Former	32 (43)	177 (49)	0.20
Current	17 (22)	95 (26)	
FVC % predicted	69.3±17.7	78.1±17.6	<0.001
***D*LCO % predicted**	62.5±19.3[¶]	67.1±19.2[+]	0.11
Prednisone	56 (74.7)	202 (56.0)	0.003
GORD treatment[§]	57 (76.0)[f]	192 (53.2)	<0.001

Data are presented as mean±SD or n (%), unless otherwise stated. FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; GORD: gastro-oesophageal reflux disease. [#]: overall tests of heterogeneity; [¶]: n=58; [+]: n=338; [§]: proton pump inhibitor or histamine 2 receptor (H_2)-antagonist; [f]: 11 out of 57 on proton pump inhibitor, 46 out of 57 on H_2-antagonist.

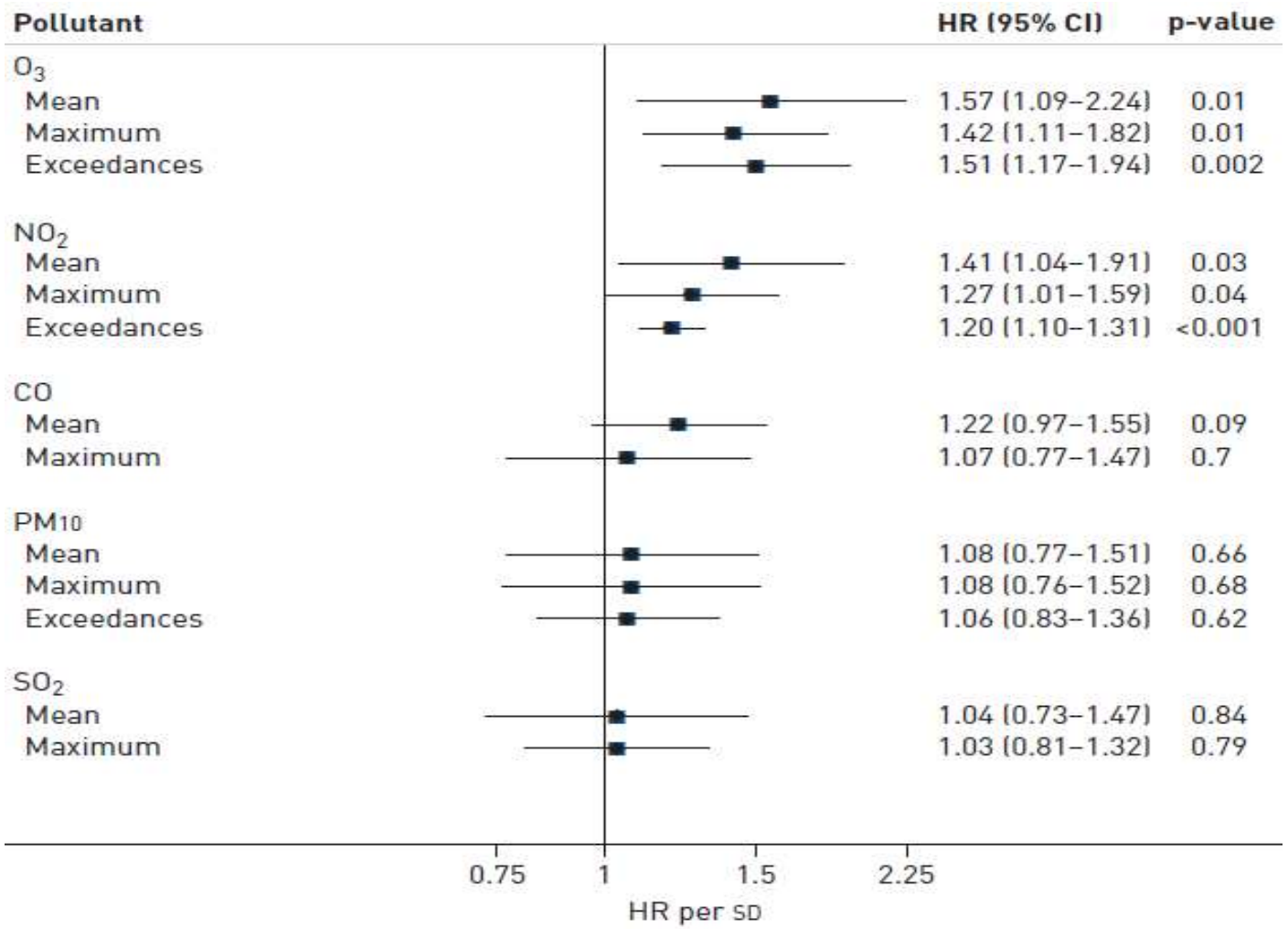
Results

❑ Acute exacerbation incidence and outcomes

- 89 acute exacerbation events occurring over 1699 patient-years, for an incidence rate of 5.2 exacerbations per 100 patient-years
- Acute exacerbation events were characterized by fever (53%) and cough (37%), with an average duration of symptoms prior to diagnosis of 10.7 days
- 49% of patients were admitted to the ICU, 8% required NIPPV support, and 45% required IMV
- Acute exacerbation was associated with high risk of subsequent acute exacerbation (hazard ratio [HR] 4.32, 95% CI 2.33-7.98) and substantially decreased survival time (HR 6.14, 95% CI 4.03-9.34)
- Short-term mortality was 37% at 1 month and 67% at 6 months

