Peroni Diego
Università di Pisa

e gli Inquinanti..

RADICI PROFONDE PER L'ADULTO DI DOMANI

CONSENSUS HELP©
HUMAN EARLY LIFE PREVENTION

PREVENZIONE PRECOCE DELLE MALATTIE NON TRASMISSIBILI E PROMOZIONE DI UN CORRETTO SVILUPPO NEUROCOGNITIVO

Per quanto concerne l'ambiente le principali domande sono:

In che misura le migliaia di **nuovi agenti chimici di sintesi e/o di scarto** che abbiamo immesso in pochi decenni **in atmosfera e catene alimentari** possono interferire con il **funzionamento, con la stabilità, con la corretta trasmissione del nostro DNA (o del nostro genoma) da una generazione all'altra?**

Quante tra queste "nuove" molecole, che non sono il prodotto di una lenta co-evoluzione molecolare, **sono state sufficientemente indagate**, tanto da poter dimostrare o escludere un loro possibile effetto dannoso sul genoma e quindi sulla salute umana?

E, analogamente, per quanto concerne l'introduzione in ambiente di sempre nuove **sorgenti di radiazioni non ionizzanti**: cosa sappiamo circa la possibilità che le diverse radiofrequenze (da sole o in sinergia con altre fonti e forme di inquinamento chimico-fisico) **possano interferire con il nostro DNA** e/o con le principali pathways segnaletiche intra- e intercellulari?

Cosa si deve intendere per inquinamento atmosferico

- **vero e proprio mix di gas tossici, metalli pesanti, particolato ultrafine, molecole tossiche persistenti che penetrano** attraverso le vie aeree, raggiungono il sangue, superano tutte le membrane biologiche (compresa la placenta, la barriera emato-cerebrale, le membrane plasmatica e nucleare..), **penetrano nel SNC e nei tessuti embrio-fetali in via di formazione**, interferiscono con tutti i meccanismi di segnalazione intercellulare e intracellulare e, di conseguenza, con tutti i principali meccanismi biochimici e molecolari, comprese **le tappe fondamentali dell'espressione genica** (favorendo le modifiche dell'assetto cromatinico, interferendo con la trascrizione e la traduzione delle sequenze geniche (codificanti) e con il folding proteico, inducendo il trasferimento di alcune "famiglie" di sequenze mobili deputate alla riformattazione genetica continua/reattiva di alcuni tessuti e in particolare del tessuto cerebrale)

- non si limita a produrre alcune migliaia di morti al giorno (secondo le stesse statistiche della WHO 5-7 milioni di morti prevenibili/anno) ma è uno dei principali determinanti di quello **stato di infiammazione sistemica cronica o subacuta di basso-grado** che ci accompagna per gran parte della nostra vita e che apre la strada a: **aterosclerosi e malattie cardiovascolari e cerebrovascolari connesse; malattie immunomediate come allergie e malattie autoimmuni; patologie endocrino-metaboliche, tra cui obesità e diabete; patologie del neurosviluppo e neuro-degenerative; tumori**, non per caso tutte patologie in grande aumento (Transizione epidemiologica del XX-XXI secolo)

La Consensus esamina le sempre più numerose evidenze scientifiche (epidemiologiche e sperimenta-li) in tema di fattori ambientali (soprattutto nutrizionali) che, in particolari **fasi di sviluppo (finestre temporali di vulnerabilità),** possono interferire sull'attuazione del **fetal programming**.

Gli inquinanti ambientali derivati da processi industriali, (**idrocarburi policiclici aromatici, ftalati, bisfenolo A, tributilina**), in particolare **gli interferenti endocrini**, sono molecole ubiquitarie nelle catene alimentari , nell'aria che respiriamo, negli utensili di uso comune, in grado di interferire negativamente sulla programmazione epigenetica del genoma operando attraverso il silenziamento di alcuni geni o il potenziamento di altri.

L'esposizione precoce a tali inquinanti, in epoca fetale, perinatale e nei primi anni di vita è così in grado di ipotecare il futuro biologico dell'individuo e gettare le basi per lo sviluppo delle malattie le cui manifestazioni tipiche si evidenzieranno dopo diversi anni o, addirittura, nelle generazioni successive (trasmissione gametica, transgenerazionale del danno).

La frequenza con cui si manifestano oggi tali malattie cardiovascolari, cancro, asma, depressione, obesità, autismo è tale da spingere alcuni autori a utilizzare definizioni inquietanti come quelle di **epidemia o pandemia**

