Maladies respiratoires : un réel enjeu de santé publique en 2024

Respiratory diseases: a real public health issue in 2024

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CHU AMIENS-PICARDIE

Cour des comptes

Mai 2024

LA SANTÉ RESPIRATOIRE

Un enjeu de « santé environnement » insuffisamment pris en considération

La Cour des comptes recommande d'intégrer la santé respiratoire dans la stratégie nationale de santé

Chronic respiratory diseases: some examples

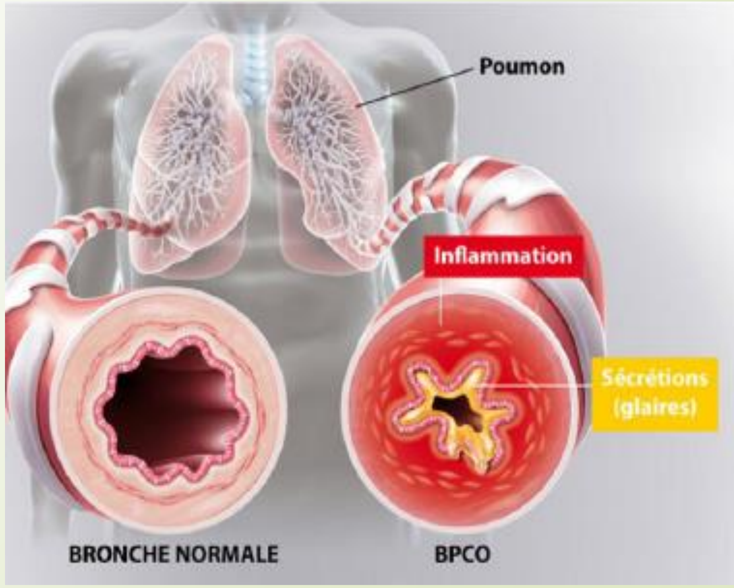
COPD, asthma and lung cancer… and a lot others respiratory diseases!

Les maladies respiratoires

- La bronchiolite, maladie d'origine virale qui touche majoritairement les très jeunes enfants, lors d'épidémies hivernales. Généralement bénigne, elle peut néanmoins dans certains cas conduire à l'hospitalisation, mais elle demeure rarement mortelle (moins de 1 %) ;
- Les infections à pneumocoques sont des infections bactériennes touchant majoritairement les personnes fragiles. La vaccination des nourrissons nés à compter du 1er janvier 2018 est obligatoire pour toute entrée en collectivité ;
- La coqueluche, également d'origine bactérienne, dont la vaccination est obligatoire pour tous les nourrissons nés après le 1er janvier 2018 ;
- La grippe, infection virale hivernale, qui affecte de deux à 6 millions de personnes chaque année, conduisant en moyenne à 10 000 décès ;
- La covid, maladie infectieuse respiratoire due au virus SARS-CoV-2, qui a émergé fin 2019 ;
- La tuberculose, maladie transmissible par voie aérienne, objet d'une déclaration obligatoire, reste marginale en France. En 2021, 4 306 cas ont été déclarés, en baisse de 7 % par rapport à 2020, baisse plus marquée que la tendance antérieure de -1,7 % en moyenne par an depuis 30 ans ;
- La légionellose, maladie également à déclaration obligatoire dont environ 2 000 cas sont recensés chaque année, avec une mortalité de 9 %. La source de contamination est principalement le réseau d'eau, à domicile ou dans des établissements accueillant du public.
- Le covid long dont les symptômes ne se limitent pas aux voies respiratoires ;
- Le syndrome d'apnées-hypopnées du sommeil, qui s'il constitue un des premiers postes de dépense de l'assurance maladie (1 Md€), a déjà fait l'objet d'enquêtes de la Cour[5] et de l'IGAS[6] ;
- Les maladies respiratoires rares, qui touchent une faible part de la population et relèvent d'une prise en charge très spécifique par la filière maladies rares et les centres de référence ;
- Les maladies pulmonaires vasculaires comme l'embolie pulmonaire et l'hypertension artérielle pulmonaire ;
- Les cancers de la plèvre ainsi que le mésothéliome : sont très majoritairement liés à une exposition à l'amiante, surtout chez les hommes, et font l'objet, à ce titre, dans certains cas, d'indemnisations. Le parcours de prise en charge des malades est en revanche similaire à celui du cancer du poumon.
- La mucoviscidose est une maladie rare, d'origine génétique, elle touche un nouveau-né sur 4 000 et se manifeste par des troubles respiratoires et pancréatiques. Au regard du nombre de personnes touchées par ces diverses maladies ou de l'existence d'une protection vaccinale, il a été décidé de les exclure du champ de ce rapport.

COPD: what is it ?

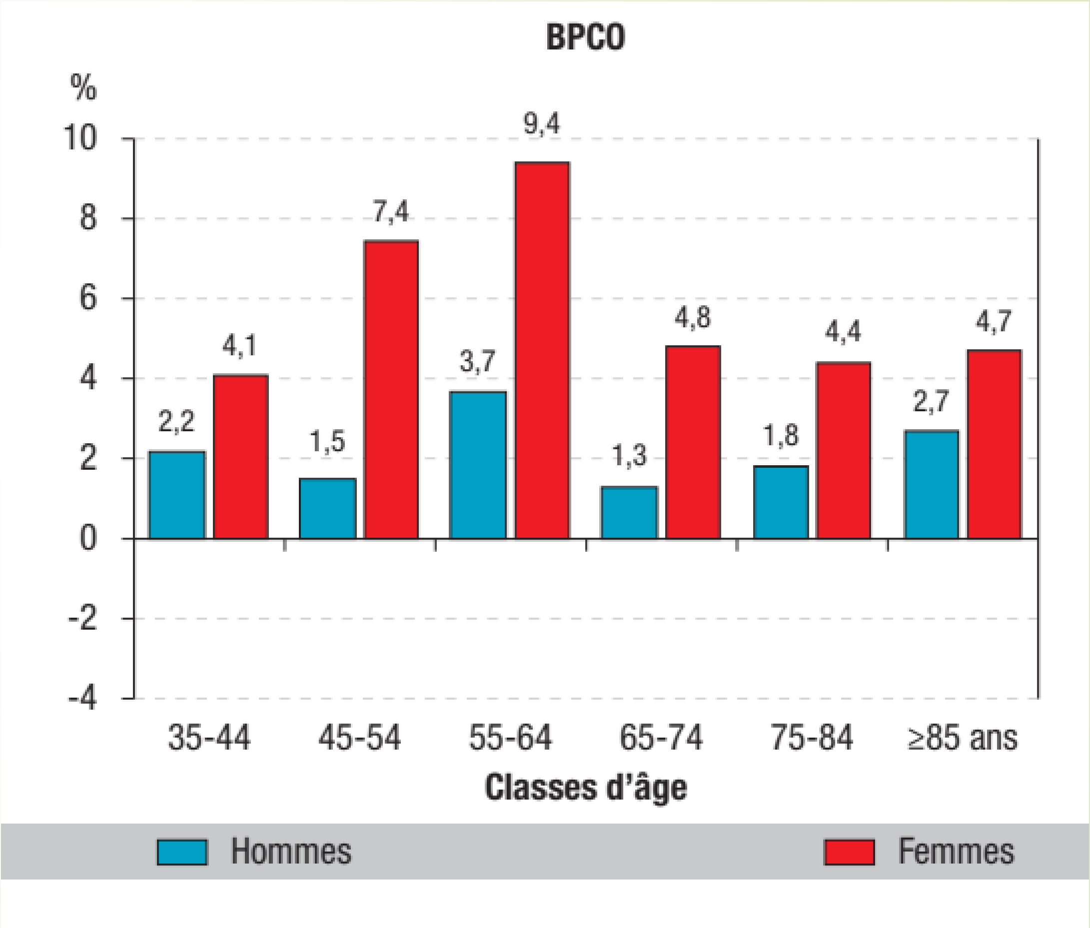
- Inflammatory bronchial disease
- Permanent and progressive airway obstruction
- Linked to toxic substances (TOBACCO ++), but also to pollutants and/or aero-contaminants of occupational origin
- Clinical manifestations = dyspnea, coughing and sputum
- At the advanced stage:
  - limitation in daily life
  - Oxygen/Ventilator Requirement
- Evolution punctuated by "exacerbations"



In France

SCREENING ++++

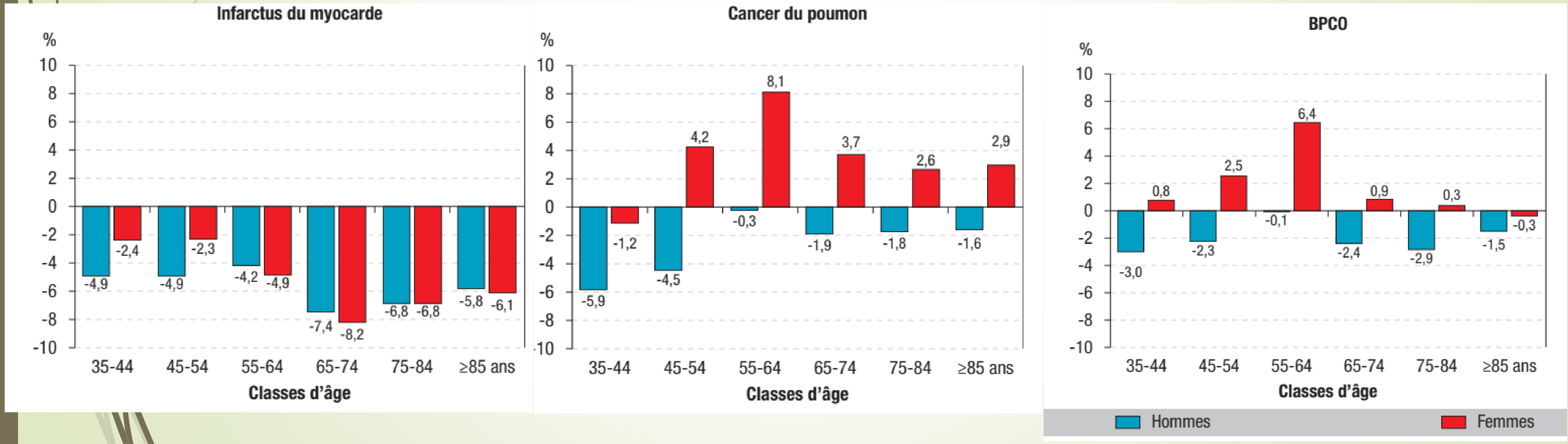
- 3.5 million of patients
- 2/3 of undiagnosed patients
- COPD = Underdiagnosed disease
- 1st cause of death from non-cancerous respiratory disease
- 3rd cause of tobacco-related mortality after lung cancer and cardiovascular diseases
- 6100 €/patient



Évolution annuelle moyenne de la morbidité liée au tabac par sexe et classe d'âge : patients hospitalisés pour une exacerbation de bronchopneumopathie chronique obstructive (BPCO) en France entre 2002 et 2015

And mortality ?