Results

❑ Association of air pollution exposure with acute exacerbation risk



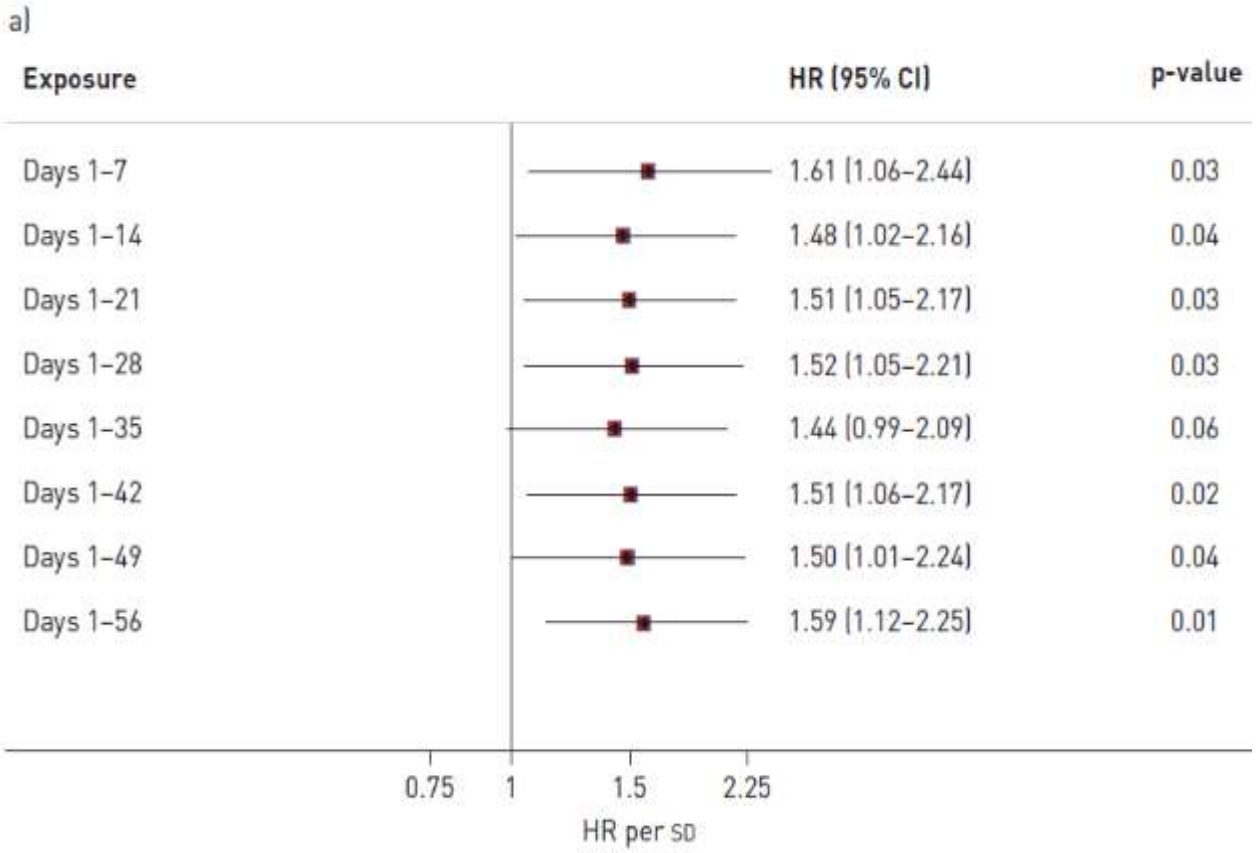
- **Acute exacerbation of IPF was significantly associated with increased mean levels, maximum levels, and number of exceedances of O_3 and NO_2 during the exposure period**
- **No consistent relationships between PM10, SO_2 or CO and acute exacerbation of IPF**