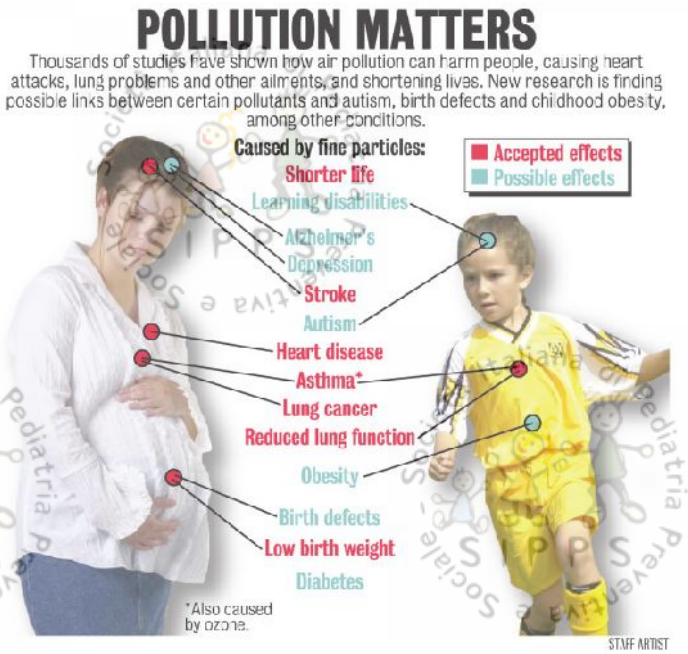
Respiratory Effects of Air Pollution on Children

Goldizen F. C. Pediatr Pulmonol 2016;51:94-108

- A substantial proportion of the global burden of disease is directly or indirectly attributable to exposure to air pollution.

- Exposures occurring during the periods of organogenesis and rapid lung growth during fetal development and early post-natal life are especially damaging.

- A greater understanding of the adverse health consequences of exposure to air pollution in early life is required to encourage policy makers to reduce such exposures and improve human health.



Respiratory Effects of Air Pollution on Children

Goldizen F. C. Pediatr Pulmonol 2016;51:94-108

Respiratory Health Effects of Air Pollution

Health Effect	Pollutant with established or suggested health effect
Short term effects	
Mucosal irritation (adult)	PM, NO_2, NO_x, Benzene, 1, 3-Butadiene, Fungal spores
Cough, wheeze, shortness of breath (adult)	O_3, 1, 3-Butadiene, PAHs
Growth	
Reduced fetal growth, premature birth, low birth weight, intra-uterine growth restriction (prenatal)	Ambient air pollution, TRAP, Maternal tobacco smoking, Environmental tobacco smoke, BMF, Wood combustion
Growth (child)	Ambient air pollution, Biomass fuel emissions
Respiratory infections	
Respiratory infections (prenatal)	$PM_{2.5}$
Respiratory infections (child)	Ambient air pollution, TRAP, PM_{10}, $PM_{2.5}$, NO_2, Indoor air pollution, Fungal spores
Lung function	
Lung function growth (prenatal)	Ambient air pollution, $PM_{2.5}$, PM_{10}, NO
Lung function growth (child)	Ambient air pollution, TRAP, $PM_{2.5}$, PM_{10}, NO_2, O_3, BMF

Respiratory Effects of Air Pollution on Children

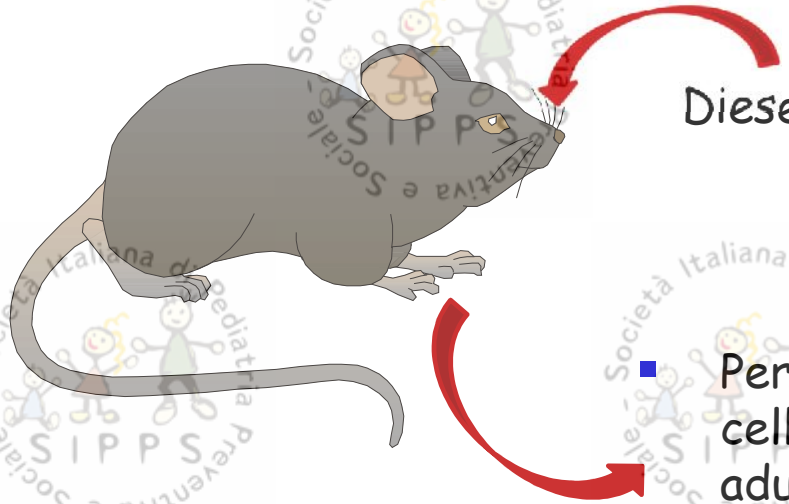
Goldizen F. C. Pediatr Pulmonol 2016;51:94-108

Respiratory Health Effects of Air Pollution

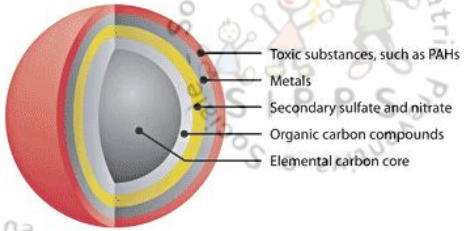
Health Effect	Pollutant with established or suggested health effect
Asthma	
Asthma exacerbation (child)	Ambient air pollution, TRAP, $PM_{2.5}$, PM_{10}, NO_2, O_3, Black carbon, Fungal spores
Asthma development (child)	Ambient air pollution, O_3, BMF, Fungal spores
Chronic Obstructive Pulmonary Disease	
COPD development (childhood exposure, adult development)	Ambient air pollution, Indoor air pollution
COPD exacerbation (adult)	Ambient air pollution, TRAP
COPD (adult)	Ambient air pollution, TRAP, Environmental tobacco smoke, Tobacco smoke, Biomass fuel emissions
Respiratory Cancers	
Lung cancer (childhood exposure, adult development)	Environmental tobacco smoke
Lung cancer (adult)	Ambient air pollution, Diesel exhaust, Gasoline exhaust, Particulate matter, Benzo[a]pyrene, Trichloroethylene, Radon, Asbestos, Formaldehyde, Black carbon, Styrene, Asphalt, Environmental tobacco smoke, Coal combustion, Wood combustion, High temperature frying
Nasopharyngeal cancer (adult)	Formaldehyde
Sinonasal cancer (adult)	Formaldehyde

Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility

Brandt EB, JACI 2015;136:295-303



Diesel exhaust particles (DEPs), coexposure with HDM



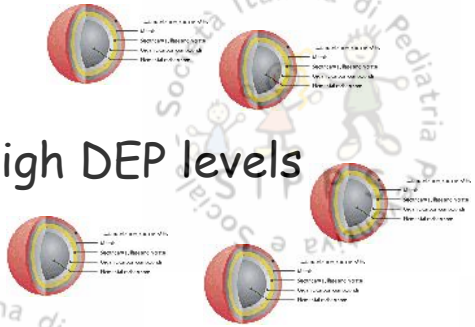
- Persistent T_H2/T_H17 $CD127^+$ effector/memory cells in the lungs, spleen, and lymph nodes of adult and neonatal mice.
- After 7 weeks of rest, a single exposure to HDM resulted in airway hyperresponsiveness and increased T_H2 cytokine levels in mice that had been previously exposed to both HDM and DEPs versus those exposed to HDM alone.

Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility

Brandt EB, JACI 2015;136:295-303

Cincinnati Childhood Allergy and Air Pollution Study birth cohort

Early-life exposure to high DEP levels



Significantly increased asthma prevalence among allergic children

but not among nonallergic children

Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility

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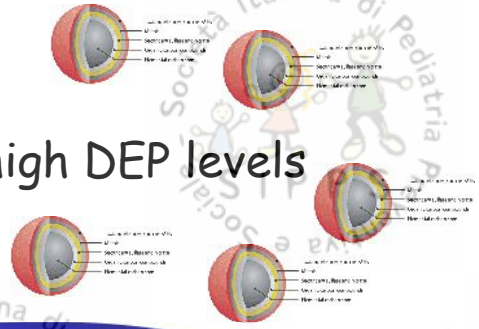
Early-life exposure to high DEP levels



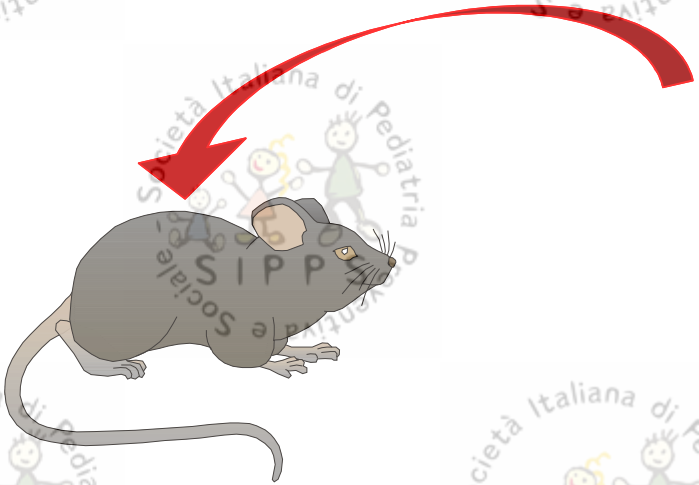
These findings suggest that DEP exposure results in accumulation of allergen-specific T_H2/T_H17 cells in the lungs, potentiating secondary allergen recall responses and promoting the development of allergic asthma.

Significantly increased asthma prevalence among allergic children

but not among nonallergic children

Diesel exhaust particles exacerbate allergic rhinitis in mice by disrupting the nasal epithelial barrier

Fukuoka A, Clin Exp All 2016;46:142-152



Nasally challenged with ragweed pollen in the presence or absence of Diesel Exhaust Particles (DEP)