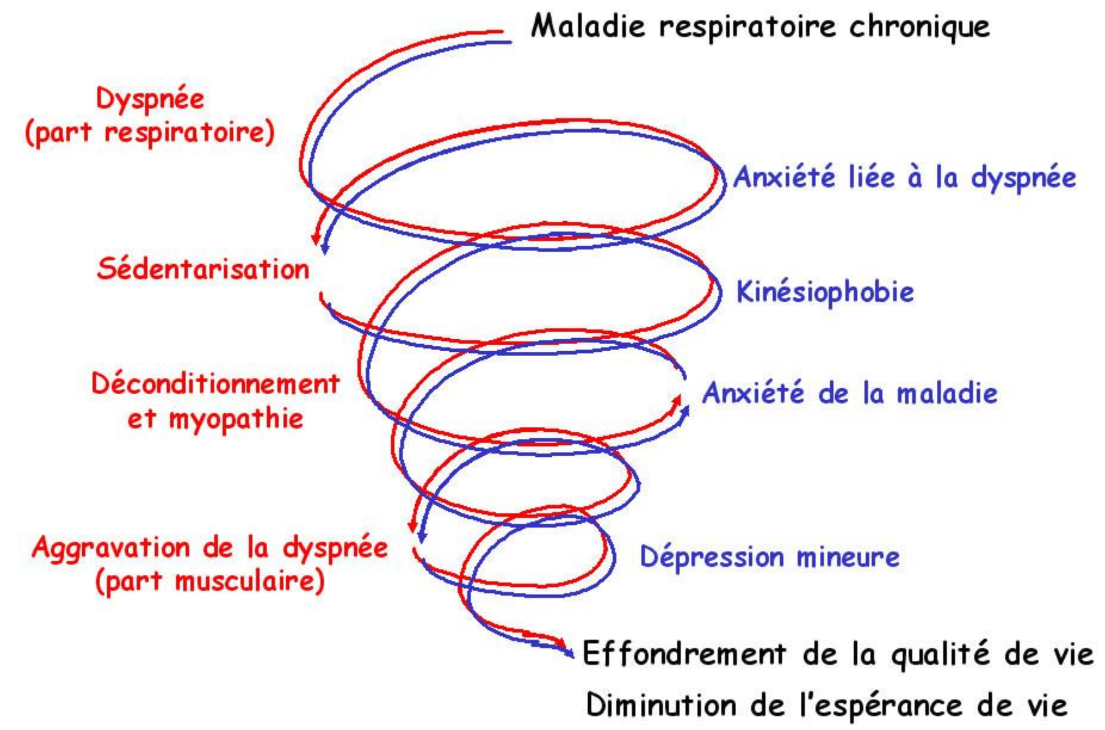
Évolution annuelle moyenne de la mortalité par infarctus du myocarde, cancer du poumon et bronchopneumopathie chronique obstructive (BPCO) en France entre 2000 et 2014, par sexe et classe d'âge



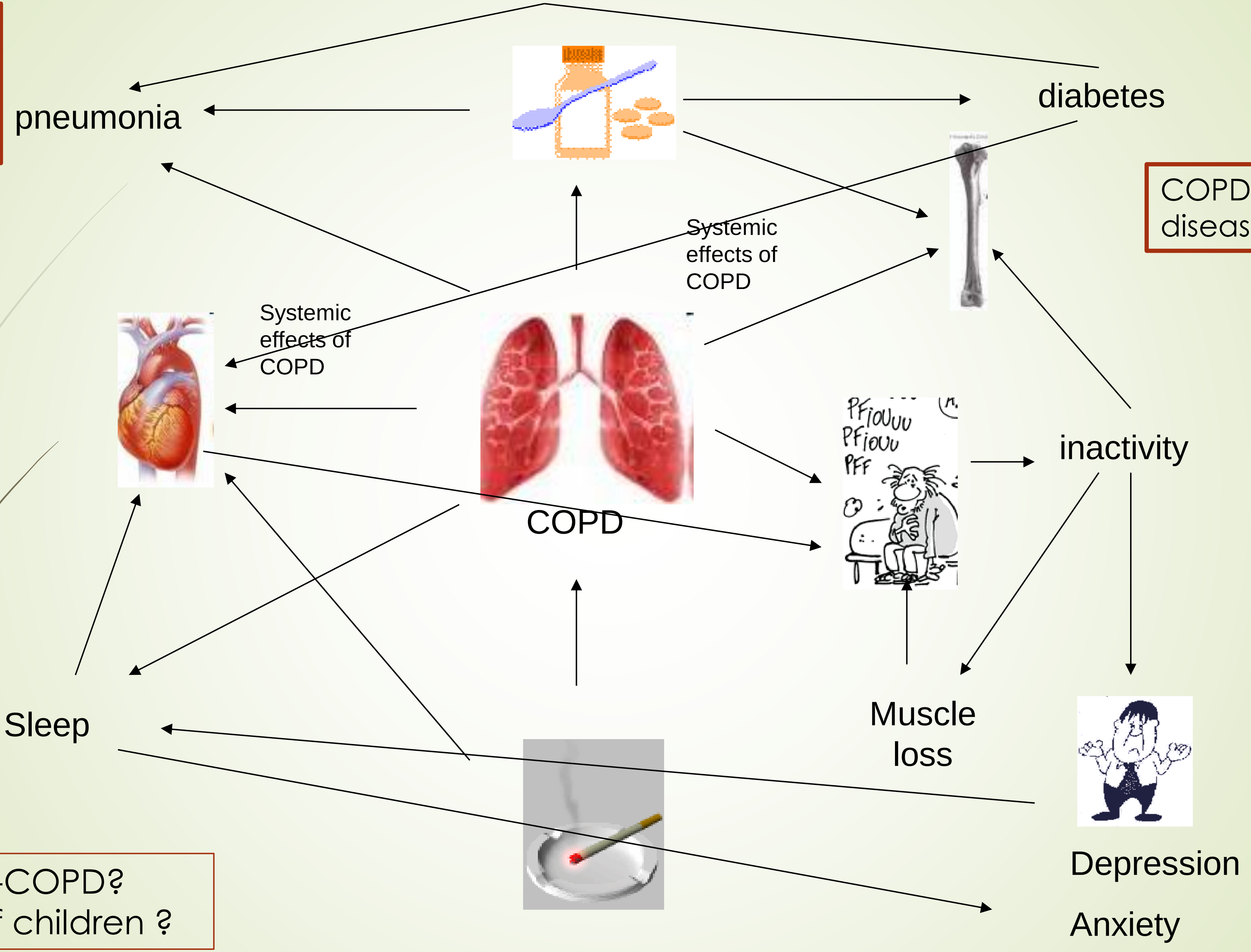
Treatments….

Stop of respiratory fonction decrease

Inhaled treatments
Oxygen=
Symptoms treatment!



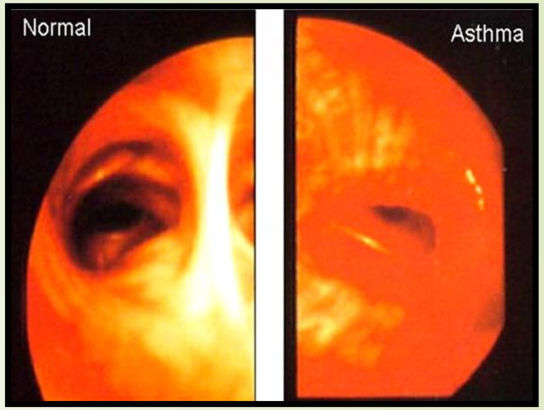
COPD more than a respiratory disease



COPD = complex disease

And pre-COPD?
COPD of children ?

Asthma (1)



- Chronic and multifactorial **inflammatory bronchial disease**, characterized by attacks of **wheezing dyspnoea**
- Triggered by different agents or by exercise
- Accompanied by clinical signs of bronchial obstruction that is totally or partially reversible between exacerbations.
- Predominant **inflammatory component** (→ Anti-inflammation drugs)
- This activation takes place in the bronchial mucosa under the effect of immunological or non-immunological stimuli: allergens, non-specific irritants, etc.
- **Bronchial hyperresponsiveness** = Bronchoconstriction = contraction of the smooth muscles surrounding the bronchi and bronchioles (→ Bronchodilators)

Asthma (2)

- Common pathology: **5 to 7%, increasing** (10 to 15% in young adults) compared to 2 to 3% 15 years ago.
- **Higher prevalence in urban areas**
- Affects both men and women
- 90% of cases occur before the age of 40
- Underdiagnosed ++++

Bronchiectasis and Cystic fibrosis

- **Permanent and irreversible increase in the caliber of the subsegmental bronchi**
- Responsible of
  - Bronchial hypersecretion
  - Stasis
  - Chronic inflammation
  - Infections
  - Bronchial hypervascularization
  - Chronic respiratory failure

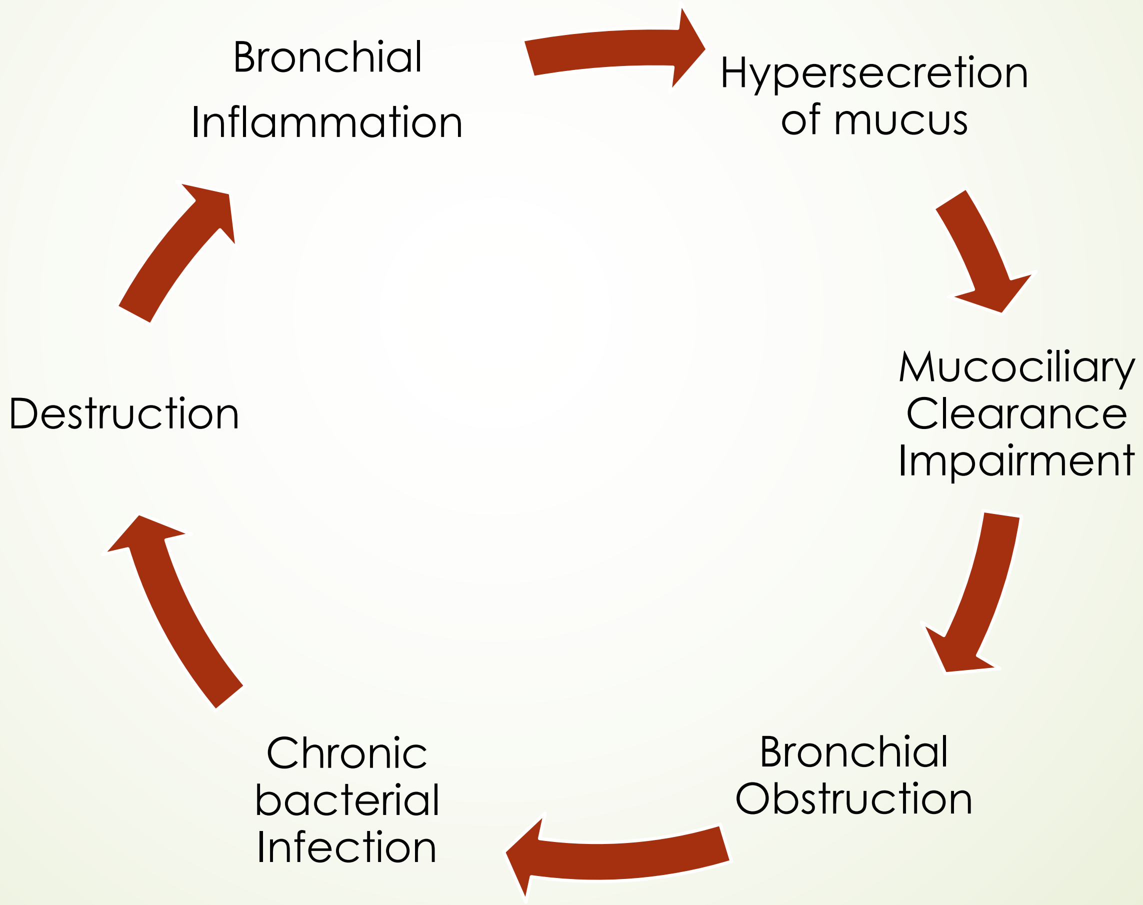
Cough and Sputum

exacerbations

hemoptysis

dyspnea

Vicious cercle of bronchiectasies



Risks factors of bronchiectasis

A lot of patients
A systemic disease ? Lung in a complex interaction with others diseases!