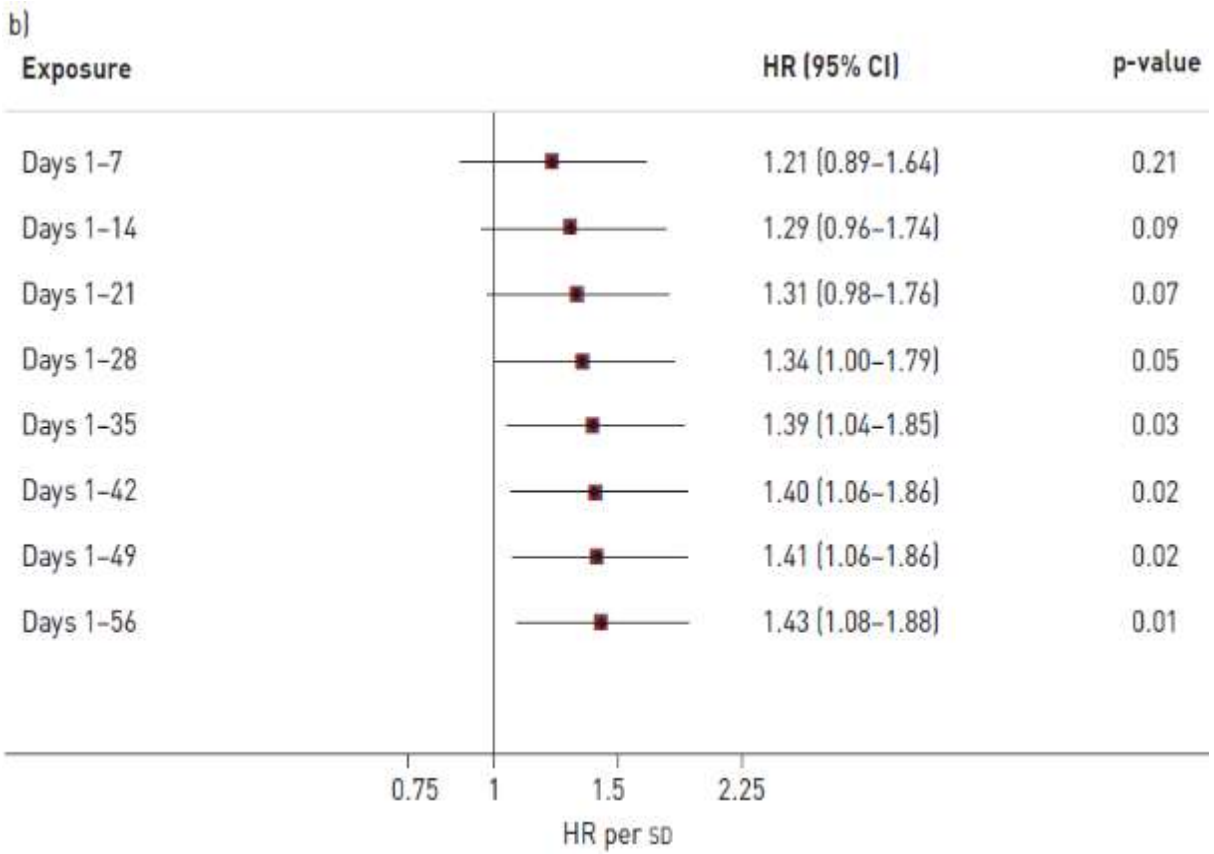
Results

❑ Association of cumulative air pollution exposure and mortality

- No statistically significant relationships between air pollution exposure and mortality
- Hazard ratios for mean O_3 and NO_2 exposure were 1.03 (95% CI 0.90-1.17) and 0.97 (95% CI 0.86-1.10), respectively, while those for maximum O_3 and NO_2 exposures were 1.02 (95% CI 0.90-1.16) and 1.06 (95% CI 0.93-1.20), respectively

Results





- **Secondary sensitivity analyses for a) O_3 and b) NO_2 exposures and risk of acute exacerbation**
- **Both cases show a consistent relationship with acute exacerbation across multiple cumulative exposure periods**

Association with lung function

- Over the past 2 decades, more than 50 publications have investigated long-term effects of ambient air pollution on lung function with most finding adverse effects
- In long-term studies, lung function is of interest as an objective measure of respiratory health and an early predictor of cardiorespiratory morbidity and mortality
- Lung function steadily increases from birth until early adulthood, culminates in a so-called plateau phase in the mid-twenties, and thereafter decreases with age
- Flow measures are markers of small-airway function, which is particularly sensitive to ozone exposure and early exposures to tobacco smoke