Ragweed-pollen-sensitized mice

Mice challenged with ragweed pollen + DEP showed increased frequency of Sneezing

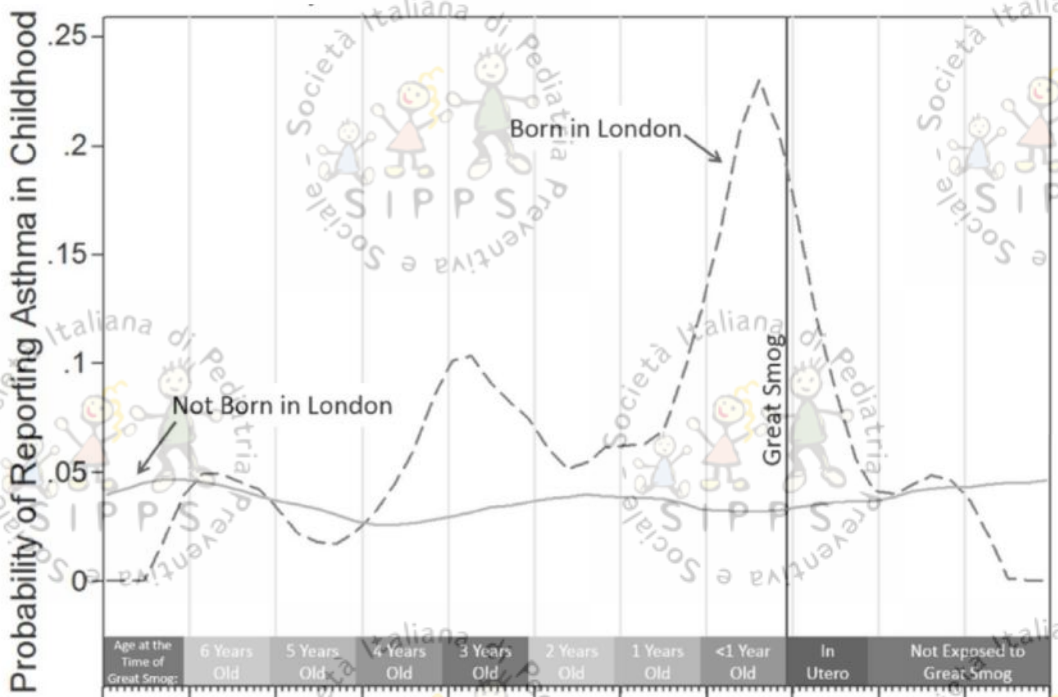
DEP reduced zonula occludens-1 (ZO-1) expression and disrupted nasal mucosal tight junction (TJs).

Early Life Exposure to the Great Smog of 1952 and the Development of Asthma.

Bharadwaj, AJCCRM, 2016

Natural experiment that uses the unanticipated pollution event by comparing the prevalence of asthma between those exposed to the Great Smog in utero or the first year of life to those conceived well before or after the incident and those residing outside the affected area at the time of the smog.

Asthma in childhood by date and location of birth



Date of Birth	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	Total
Born in London	31	56	52	39	38	34	38	15	42	37	36	418
Born Elsewhere	194	246	256	267	211	229	228	129	221	268	249	2,498
Total	225	302	308	306	249	263	266	144	263	305	285	2,916

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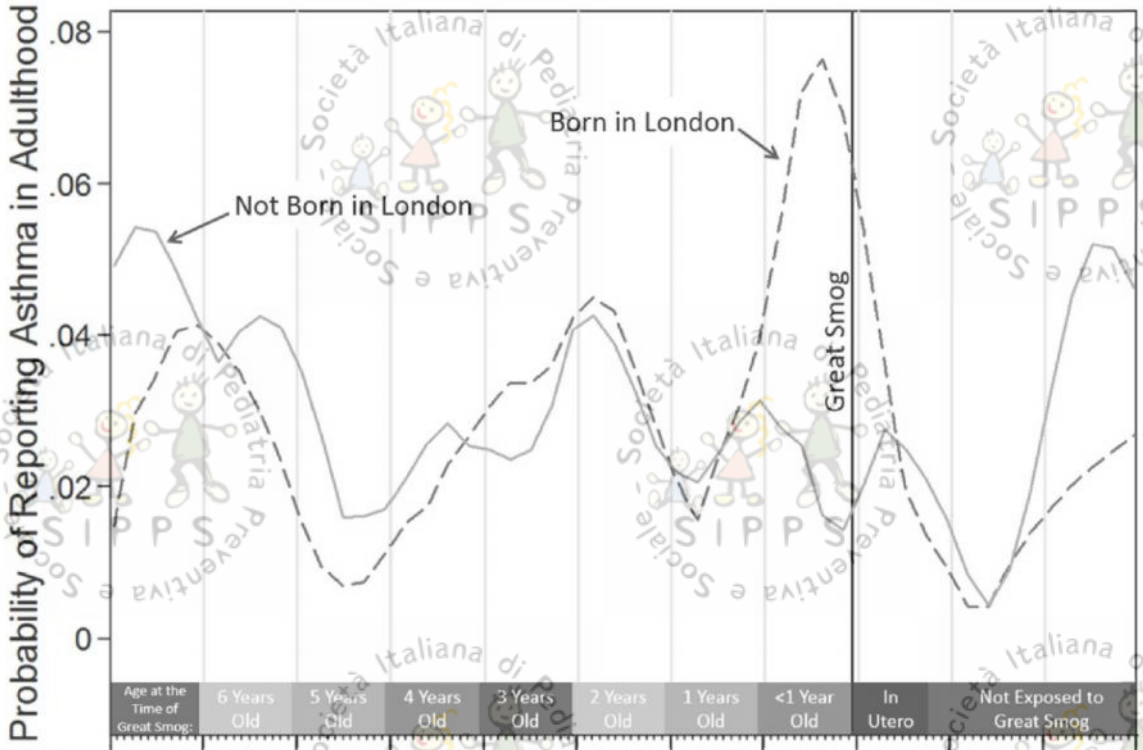
Asthma in adulthood by date and location of birth