- Poor mucociliary clearance:
  - Primary ciliary dyskinesia
  - "Anatomical" obstruction of the bronchi
- Mucus abnormality: Cystic fibrosis, ENaC mutations
- Inflammation of the airways of autoimmune origin:
  - Digestive inflammatory diseases
  - Sjogren, rheumatoid arthritis
- Immunosuppression: Lymphoma, Immunosuppressive Therapies…
- Non-infectious non-autoimmune inflammatory state: alpha 1 antitrypsin deficiency, GERD, toxic inhalation, asthma, ABPA, COPD...

Bronchiectasis = disability ?

Maladie gênante	50%
Maladie à cacher	7%
Absentéisme scolaire	37%
Privation de sport dans l'enfance	50%
Privation de sport à l'âge adulte	91%
Handicap à la vie professionnelle	50%
Responsable d'un célibat	15%
Renfermés sur eux-mêmes	19%
Dégagent une impression de tristesse	17%

Vicious cercle of bronchiectasies

Anti-inflammatory drugs (macrolides)

Bronchial Inflammation

Hypersecretion of mucus

Hydratation
Physiotherapy

Mucociliary Clearance Impairment

Bronchial Obstruction

Chronic bacterial Infection

Destruction

Antibiotics if exacerbation

And for all patients = prevention with vaccines

Le Monde

« Les pics de pollution sont associés à des infections respiratoires plus fréquentes »

Le pneumologue Bruno Housset demande, dans une tribune au « Monde », aux responsables politiques que la norme Euro 7 sur les émissions polluantes des véhicules entre rapidement en vigueur, car il s'agit d'une urgence de santé publique.

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Some data to better understand

- According to WHO (2022):
  - 9 out of 10 people live in places where pollution exceeds recommended levels
  - More than 7 million premature deaths
  - 17% of deaths secondary to lower respiratory tract infections are linked to pollution

- Air = 78% nitrogen, 21% oxygen and 1% other gases = aerosol of particles

- Contamination of this air with the presence of contaminating gases and particles in the atmosphere (CO, Nox, O3, SO2, VOCs, PM)

- Bio-aerosol = cell and plant fragments, bacteria, fungi, viruses, spores...

Necropsy Evidences on the Relation of Smoky Atmosphere to Pneumonia*

SAMUEL R. HAYTHORN, M.D., AND HARRY B. MELLI

AMERICAN JOURNAL OF PUBLIC HEALTH Apr., 1938

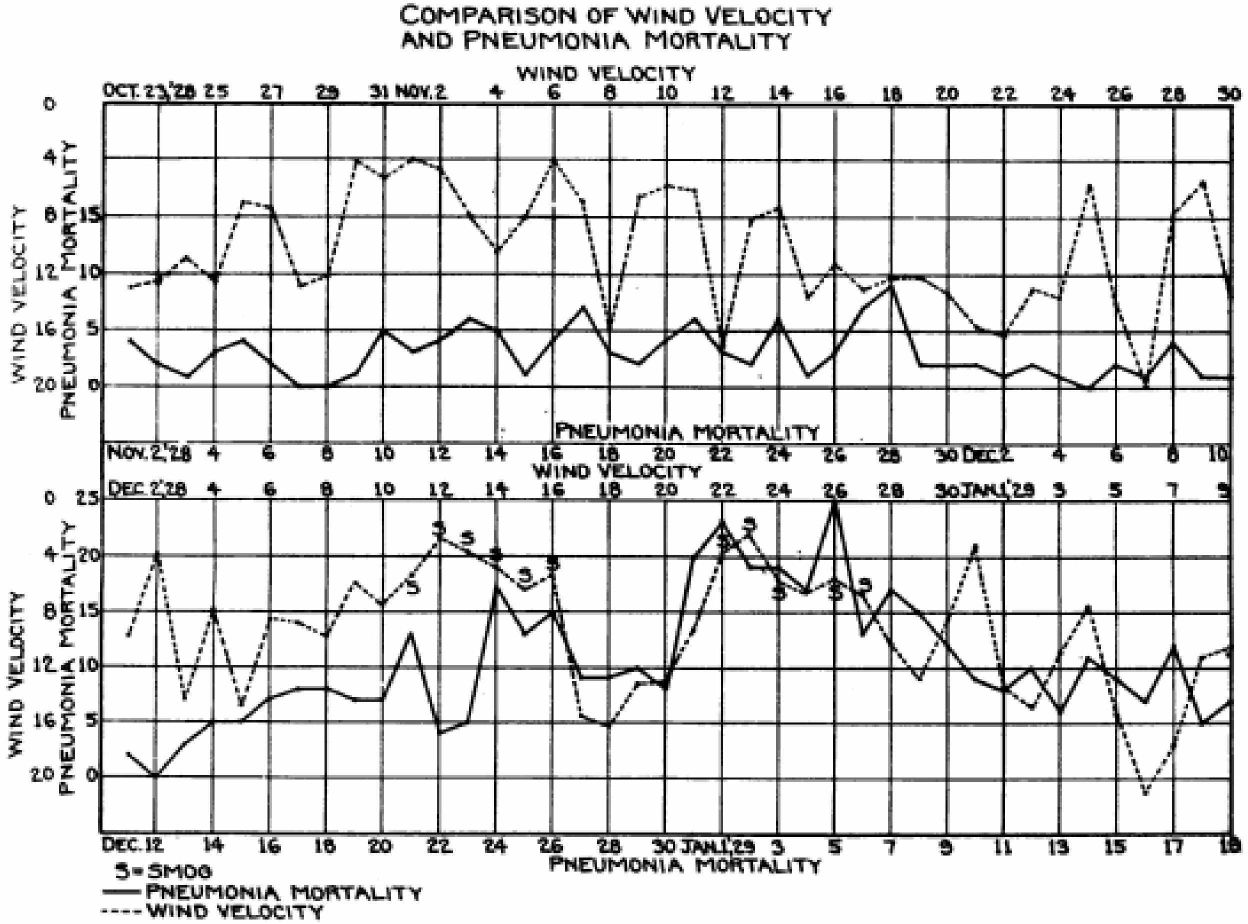
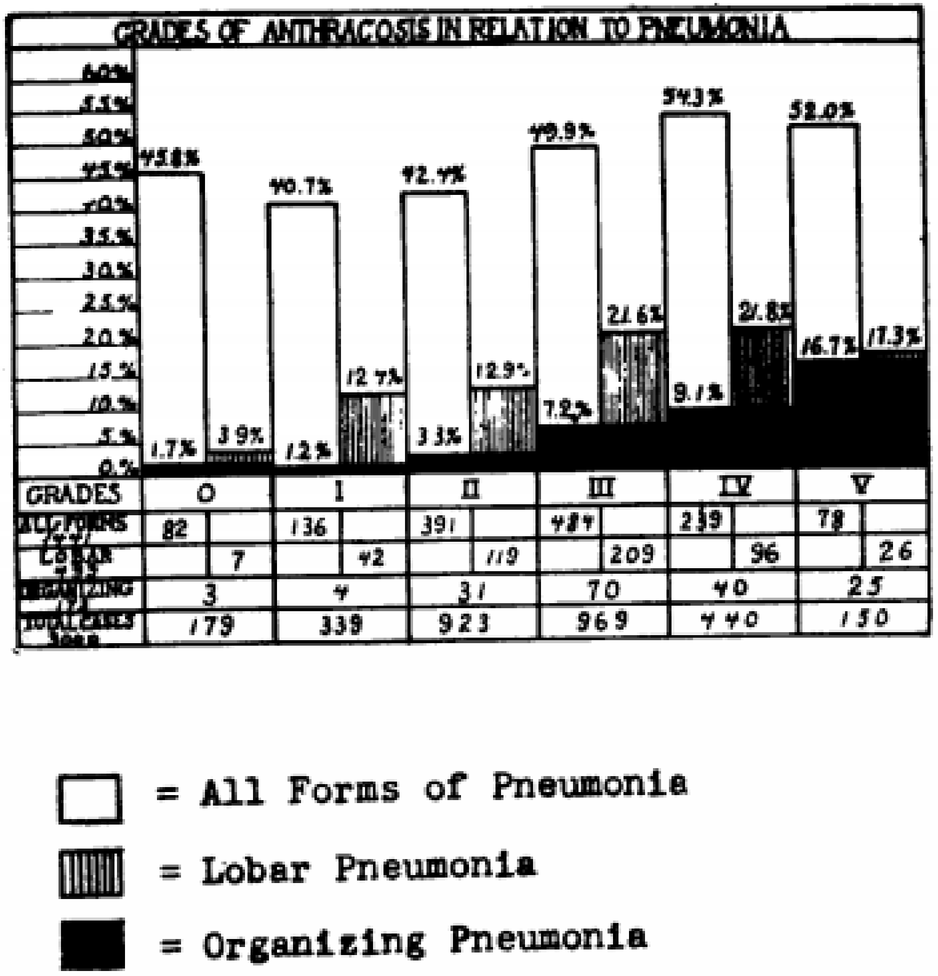


CHART 2



MORTALITY FROM FOG IN LONDON, JANUARY, 1956

BY

W. P. D. LOGAN, M.D., Ph.D., D.P.H.

Chief Medical Statistician, General Register Office

BRITISH MEDICAL JOURNAL

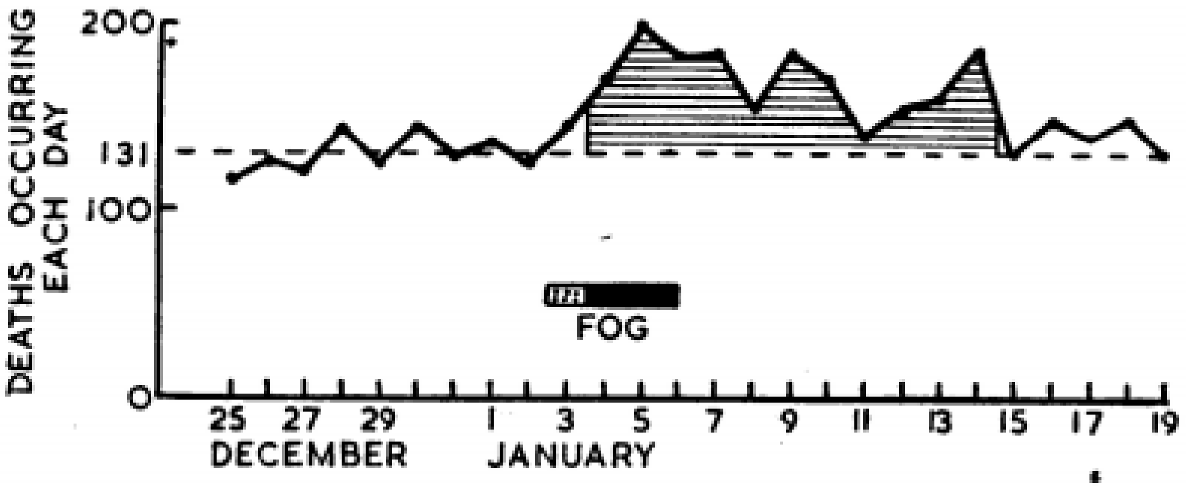


FIG. 1.—Deaths (all causes) occurring each day in London Administrative County from December 25, 1955, to January 19, 1956. Shaded area represents deaths in excess of 131 per day during period January 4 to 14.