Long-Term Effects of Ambient Air Pollution on Lung Function

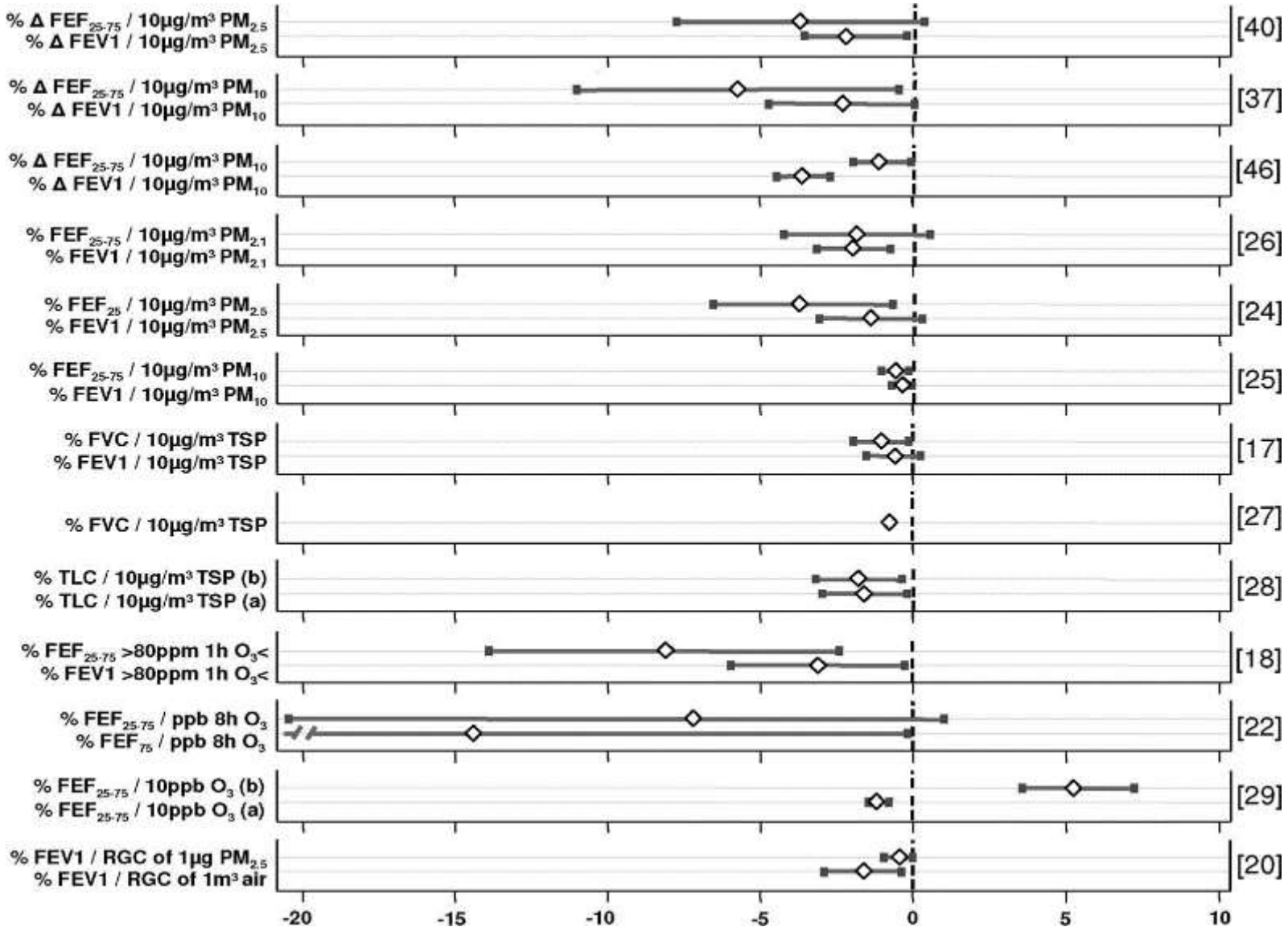
A Review

Thomas Götschi,[a] *Joachim Heinrich,*[b] *Jordi Sunyer,*[c,d] *and Nino Künzli*[a,c,e]

Epidemiology 2008;19:690-701

- **Reviewed 58 publications; 41 were cross-sectional studies and 17 were longitudinal studies**
- **37 studies investigated children**
- **Air pollution measurements were predominantly made at the community level, using centrally located monitors that sampled several pollutants**

Results : effect estimates from studies of long-term effects of air pollution on lung function in children



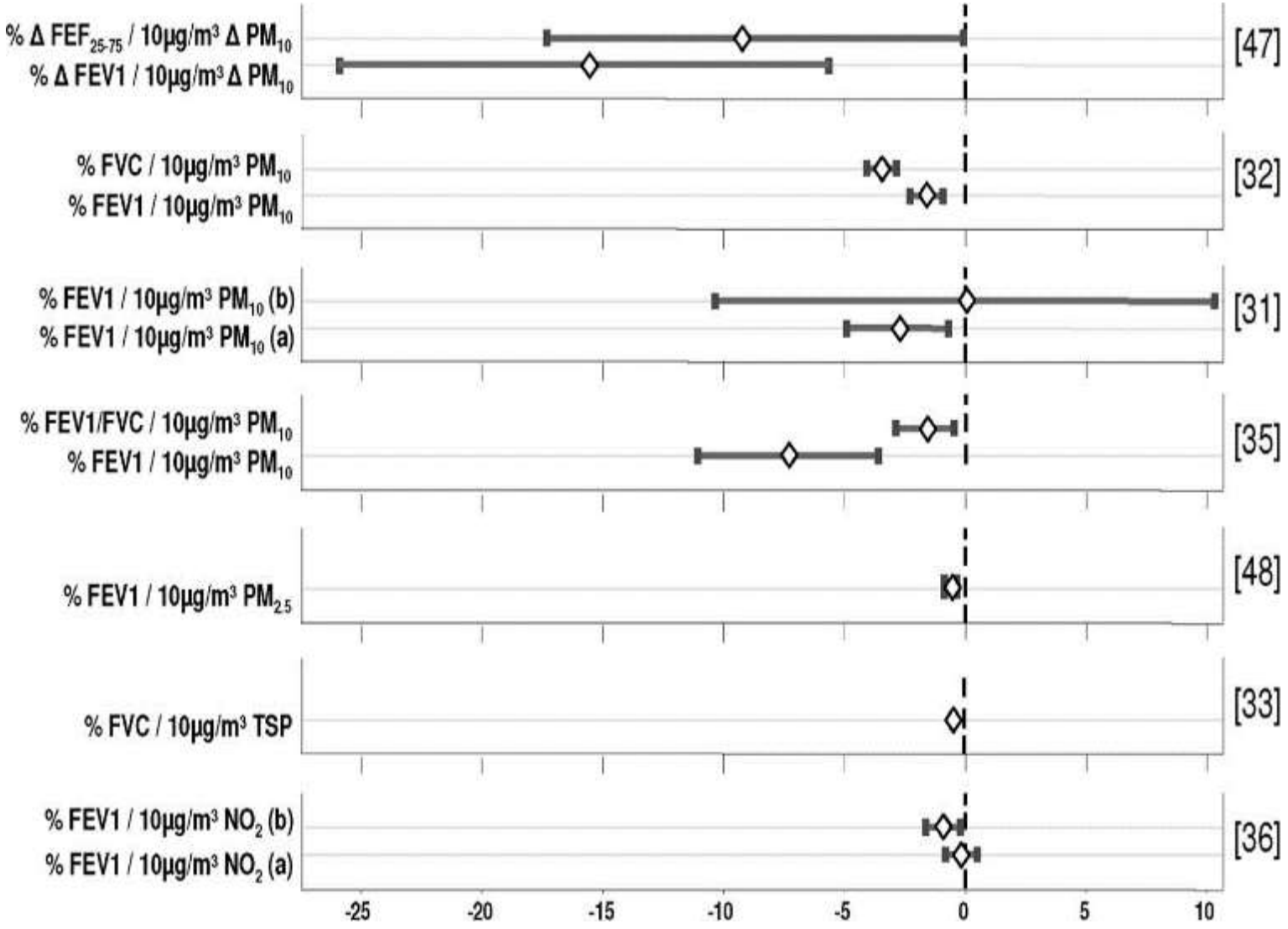
[18] Galizia A et al. Environ Health Perspect. 1999