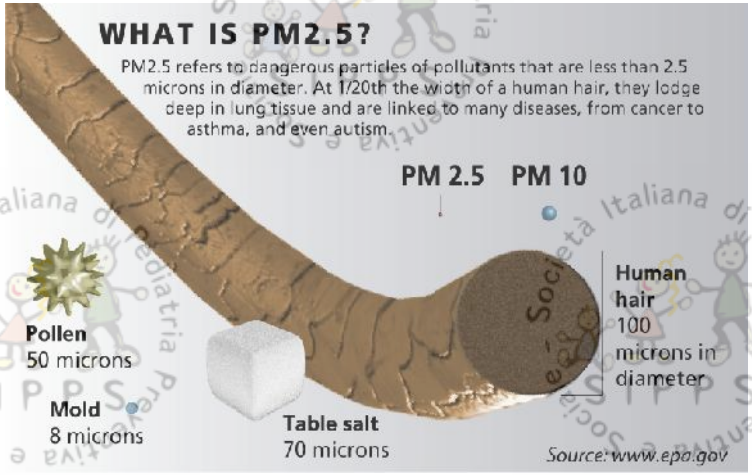
Date of Birth	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	Tot
Born in London	31	56	52	39	38	34	38	15	42	37	36	4
Born Elsewhere	194	246	256	267	211	229	228	129	221	268	249	2,4
Total	225	302	308	306	249	263	266	144	263	305	285	2,9

Prenatal Particulate Air Pollution and Asthma Onset in Urban Children. Identifying Sensitive Windows and Sex Differences

Hsu HHL, AJRCCM 2015;192:1052-1059

- ✓ 736 full-term (≥37 wk) children;
- ✓ Each mother's daily $PM_{2.5}$ exposure estimated over gestation using a validated satellite-based spatiotemporal resolved model;
- ✓ Associations between weekly averaged $PM_{2.5}$ levels over pregnancy and physician-diagnosed asthma in children by age 6 yrs.

Increased $PM_{2.5}$ exposure levels at 16-25 weeks gestation significantly associated with early childhood asthma development and sex was significant *(p=0.01)* with sex-stratified analyses showing that the association exists only for boys.

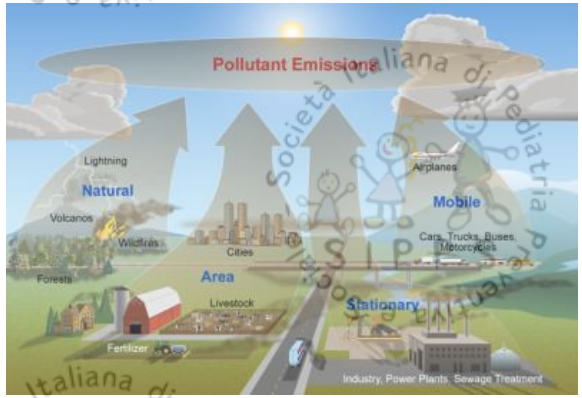


It Starts at the Beginning: Effect of Particulate Matter In Utero. *Editorial* *Sack C, AJRCCM 2015;192:1025*

- There is convincing evidence that exposure to ambient air pollution is associated with increased asthma symptoms, exacerbations, and a decline in lung function in children.

- Recent studies suggest this relationship may begin in utero, when cells are particularly sensitive to the oxidative damage caused by environmental toxins.

- The timing of exposure during gestation may be crucial in determining specific effects on immune system development and the different stages of fetal lung maturation.



Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence

Schultz ES. AJRCCM 2016;193:171-177

Rationale:

Exposure to air pollution during infancy has been related to lung function decrements in 8-year-old children, but whether the negative effects remain into adolescence is unknown.

Objectives:

To investigate the relationship between long-term air pollution exposure and lung function up to age 16 years.

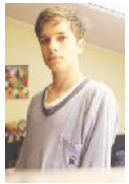
Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence

Schultz ES. AJRCCM 2016;193:171-177

- ✓ 2,278 children from the Swedish birth cohort BAMSE.

- ✓ Spirometry at age 16 years.
- ✓ Outdoor air pollution from local road traffic (nitrogen oxides [NO_x] and PM_{10}) for residential, daycare, and school addresses during the lifetime.

Exposure to traffic-related air pollution during the first year of life was associated with



FEV_1 at age 16 years of -15.8 ml for a 10 µg/m^3 difference in NOx **predominately in males (-30.4 ml), and in subjects not exposed to maternal smoking during pregnancy or infancy.**

Early-Life Exposures and Later Lung Function Add Pollutants to the Mix *Editorial*

Litonjua AA. AJRCCM 2016;193:110-111

- This study is the first to show that traffic-related air pollution exposures in the first year of life produce a deleterious effect on the child's lung function that manifests many years later, during adolescence.