TABLE I.—*Deaths by Day of Occurrence and from Selected Causes. December 25, 1955, to January 19, 1956. London Administrative County*

	All Causes	Influ-enza	Pneu-monia	Bronch-itis		All Causes	Influ-enza	Pneu-monia	Bronch-itis
Dec. 25	117		8	13	Jan. 7	186	1	21	30
,, 26	127		7	9	,, 8	156		12	40
,, 27	119		10	12	,, 9	184	1	13	35
,, 28	143	1	16	15	,, 10	169	1	14	33
,, 29	126		11	15	,, 11	139		13	23
,, 30	145	1	15	19	,, 12	154	2	12	27
,, 31	128		11	16	,, 13	161	1	12	25
Jan. 1	136	1	9	17	,, 14	184	2	20	19
,, 2	127		7	10	,, 15	129		11	24
,, 3	145		10	29	,, 16	149	1	11	17
,, 4	168		17	27	,, 17	139	2	12	20
,, 5	199	1	13	24	,, 18	148	1	12	17
,, 6	181		13	37	,, 19	130	1	6	19

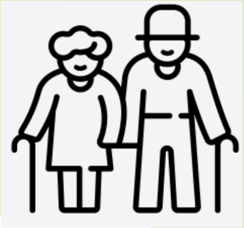
TABLE V.—*Deaths Occurring in London Administrative County During December 25 to January 3 and During January 4 to 13 from Bronchitis and Pneumonia*

	Bronchitis	Pneumonia
Dec. 25–Jan. 3	155	104
Jan. 4–13	301	140
Increase	94%	35%

Short-Term Elevation of Fine Particulate Matter Air Pollution and Acute Lower Respiratory Infection

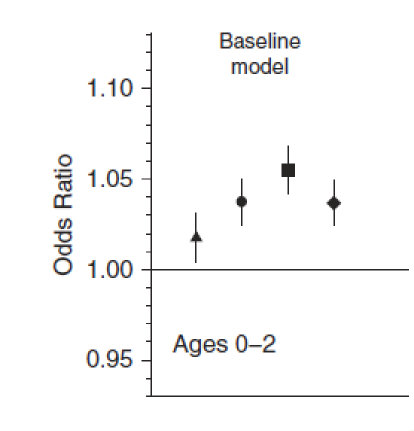
Benjamin D. Horne[1,2], Elizabeth A. Joy[3,4], Michelle G. Hofmann[5,6], Per H. Gesteland[2,5,6], John B. Cannon[7], Jacob S. Lefler[7], Denitza P. Blagev[8], E. Kent Korgenski[5], Natalie Torosyan[9], Grant I. Hansen[10], David Kartchner[9,11], and C. Arden Pope III[7]

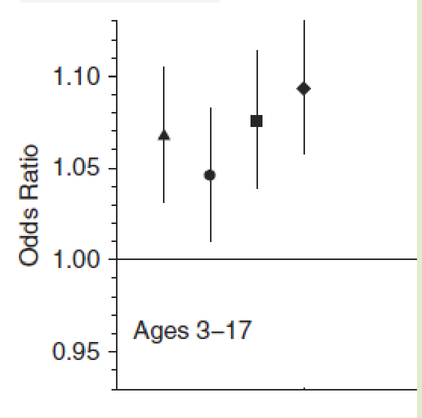


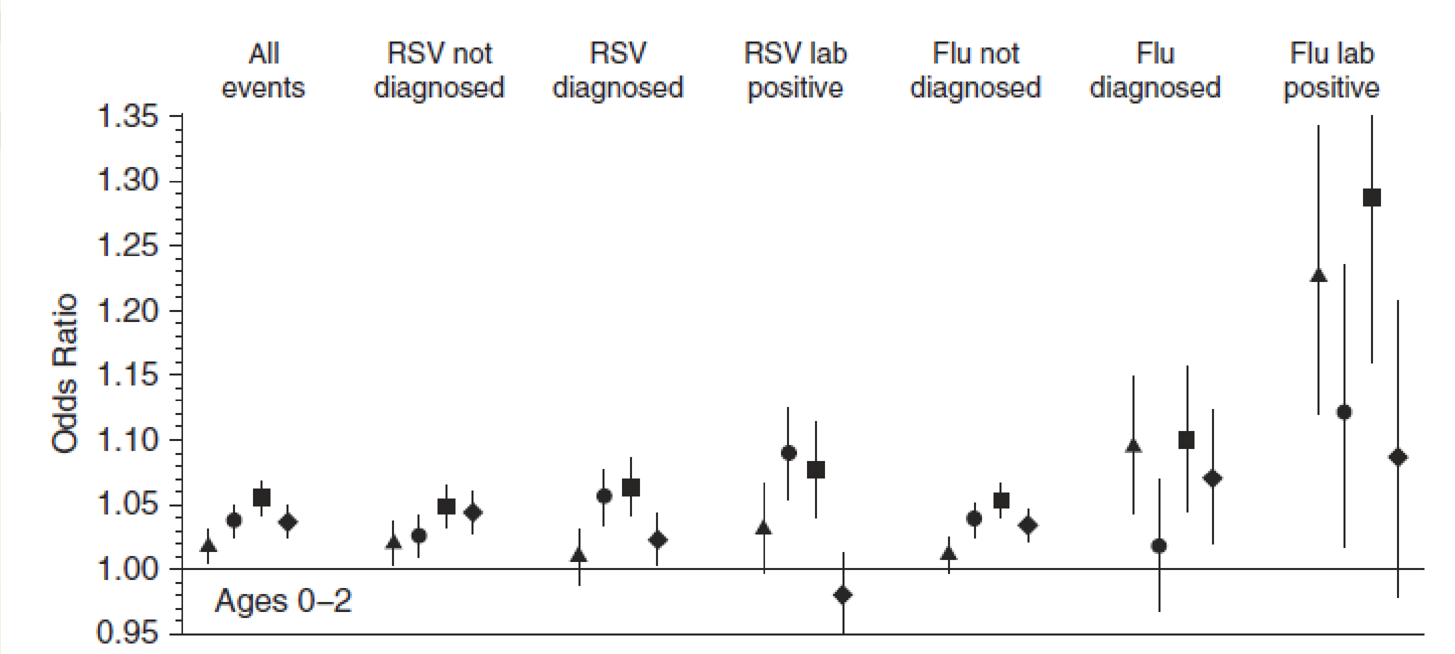



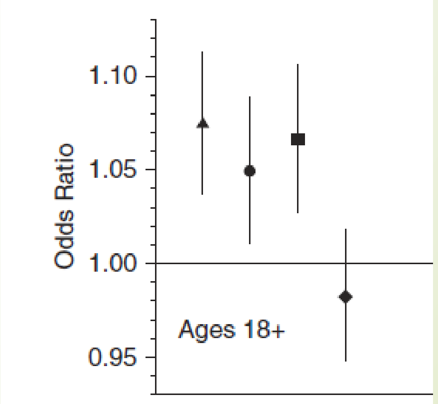
RSV and flu

- 130295 children:
  - Increased risk of lower respiratory infection after 1 week of exposure to increased PM2.5 and maximum risk after 3 weeks
  - Cumulative OR (28 days) of 1.15 per PM2.5 increase of 10 µg/m3









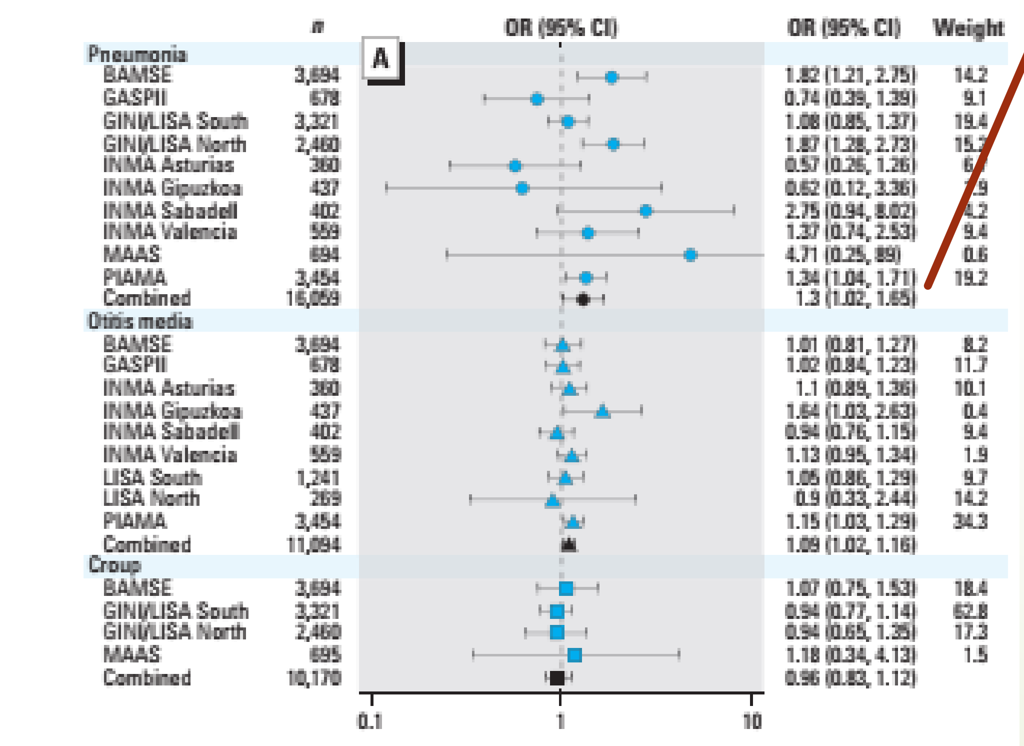
∆ 0-6
○ 7-13
□ 14-20
◊ 21-27

Air Pollution and Respiratory Infections during Early Childhood: An Analysis of 10 European Birth Cohorts within the ESCAPE Project

Elaina A. MacIntyre,[1] Ulrike Gehring,[2] Anna Mölter,[3] Elaine Fuertes,[1,4] Claudia Klümper,[5] Ursula Krämer,[5] Ulrich Quass,[6] Barbara Hoffmann,[5,7] Mireia Gascon,[8,9] Bert Brunekreef,[2,10] Gerard H. Koppelman,[11,12] Rob Beelen,[2] Gerard Hoek,[2] Matthias Birk,[1] Johan C. de Jongste,[13] H.A. Smit,[10] Josef Cyrys,[14] Olena Gruzieva,[15] Michal Korek,[15] Anna Bergström,[15] Raymond M. Agius,[3] Frank de Vocht,[3] Angela Simpson,[16] Daniela Porta,[17] Francesco Forastiere,[17] Chiara Badaloni,[17] Giulia Cesaroni,[17] Ana Esplugues,[9,18] Ana Fernández-Somoano,[9,19] Aitana Lerxundi,[20,21] Jordi Sunyer,[8,9,22,23] Marta Cirach,[8,9] Mark J. Nieuwenhuijsen,[8,9] Göran Pershagen,[15] and Joachim Heinrich[1]