[22] Kunzli N et al. Environ Res. 1997

[37] Avol EL et al. AJRCCM. 2001

[40] Gauderman WJ et al. NEJM. 2004

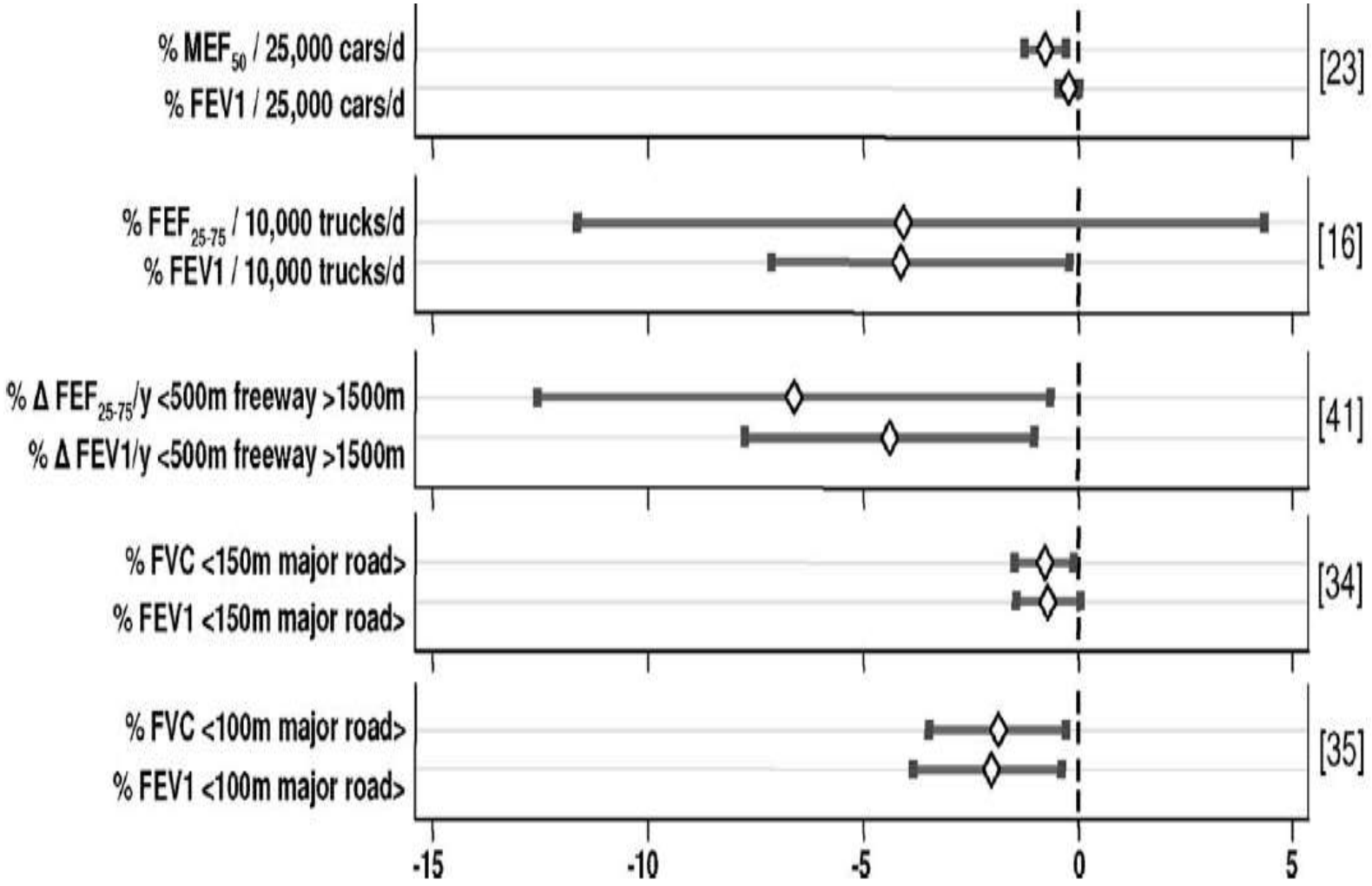
Results : effect estimates from studies of long-term effects of air pollution on lung function in adults



[35] Schikowski T et al. Respir Res. 2005

[47] Downs SH et al. NEJM. 2007

Results : effect estimates from studies of long-term effects of traffic on lung function



[16] Fritz GJ et al. Int J Hyg Environ Health. 2001

[41] Gauderman WJ et al. Lancet. 2007

Conclusion

- There are adverse long-term effects of air pollution on lung function growth in children, resulting in deficits of lung function at the end of adolescence
- However, no study has followed up adolescents until they reached the plateau phase of early adulthood; therefore, it is not known whether growth deficits will be compensated by a prolonged growth phase, or whether these subjects will enter the lung function decline phase of later adulthood with a reduced lung function
- Certain issues still remain unresolved like the most relevant age period vulnerable to the long-term effects of air pollution as well as the exposure windows

Long-Term Exposure to Primary Traffic Pollutants and Lung Function in Children: Cross-Sectional Study and Meta-Analysis

Francesco Barone-Adesi[1]*, Jennifer E. Dent[1], David Dajnak[2], Sean Beevers[2], H Ross Anderson[1,2], Frank J. Kelly[2], Derek G. Cook[1], Peter H. Whincup[1]

PLOS ONE | DOI:10.1371/journal.pone.0142565 November 30, 2015

- **Associations between primary traffic pollutants and lung function were investigated in 4884 children aged 9-10 years who participated in the Child Heart and Health Study in England (CHASE)**
- **Results from a meta-analysis were combined with the distribution of the values of FEV_1 in CHASE to estimate the prevalence of children with abnormal lung function (FEV_1<80% of predicted value) expected under different scenarios of NO_2 exposure**