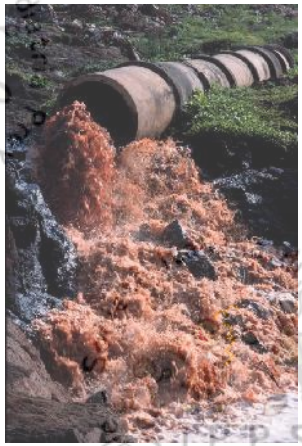
- The strongest association of pollution with lung function was with the estimated exposure during the first year of life, suggesting this is a critical period of exposure.

Prenatal exposure to persistent organic pollutants and offspring allergic sensitization and lung function at 20 years of age

Hansen S. Clin Exper Allergy 2016;46:329–336.

- Persistent organic pollutants (POPs) are a diverse class of organohalogen compounds:

  - Polychlorinated biphenyls (PCBs) previously used as coolants* and additive in thermal oils
  - Legacy organochlorine pesticides
  - By-products formed in various thermal processes such as dioxins and furans.



* A **coolant** is a fluid which flows through or around a device to prevent the device from overheating,

Prenatal exposure to persistent organic pollutants and offspring allergic sensitization and lung function at 20 years of age

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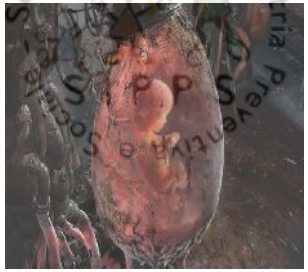
- Due to their thermodynamic stability and lipophilicity, POPs bioaccumulate in human and animal adipose tissue and are readily transported across the placental barrier.



- Although the production and use of many of these chemicals have been severely restricted and in some cases banned for several decades, humans are still exposed via the diet, primarily through the consumption of fatty fish.

Prenatal exposure to persistent organic pollutants and offspring allergic sensitization and lung function at 20 years of age

Hansen S. Clin Exper Allergy 2016;46:329–336.

- ✓ A Danish cohort of 965 pregnant women established in 1988–1989.
- ✓ 6 persistent organic pollutants (POPs) quantified in archived maternal serum drawn in gestational week 30 (n = 872).
- ✓ At age 20, 421 offspring attended a clinical examination, sIgE and lung function.

There were no associations between maternal concentrations of POPs and offspring allergic sensitization at 20 years of age.

Maternal concentrations of POPs were, however, positively associated with offspring airway obstruction ($FEV_1/FVC < 75\%$).

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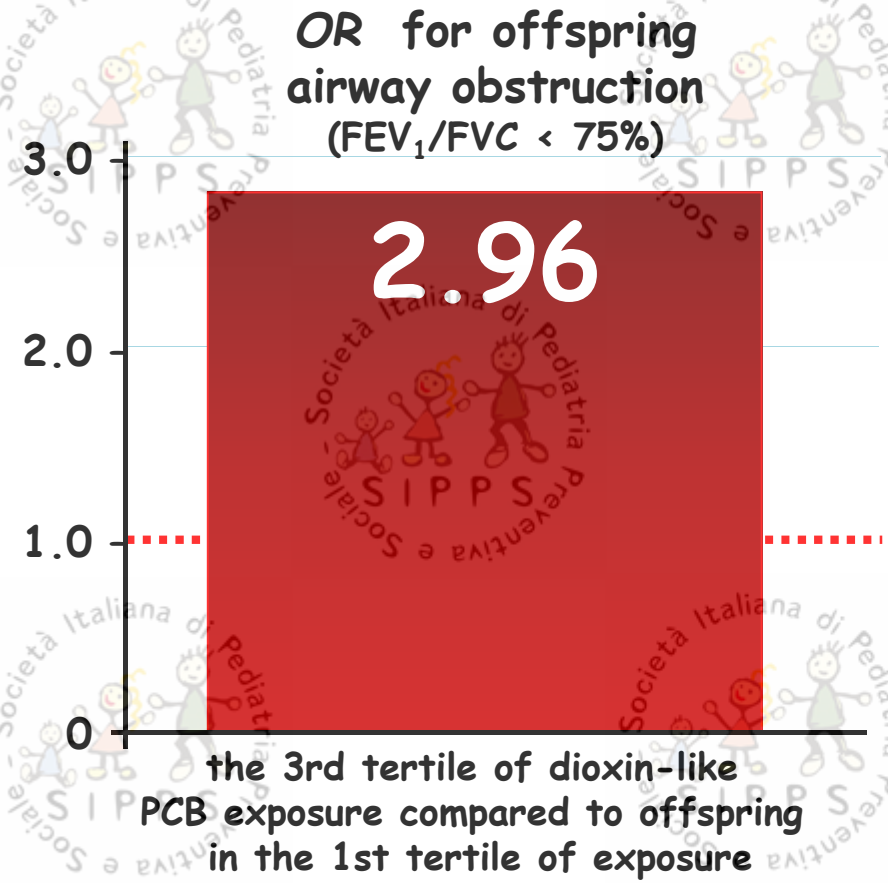


Association of Improved Air Quality with Lung Development in Children

Gauderman W. NEJM 2015;372:905-13

BACKGROUND

- Air-pollution levels have been trending downward progressively over the past several decades in southern California, as a result of the implementation of air quality-control policies.