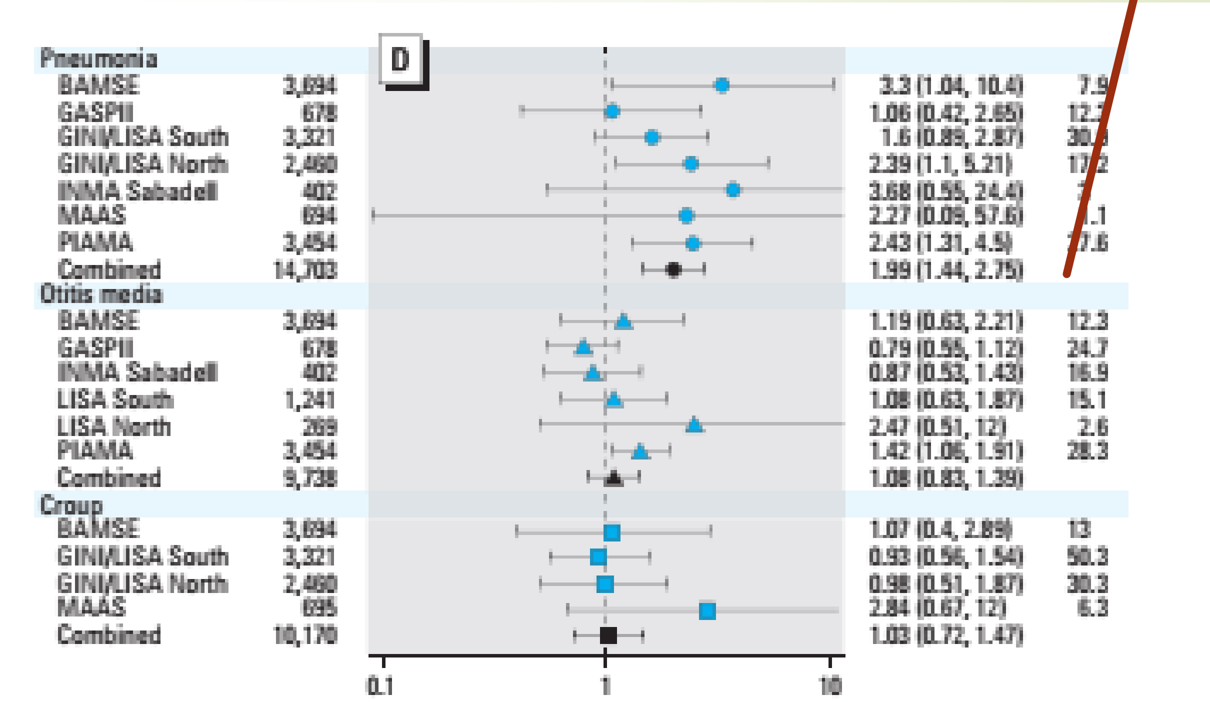
- Follow-up of 10 birth cohorts, different countries
- Follow-up pneumonia, laryngitis and otitis
- Exposure modelling

1.3 (1.02, 1.65)



NO_2

1.99 (1.44, 2.75)



PM 2.5

Table 2. Combined estimates from random-effects meta-analyses for residential air pollution and respiratory infections during early life (up to 36 months).[a]

	Crude[b]			Adjusted[c]		
	OR (95% CI)	I^2	*p*-Value	OR (95% CI)	I^2	*p*-Value
Pneumonia						
NO_2	1.25 (1.04, 1.50)*	37.1	0.112	1.30 (1.02, 1.65)*	52.9	0.024
NO_x	1.23 (1.06, 1.41)*	22.2	0.239	1.26 (1.04, 1.52)*	44.0	0.066
$PM_{2.5}$	2.13 (0.82, 5.49)	79.7	0.000	2.58 (0.91, 7.27)	81.7	0.000
$PM_{2.5}$ absorbance	1.78 (1.30, 2.43)*	0	0.734	1.99 (1.44, 2.75)*	0	0.663
PM_{10}	1.55 (1.03, 2.34)*	29.2	0.205	1.76 (1.00, 3.09)*	51.2	0.051
Coarse PM	1.23 (1.02, 1.47)*	0	0.626	1.24 (1.03, 1.50)*	0	0.579
Traffic, nearest street	1.08 (1.03, 1.14)*	0	0.997	1.09 (1.03, 1.15)*	0	0.969
Traffic, major streets	1.19 (1.08, 1.31)*	0	0.979	1.21 (1.09, 1.34)*	0	0.843

Table 3. Adjusted combined estimates for air pollution exposure at the birth address and respiratory infection by year of life [OR (95% CI)].

	Pneumonia[a] (*n* = 12,891)	Otitis media[b] (*n* = 8,722)	Croup[c] (*n* = 9,101)
Respiratory infections during the first year[d] of life			
NO_2	1.47* (1.15, 1.89)	1.19* (1.07, 1.33)	1.05 (0.83, 1.32)
NO_x	1.45* (1.21, 1.75)	1.09 (0.98, 1.22)	1.10 (0.90, 1.36)
$PM_{2.5}$	4.06* (1.93, 8.57)	1.21 (0.64, 2.28)	1.15 (0.67, 1.97)
$PM_{2.5}$ absorbance	2.71* (1.68, 4.37)	1.32 (0.99, 1.75)	1.04 (0.59, 1.83)
PM_{10}	1.77* (1.18, 2.67)	1.24 (0.76, 2.02)	1.07 (0.75, 1.53)
Coarse PM	1.46* (1.11, 1.92)	1.16 (0.80, 1.70)	1.02 (0.80, 1.30)
Traffic, nearest street	1.14* (1.07, 1.22)	0.99 (0.94, 1.04)	1.03 (0.94, 1.13)
Traffic, major streets	1.31* (1.15, 1.50)	1.03 (0.93, 1.14)	1.00 (0.81, 1.24)
Respiratory infections during the second year[e] of life			
NO_2	1.40* (1.04, 1.88)	1.07 (0.96, 1.20)	0.92 (0.78, 1.09)
NO_x	1.29* (1.07, 1.55)	1.02 (0.89, 1.17)	0.92 (0.78, 1.08)
$PM_{2.5}$	2.65 (0.63, 11.2)	1.06 (0.64, 1.74)	0.76 (0.51, 1.15)
$PM_{2.5}$ absorbance	1.90 (0.93, 3.87)	1.20 (0.80, 1.79)	0.89 (0.59, 1.35)
PM_{10}	1.42 (0.99, 2.03)	1.00 (0.84, 1.19)	0.83 (0.63, 1.09)
Coarse PM	1.24 (0.98, 1.56)	1.00 (0.89, 1.13)	0.89 (0.73, 1.08)
Traffic, nearest street	1.05 (0.98, 1.13)	0.96 (0.90, 1.03)	0.93 (0.81, 1.07)
Traffic, major streets	1.10 (0.90, 1.34)	0.96 (0.83, 1.10)	1.00 (0.88, 1.14)

Risk of PM2.5 and pneumonia during the first 2 years of life!!

Associations between Source-Specific Particulate Matter and Respiratory Infections in New York State Adults

Daniel P. Croft,[*,†] Wangjian Zhang,[⊥] Shao Lin,[⊥] Sally W. Thurston,[‡] Philip K. Hopke,[†,§,#] Edwin van Wijngaarden,[§,∥] Stefania Squizzato,[§] Mauro Masiol,[§] Mark J. Utell,[†,∥] and David Q. Rich

FLU

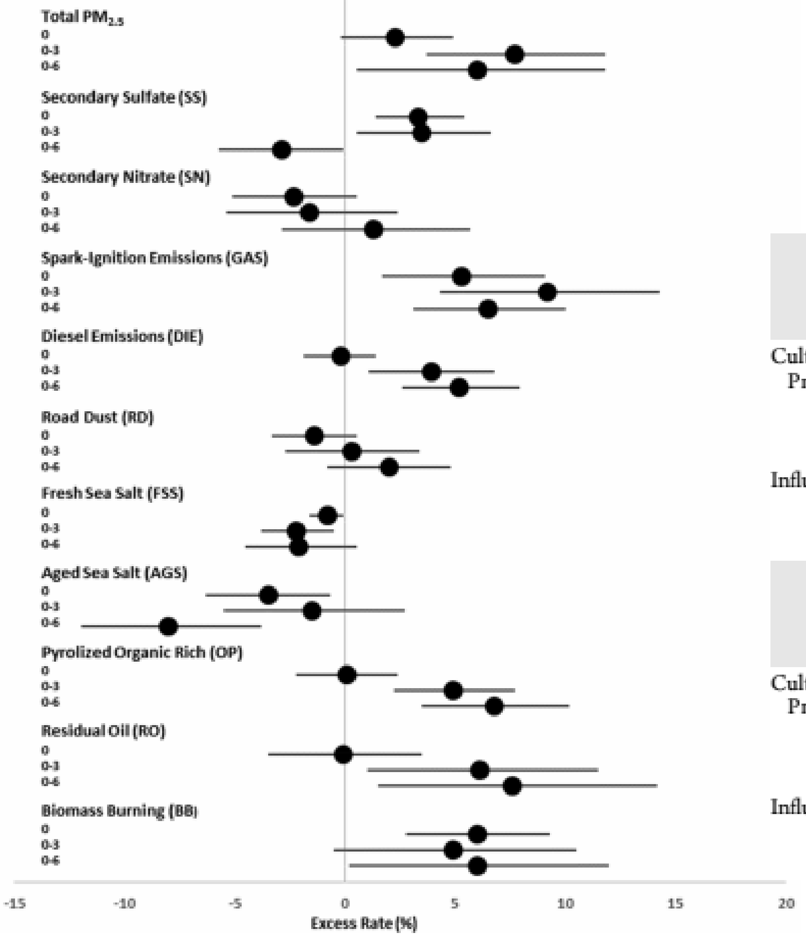
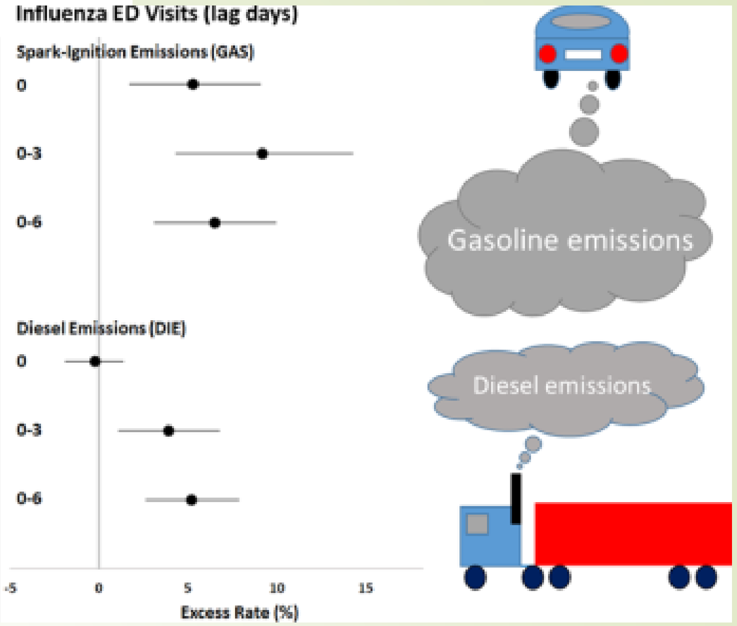


Figure 2. Excess rate of influenza ED visits associated with each interquartile range increase in total $PM_{2.5}$ and source-specific $PM_{2.5}$ concentrations on lag day(s) 0, 0−3, and 0−6.