Results

- In CHASE, there were non-significant inverse associations between all pollutants except ozone and both FEV1 and FVC
- In the meta-analysis, a 10 μg/m^3 increase in NO_2 was associated with an 8 ml lower FEV1 (95% CI -14ml to -1ml;**p=0.016**)
- Based on these results, a 10 μg/m^3 increase in NO_2 level would translate into a 7% (95% CI: 4% to 12%) increase of the prevalence of children with abnormal lung function (507 children per 100,000)

  - **The meta-analysis included studies published between 1990 and 2015 reporting cross-sectional associations between NO_2 and lung function among children or adolescents**
  - **Study participants were children or adolescents (age 0-18 years)**

Results : associations between concentration of pollutants and lung function (CHASE study)

	IQR ($\mu g/m^3$)	lung function	Basic model: Effect of 1 IQR increase in the levels of the pollutant (95% CIs)	Basic model: p-value	Confounder model: Effect of 1 IQR increase in the levels of the pollutant (95% CIs)	Confounder model: p-value
NO_2	4.9	FVC	-12 (-25 to 2)	0.08	-9 (-24 to 6)	0.24
		FEV_1	-5 (-16 to 7)	0.41	-5 (-18 to 8)	0.47
NO	7.7	FVC	-8 (-20 to 4)	0.19	-5 (-18 to 9)	0.49
		FEV_1	-3 (-13 to 7)	0.57	-2 (-14 to 9)	0.67
NO_x	12.6	FVC	-9 (-22 to 3)	0.15	-6 (-20 to 8)	0.39
		FEV_1	-4 (-14 to 7)	0.51	-3 (-15 to 9)	0.60
O_3	2.9	FVC	14 (-2 to 30)	0.08	10 (-7 to 28)	0.24
		FEV_1	6 (-7 to 20)	0.37	5 (-9 to 20)	0.48
Oxidants ($NO_2 + O_3$)	2.0	FVC	-9 (-19 to 2)	0.12	-7 (-19 to 5)	0.27
		FEV_1	-3 (-12 to 6)	0.49	-4 (-14 to 7)	0.49
PM_{10}	1.2	FVC	-8 (-20 to 5)	0.24	-5 (-19 to 8)	0.44
		FEV_1	-3 (-14 to 7)	0.55	-4 (-16 to 8)	0.53
PM_{10} Exhaust	0.2	FVC	-5 (-16 to 6)	0.34	-3 (-16 to 9)	0.59
		FEV_1	-2 (-11 to 8)	0.70	-2 (-13 to 8)	0.69
PM_{10} Non-exhaust	0.7	FVC	-4 (-13 to 6)	0.46	-2 (-13 to 8)	0.70
		FEV_1	-1 (-9 to 7)	0.84	-1 (-10 to 8)	0.80
$PM_{2.5}$	0.7	FVC	-11 (-25 to 4)	0.15	-8 (-24 to 8)	0.32
		FEV_1	-6 (-18 to 6)	0.35	-7 (-20 to 7)	0.35
$PM_{2.5}$ Exhaust	0.2	FVC	-5 (-16 to 6)	0.34	-3 (-16 to 9)	0.59
		FEV_1	-2 (-11 to 8)	0.70	-2 (-13 to 8)	0.69
$PM_{2.5}$Non-exhaust	0.2	FVC	-3 (-13 to 6)	0.49	-2 (-12 to 8)	0.72
		FEV_1	-1 (-9 to 7)	0.79	-1 (-10 to 7)	0.74
PM coarse	0.5	FVC	-5 (-16 to 6)	0.37	-3 (-15 to 8)	0.60
		FEV_1	-1 (-10 to 8)	0.79	-2 (-11 to 8)	0.76

Results : effect of increase in NO_2 exposure on absolute differences in FEV_1 in children