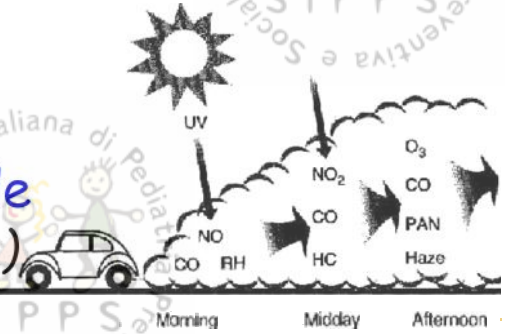
- We assessed whether long-term reductions in pollution were associated with improvements in respiratory health among children.

Association of Improved Air Quality with Lung Development in Children

Gauderman W. NEJM 2015;372:905-13

- ✓ Lung function annually in 2120 children
- ✓ Children from 3 separate cohorts corresponding to 3 separate calendar periods: 1994–1998, 1997–2001, and 2007–2011.
- ✓ Mean ages 11 years at the beginning of the period and 15 years at the end.

Improvements in 4-year growth of both FEV_1 and FVC were associated with declining levels of:



- nitrogen dioxide *(P<0.001 for both)*
- particulate matter with an aerodynamic diameter of less than 2.5 µm *(P = 0.008 for FEV_1 and P<0.001 for FVC)* and less than 10 µm *(P<0.001 for FEV_1 and FVC).*

Association of Improved Air Quality with Lung Development in Children

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Significant improvements in lung-function development were observed in both boys and girls and in children with asthma and children without asthma

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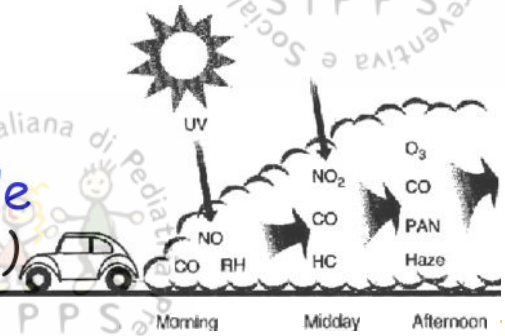

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Association of Improved Air Quality with Lung Development in Children

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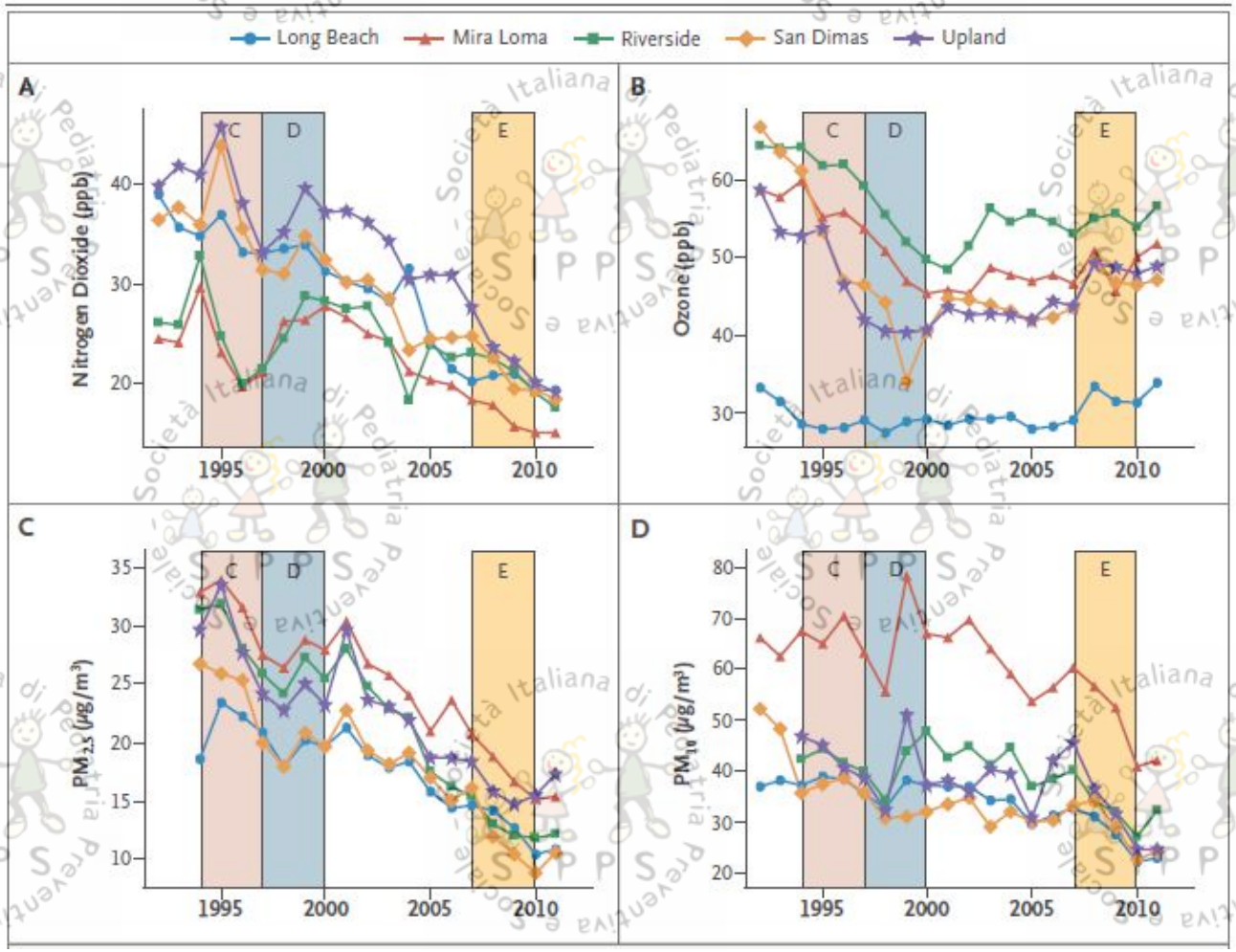
Levels of Four Air Pollutants:
A: nitrogen dioxide
B: Ozone
C: $PM_{2.5}$
D: PM_{10}