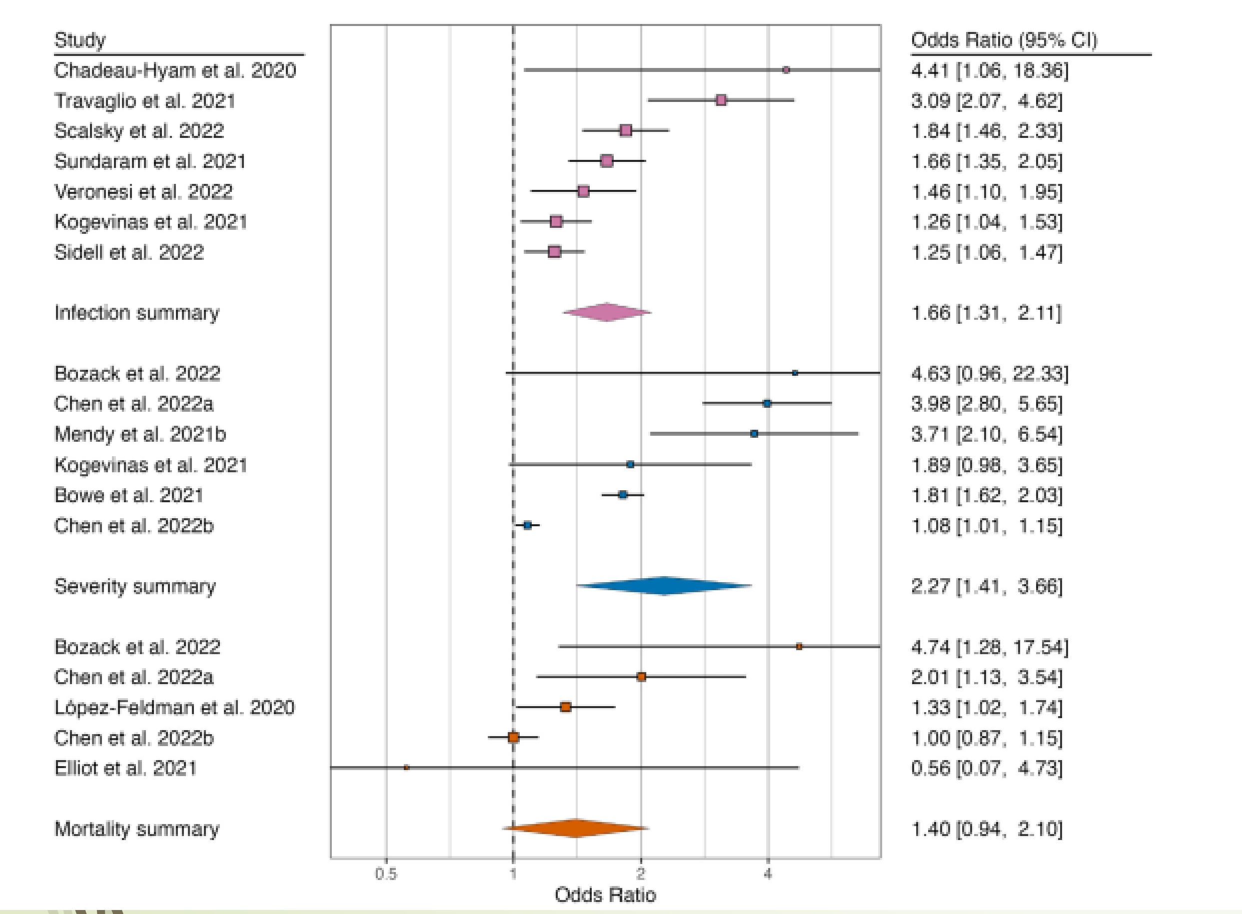
Outcome	Lag	Total $PM_{2.5}$ (in the PMF File) N cases	IQR ($\mu g/m^3$)	Excess Rate % (95% CI)	p-value	Secondary Sulfate (SS) N cases	IQR ($\mu g/m^3$)	Excess Rate % (95% CI)	p-value
Culture-Negative Pneumonia	0	22 024	6	0.4 (−1.4, 2.3)	0.67	21 540	2.1	0.7 (−0.6, 2.0)	0.30
	0−3	15 403	4.84	0.3 (−2.2, 2.8)	0.83	14 826	1.75	3.0 (1.1, 5.0)	0.002
	0−6	16 750	4.05	−1.3 (−3.7, 1.2)	0.30	16 040	1.41	1.4 (−0.5, 3.3)	0.14
Influenza	0	11 490	5.7	2.3 (−0.2, 4.9)	0.07	11 293	1.74	3.3 (1.4, 5.4)	<0.001
	0−3	7741	4.93	7.7 (3.7, 11.8)	<0.001	7530	1.47	3.5 (0.5, 6.6)	0.02
	0−6	8509	6.03	6.0 (0.5, 11.8)	0.03	8190	1.18	−2.9 (−5.7, −0.1)	0.04

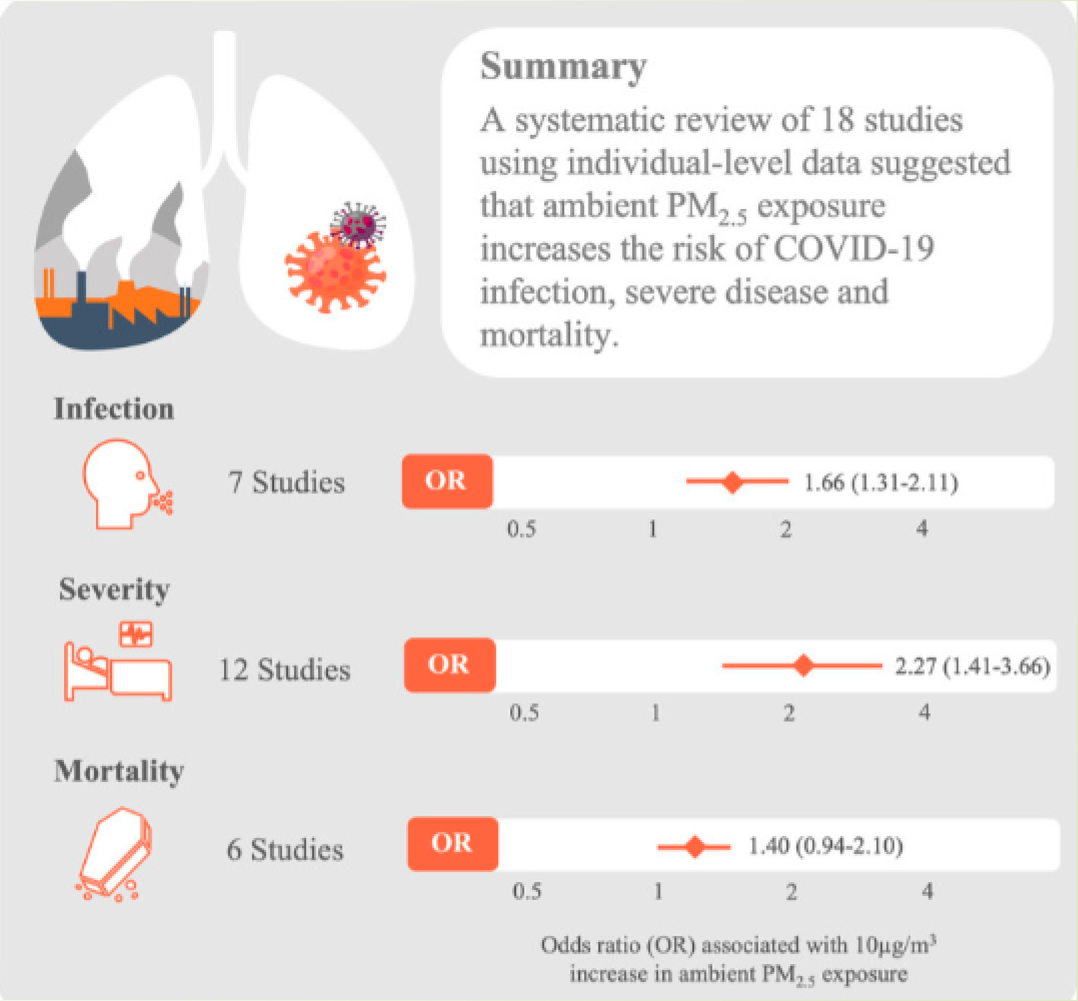
Outcome	Lag	Spark Ignition Emissions (GAS) N cases	IQR ($\mu g/m^3$)	Excess Rate % (95% CI)	p-value	Diesel (DIE) N cases	IQR ($\mu g/m^3$)	Excess Rate % (95% CI)	p-value
Culture-Negative Pneumonia	0	21 540	2.68	1.5 (−1.6, 4.7)	0.36	21 540	0.49	−0.8 (−2.0, 0.4)	0.20
	0−3	14 826	1.73	0.5 (−2.9, 4.0)	0.77	14 826	0.71	−1.9 (−4.9, 1.2)	0.23
	0−6	16 040	1.44	1.3 (−2.0, 4.7)	0.44	16 040	0.76	−3.7 (−7.4, 0.2)	0.06
Influenza	0	11 293	2.26	5.3 (1.7, 9.1)	0.004	11 293	0.43	−0.2 (−1.9, 1.4)	0.77
	0−3	7530	1.77	9.2 (4.3, 14.3)	<0.001	7530	0.38	3.9 (1.1, 6.8)	0.01
	0−6	8190	1.09	6.5 (3.1, 10.0)	<0.001	8190	0.33	5.2 (2.6, 7.9)	<0.001

Particulate matter air pollution and COVID-19 infection, severity, and mortality: A systematic review and meta-analysis

Nicola Sheppard [a], Matthew Carroll [b], Caroline Gao [c,d], Tyler Lane [c,*]