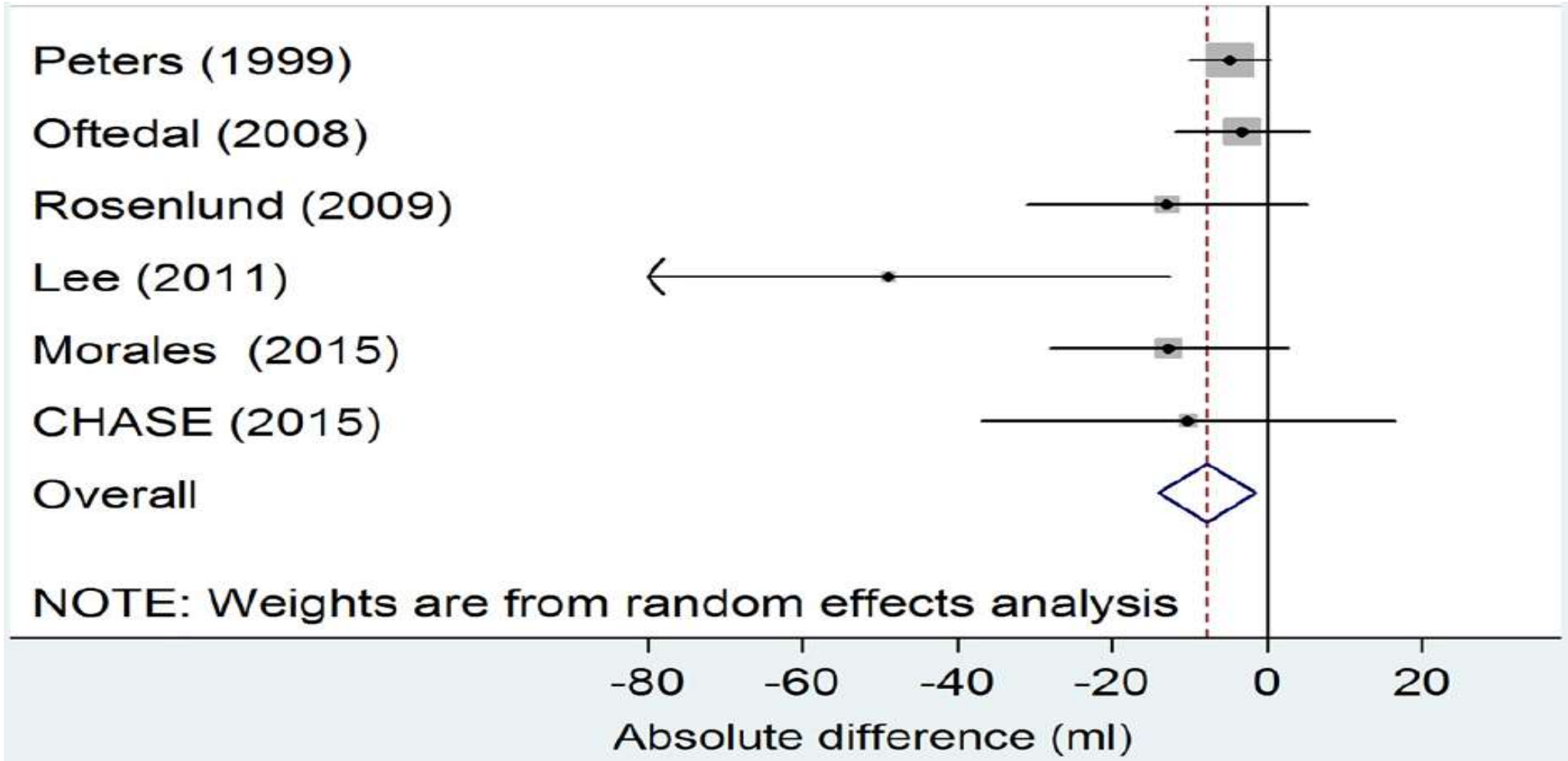
Author	n. subjects	Age	Mean NO_2 Level (expressed in µg/m3)	Exposure assessment	Exposure period	Absolute difference in FEV_1 (ml) per 10 µg/m^3 increase in NO_2 level
Peters 1999 [29]	2781	9–16	42	fixed monitoring stations	5 years	-5 (-10 to 0)
Oftedal 2008 [30]	2307	9–11	29	Dispersion model	10 years	-3 (-12 to -5)
Rosenlund 2009 [8]	1195	9–14	45	LUR	1 year	-13 (-31 to 5)
Lee 2011 [32]	3957	12–13	13	fixed monitoring stations	1 year	-49 (-85 to 13)
Morales 2015 [33]	567	4–5	29	LUR	1 year	-13 (-28 to 3)
CHASE 2015	4932	9–10	40	Dispersion model	2 years	-10 (-37 to 16)

LUR : land use regression

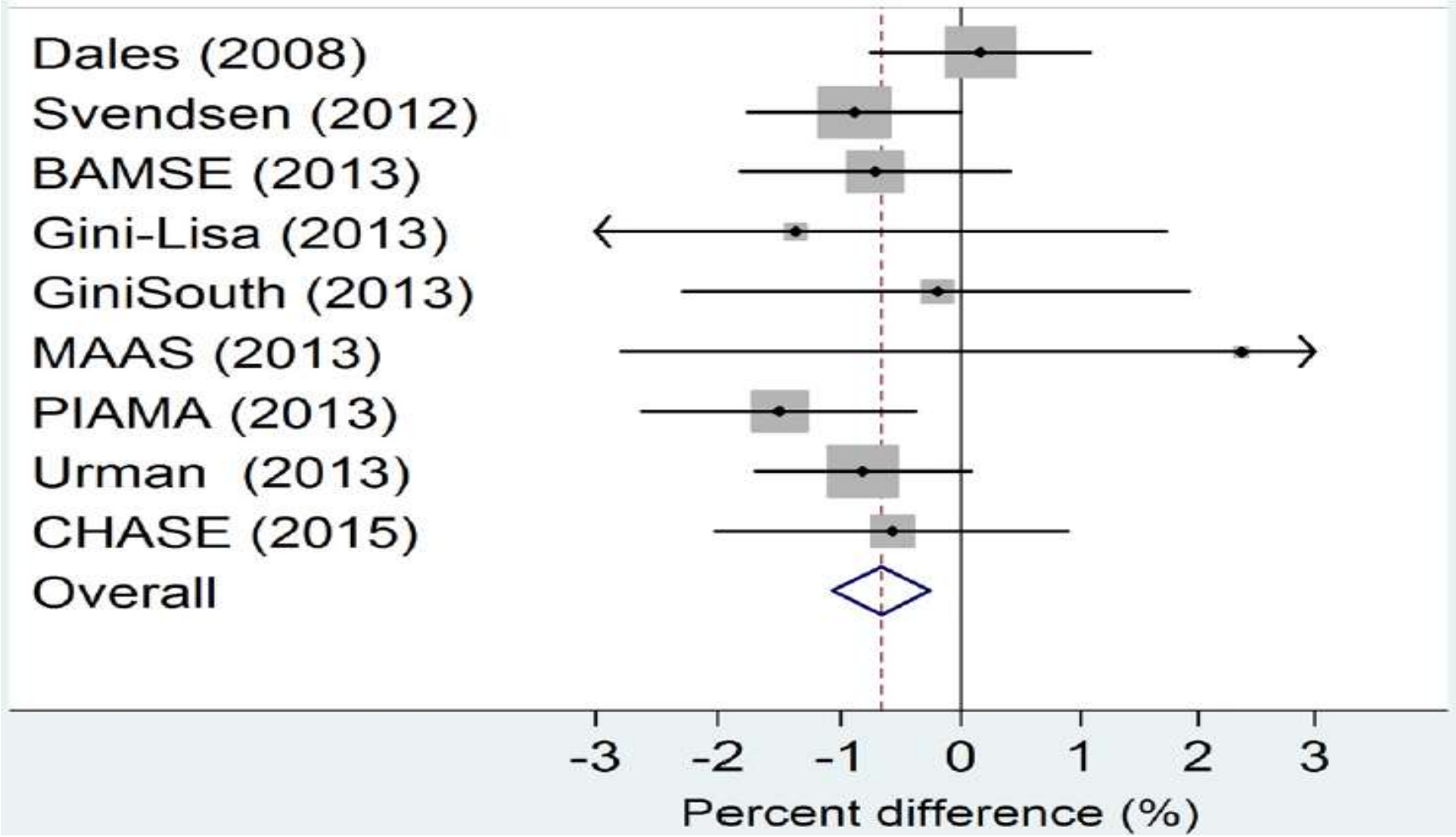
Results : effect of increase in NO_2 exposure on percent reduction in lung function in children