from 1994 to 2011 in Five Southern California Communities



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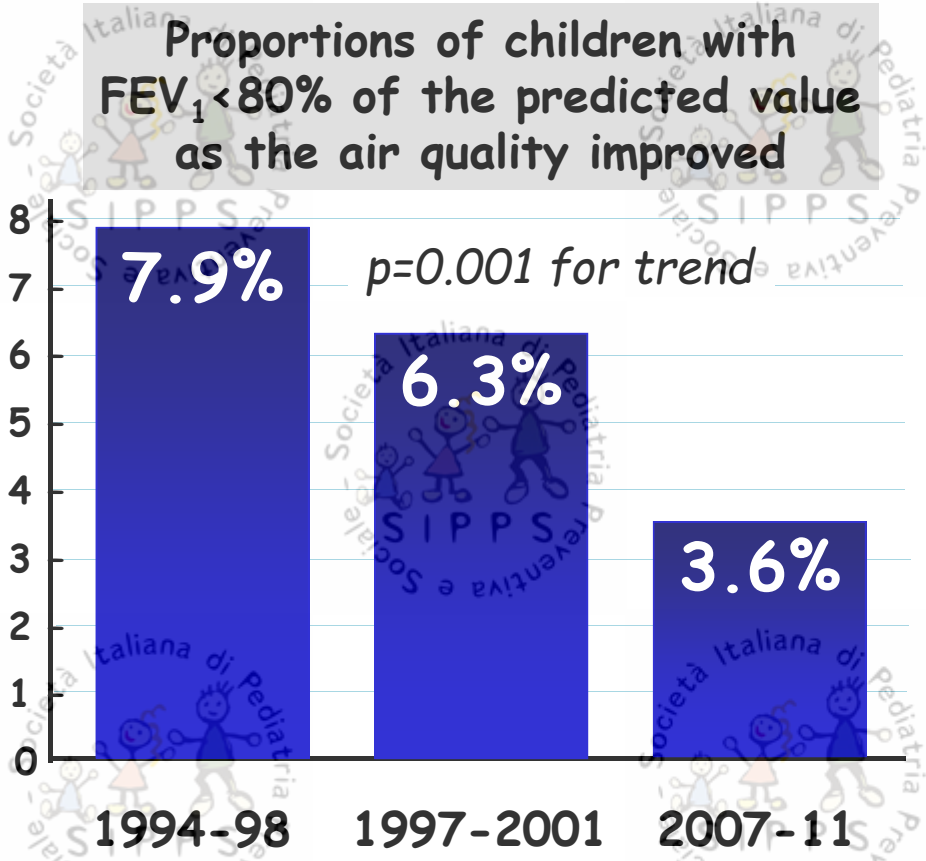

GOOD PRACTICE POINTS

Suggerimenti generali per minimizzare l'esposizione ad agenti inquinanti

- ridurre drasticamente l'esposizione materno-fetale al traffico veicolare
- ridurre l'esposizione a campi elettromagnetici
- acquistare prodotti biologici,
- mangiare pesce pescato in loco e di dimensioni ridotte
- filtrare l'acqua del rubinetto,
- utilizzare pentolame in ghisa e acciaio inossidabile anziché in materiali antiaderenti
- acquistare i prodotti per la cura personale, come shampoo, cosmetici e dentifrici in modo intelligente
- evitare smalti per unghie e tinture per capelli scure e controllare gli altri prodotti riportati nel-la banca dati cancerogeni dell'Istituto Superiore di Sanità (https://w3.iss.it/site/BancaDatiCancerogeni/)