COVID-19



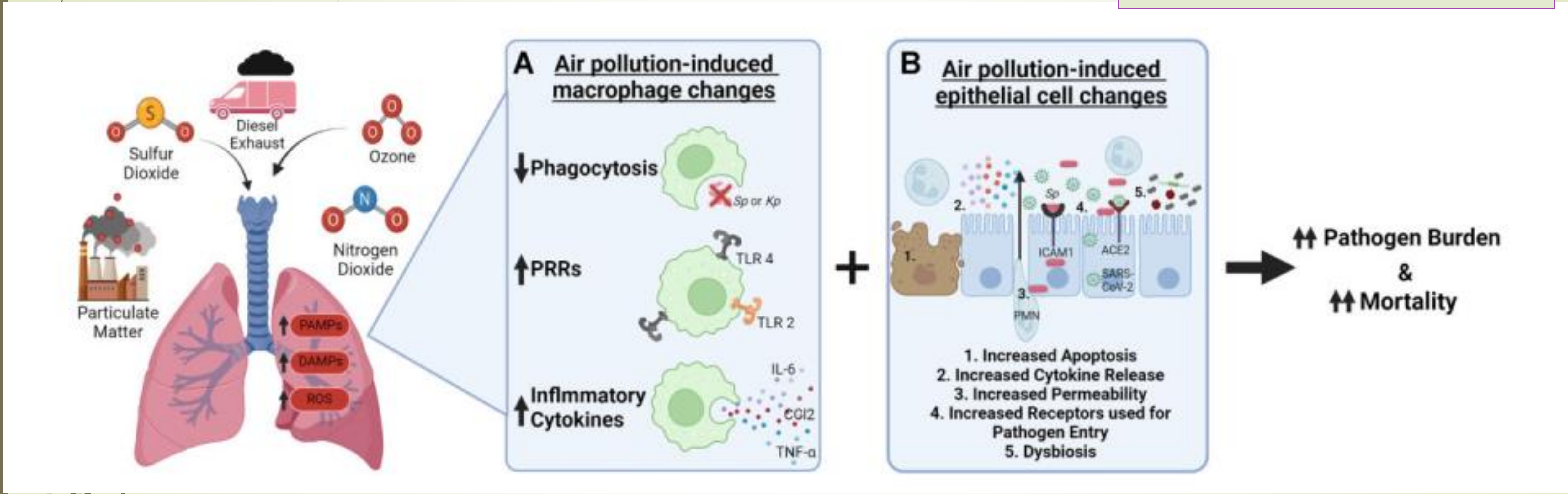


PM2.5, O3 and NO2: oxidative stress and decreased host response
Chauhan, 2003, Ciencewicki 2007, Kelly 2003

Diesel and O3 decrease some proteins in surfactant
Ciencewicki 2007, Gowdy 2008

Phagocytosis Alteration
Becker 1999, Chauhan 2003

Downregulation des toll-like receptors 4 of alveolar macrophages exposed to PM
Morrow 1988



Damage to integrity of the epithelial barrier by PM
Carballo 2011, Wang 2012

Decreased ciliary movements after exposure to pollutants and change in viscosity
Grose 1980, Pedersen 1990, Xiao 2013

Increased angiotensin receptor 2 expression in the respiratory epithelium (SARS-CoV-2)
Hoffmann 2020, Lin 2018, Paital 2021

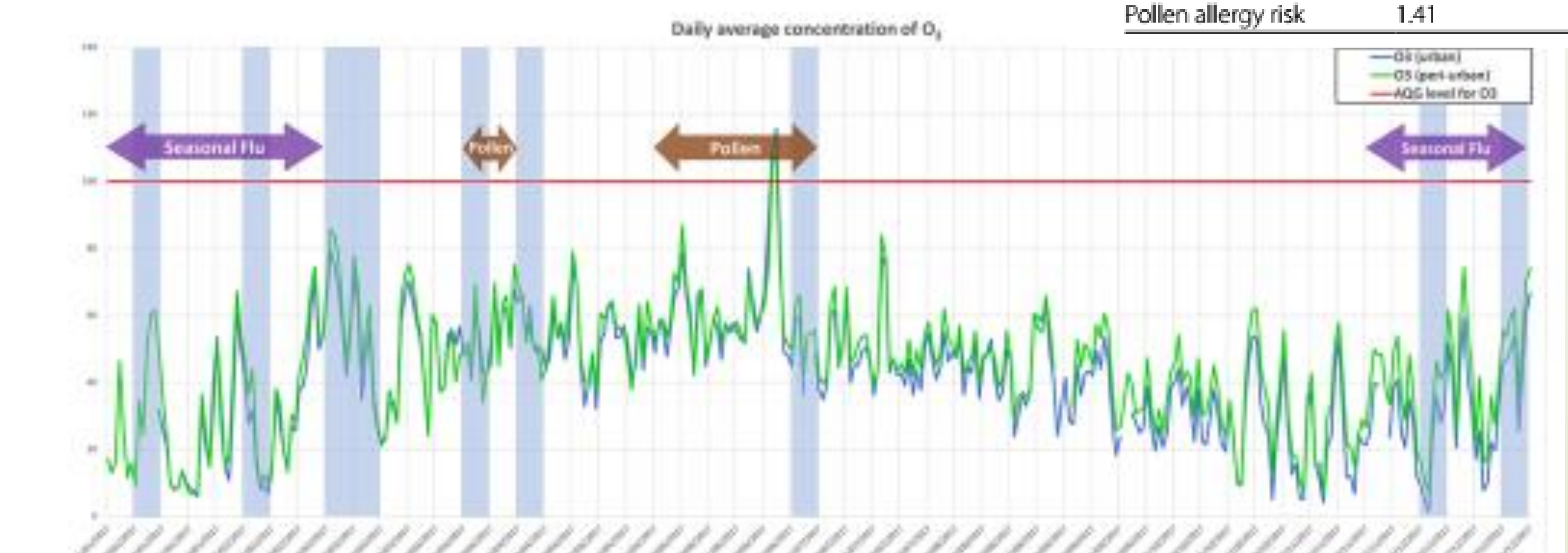
And for chronic diseases?

Association between acute exacerbation of chronic obstructive pulmonary disease and short-term exposure to ambient air pollutants in France

Damien Basille[1,2*], Lola Soriot[1], Florence Weppe[1], Peggy Desmettres[3], Paulo Henriques[4], Nicolas Benoit[5], Stéphanie Devaux[1], Momar Diouf[6], Vincent Jounieaux[1,2] and Claire Andrejak[1,2]

Table 2 Multivariate analysis on the daily risk of emergency room visits for acute exacerbation of COPD

	Relative risk (RR)	95%CI	*p*-value
$PM_{2.5}$	1.06	1.00–1.11	0.049
NO_2	1.02	1.00–1.05	0.073
O_3	1.01	1.00–1.03	0.114
PM_{10}	0.96	0.91–1.01	0.119
Hygrometry	1.00	0.98–1.02	0.739
Temperature	1.01	0.97–1.04	0.774
Influenza circulation	1.52	0.98–2.36	0.061
Pollen allergy risk	1.41	0.92–2.17	0.116



IMPACT DE L'EXPOSITION À LA POLLUTION ATMOSPHÉRIQUE D'ORIGINE AUTOMOBILE SUR LA MORBIDITÉ RESPIRATOIRE ET ALLERGIQUE AU COURS DE L'ENFANCE : LEÇONS DE LA COHORTE PARIS

// IMPACT OF TRAFFIC-RELATED AIR POLLUTION ON RESPIRATORY AND ALLERGIC MORBIDITY IN CHILDHOOD: LESSONS FROM THE PARIS COHORT

Associations entre l'exposition pré- et postnatale à la pollution atmosphérique d'origine automobile et l'incidence des diagnostics de maladies respiratoires et allergiques, chez les enfants de la cohorte Paris, entre 0 et 8-9 ans (N=1 014)

	Exposition prénatale à la PAA [a]	Exposition postnatale à la PAA [b]	
	Grossesse entière	1re année de vie	Entre la naissance et chaque date de point
Modèle de Cox	HRa [c] (IC95%)	HRa [d] (IC95%)	HRa [d] (IC95%)
Incidence du diagnostic d'asthme	0,86 [0,64-1,16]	1,21 [1,02-1,43]	1,19 [1,06-1,34]
Incidence du diagnostic de dermatite atopique	1,05 [0,89-1,23]	1,01 [0,92-1,10]	1,01 [0,94-1,08]
Incidence du diagnostic de rhume des foins	0,74 [0,47-1,18]	0,77 [0,57-1,03]	0,85 [0,67-1,08]

Finally

- Pollution = risk factors for occurrence of infection... and their severity
- Viruses, bacteria, fungi = factors that promote respiratory diseases and/or exacerbation of CRD
- Pollution = promotes exacerbations of chronic diseases
- And don't forget the link between PM2.5 and the occurrence of lung cancer
- Lung in interaction with environment!

Cour des comptes

Mai 2024

LA SANTÉ RESPIRATOIRE

Un enjeu de « santé environnement » insuffisamment pris en considération

La Cour des comptes recommande d'intégrer la santé respiratoire dans la stratégie nationale de santé

One Health!

Ambient air
=
Environment

Oral cavity

LUNG

DIGESTIVE TRACT

Permanent interactions

« An healthy microbiote for an healthy body»

Dysbiosis: Disease Conditions
Therapeutic perspectives!!

« Symbiosis »

Energy – Protection – Homeostasis

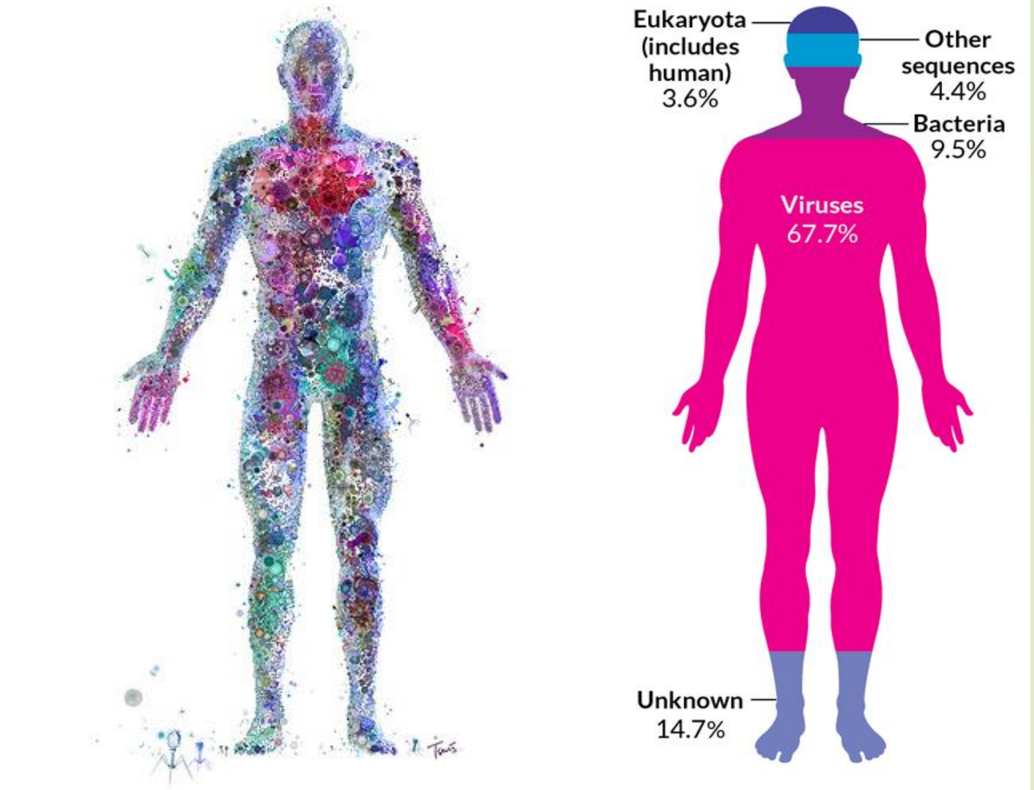
« Capital Flora »