Author	n. subjects	Age	Mean NO_2 Level (expressed in µg/m3)	Exposure assessment	Exposure period	Percentage (%) difference in FEV_1 (ml) per 10 µg/m^3 increase in NO_2 level
Dales 2008 [31]	2328	9–11	26	LUR	1 year	0.2 (-0.7 to 1.1)
Svendsen 2012 [9]	2032	9–10	50	LUR	1 year	-0.9 (-1.8 to 0.0)
Gehring 2013 (BAMSE) [6]	2527	8	14	LUR	1 year	-0.7 (-1.8 to 0.4)
Gehring 2013 (Gini-Lisa) [6]	627	6	22	LUR	1 year	-1.4 (-4.4 to 1.7)
Gehring 2013 (Gini South) [6]	948	6	23	LUR	1 year	-0.2 (-2.2 to 2.0)
Gehring 2013 (MAAS) [6]	581	8	23	LUR	1 year	2.4 (-2.8 to 7.8)
Gehring 2013 (PIAMA) [6]	1036	8	23	LUR	1 year	-1.5 (-2.6 to -0.4)
Urman 2013 [25]	1811	10–11	25	LUR	1 year	-0.8 (-1.7 to 0.1)
CHASE 2015	4932	9–10	40	Dispersion model	2 years	-0.6 (-2.0 to 0.9)

Results : random effects meta-analysis of the association between concentration of NO_2 and FEV_1 (linear models)



Results : random effects meta-analysis of the association between concentration of NO_2 and FEV_1 (log-linear models)



Conclusion

- Exposure to traffic pollution may cause a small overall reduction in lung function and thereby increase the prevalence of children with clinically relevant declines in lung function

Indoor air pollutants and the lung

- Almost 3 billion people worldwide burn solid fuels indoors
- There are 4 principal categories of indoor air pollution : combustion products, chemicals, radon, and biological products

Sood A. Clin Chest Med. 2012;33(4):649-665

Indoor fuels

Solid fuels
Agricultural Crop Residues
Animal Dung
Wood
Charcoal
Coal
Liquid fuels
Kerosene
Ethanol & Methanol
Liquefied Petroleum Gas
Gas Fuels
Natural Gas
Methane Gas
Electricity

Sood A. Clin Chest Med. 2012;33(4):649-665

Mechanisms by which solid fuel smoke may affect respiratory outcomes

Neutrophilic inflammation

Macrophage phagocytic dysfunction and surface adherence

Increased MMP activity (pro-MMP-2; pro-MMP-9, and MMP-9)

Greater MMP gene expression (MMP-2 and MMP-12)

Pulmonary surfactant deactivation

Reduced bacterial clearance

Reduced mucociliary clearance

Upregulated arginase activity

Greater oxidative stress

Increased apoptosis

DNA damage

Break in integrity of the pulmonary air-blood barrier.

Diseases associated with smoke from solid fuel use

Strongly associated respiratory outcomes
COPD- emphysema/chronic bronchitis
Acute respiratory tract infections/pneumonia
Lung cancer (coal smoke)
Weakly associated respiratory outcomes
Asthma
Tuberculosis
Interstitial lung disease
Associated non-pulmonary outcomes
Cataract
Pregnancy-related complications
Nasopharyngeal cancer
Ischemic heart disease
Cor pulmonale

Po JY et al. Thorax. 2011;66:232-239

Respiratory Outcome	Number of studies included in meta-analysis	Strength of association
Acute respiratory tract infection in children**	8 *	3.53 (1.93, 6.43)
Asthma in children	4	0.50 (0.12, 1.98)
Asthma in women	5	1.34 (0.93, 1.93)
Chronic bronchitis in women	6	2.52 (1.88, 3.38)
COPD in women	6	2.40 (1.47, 3.93)

- ***All studies included in the meta-analysis are from developing countries except 1 from the United States that examined acute respiratory infections in American Indian children**
- ****Acute respiratory tract infection in this meta-analysis included both upper and lower respiratory tract infections**

Take home message

- Air pollutants can affect the lung in numerous ways : inflammation, oxidative stress, cell cycle death
- Have been shown to trigger acute episodes in asthma and COPD, other allergic airway diseases, and may be IPF; however, no long-term effects in these diseases have been proven strongly till now
- Strongly associated with lung cancer