Environmental and genetic factors
Fragility of the microbiota

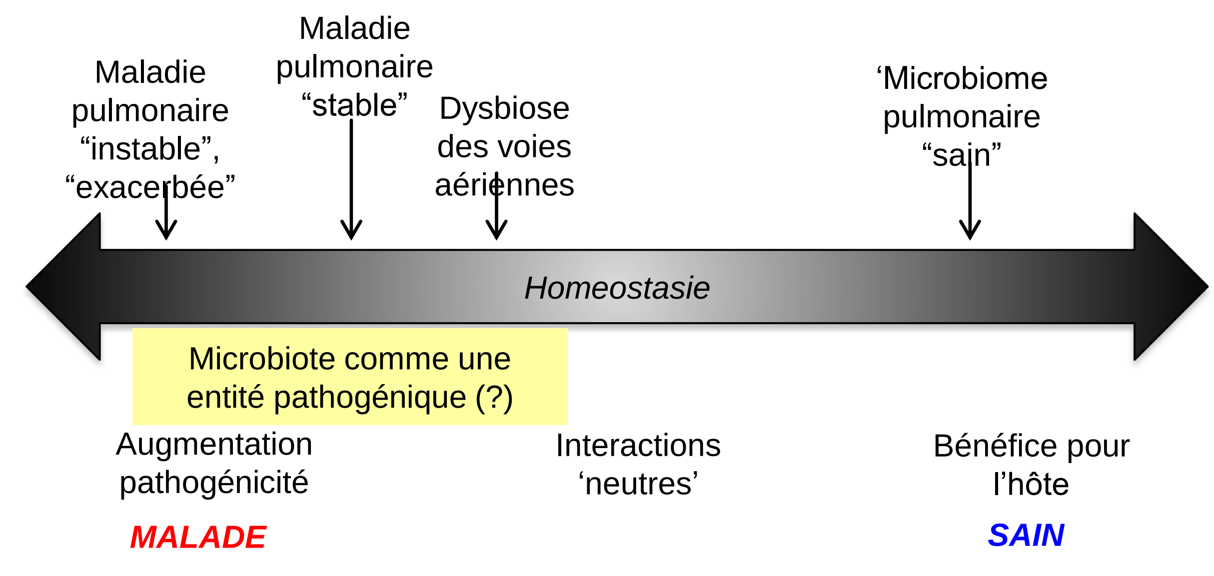
One Health!

Microbiota: All microorganisms living in humans

- Bacteria
- Virus and phage
- Fungi



Microbiota in humans… and in environment!



And EXPOSOME….

Exposome

The exposome: from concept to utility

Christopher Paul Wild

The exposome: a new paradigm to study the impact of environment on health

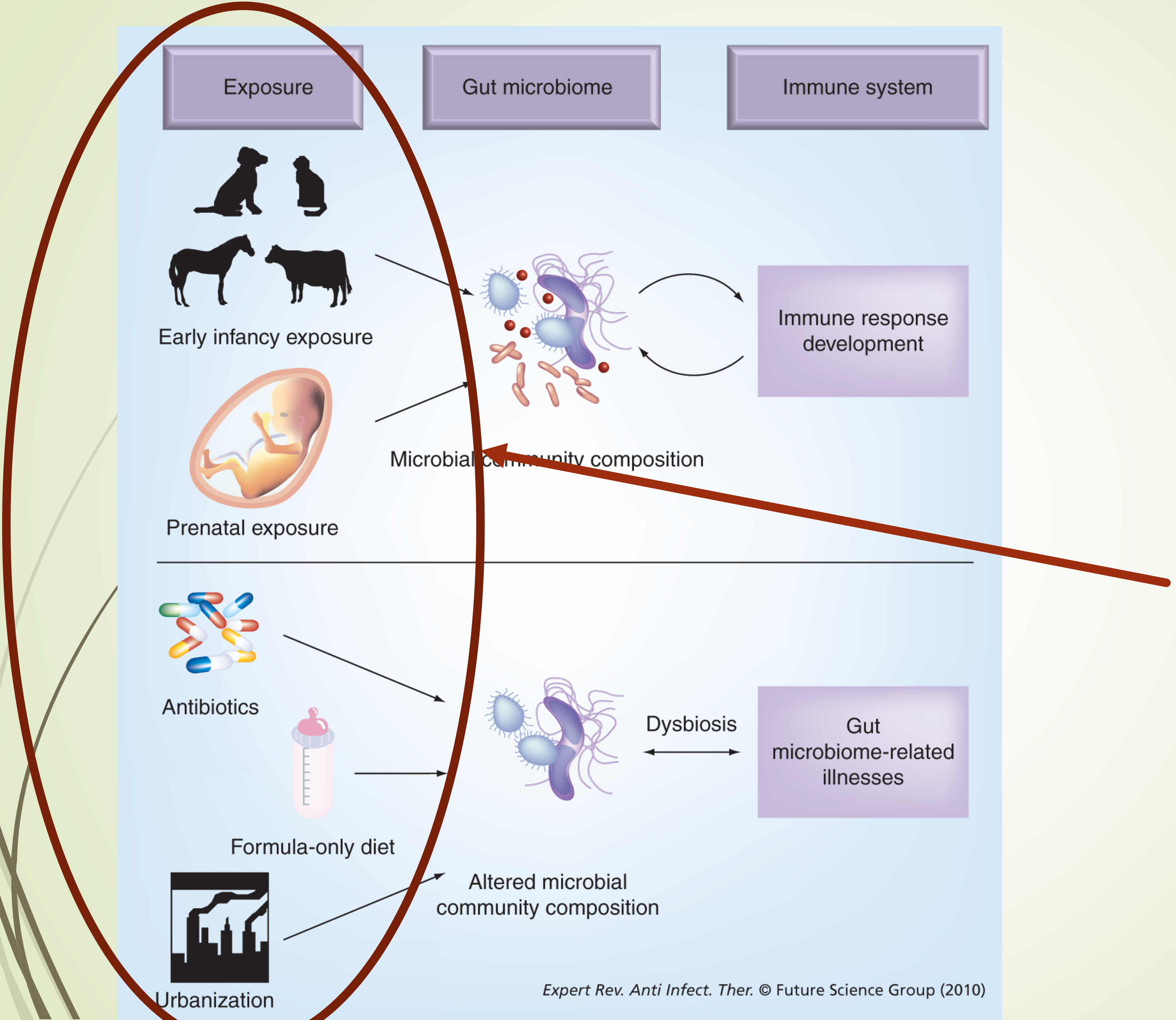
Martine Vrijheid

The exposome concept: a challenge and a potential driver for environmental health research

Why do some people develop the disease and others don't? What evolution?

The exposome concept: how has it changed our understanding of environmental causes of chronic respiratory diseases?

Alicia Guillien [1,7], Manosij Ghosh[2,7], Thomas Gille [3,4,5] and Orianne Dumas [6]



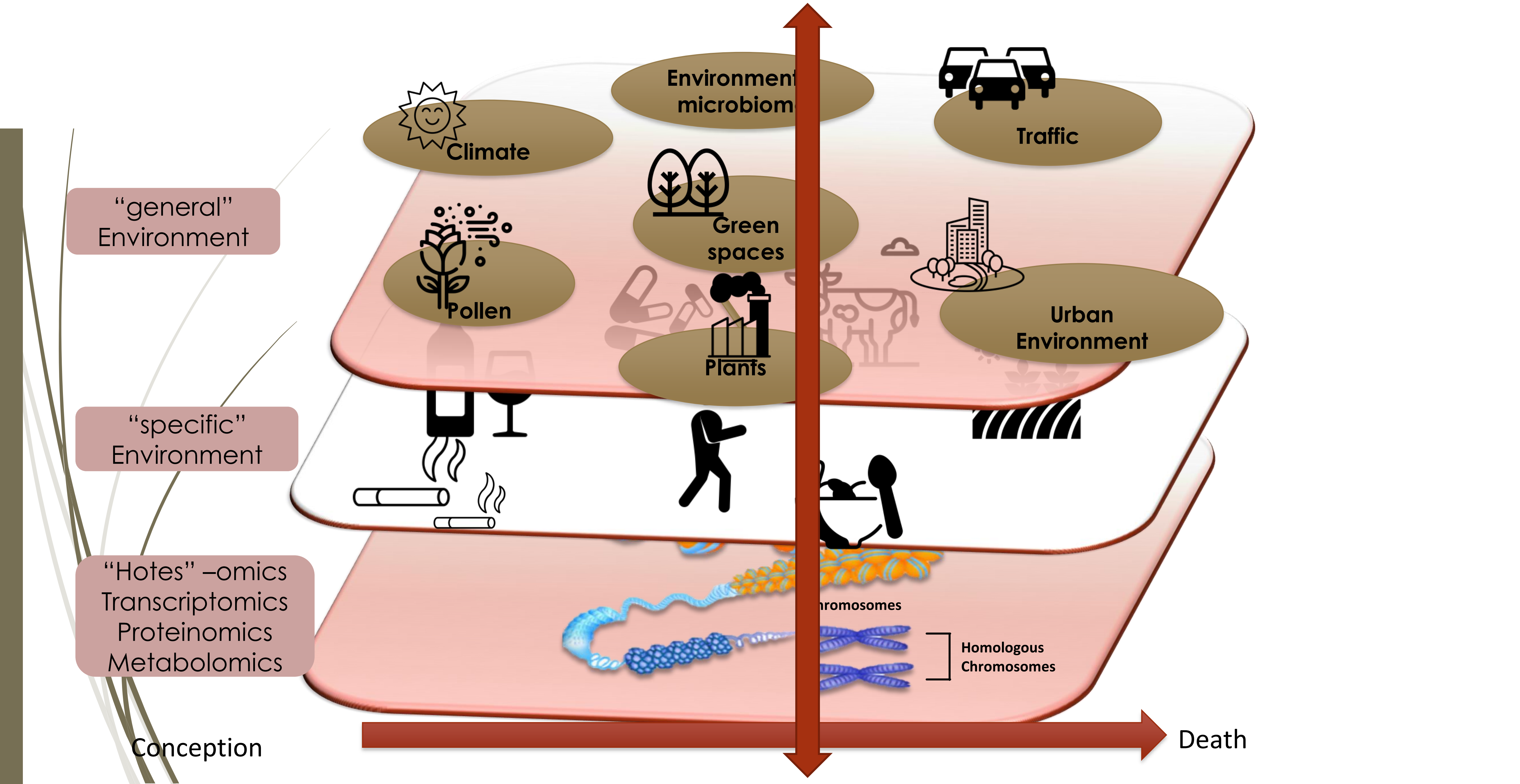
And so go back to microbiome?

Exposome ?

Definition=Exposome

- Defined for the 1st time by Wild in 2005
- **EVERY exposure** for each individual from **CONCEPTION to DEATH**, as a complement to the genome

- 3 categories
  - Internal
  - "Specific" external
  - "General" external



"general" Environment
"specific" Environment
"Hotes" –omics
Transcriptomics
Proteinomics
Metabolomics
Climate
Environment
microbiom
Traffic
Green
spaces
Pollen
Urban
Environment
Plants
hromosomes
Homologous
Chromosomes
Conception
Death

Exposome: where are we?


Published in final edited form as:
Exposome. 2021 ; 1(1): . doi:10.1093/exposome/osab001.

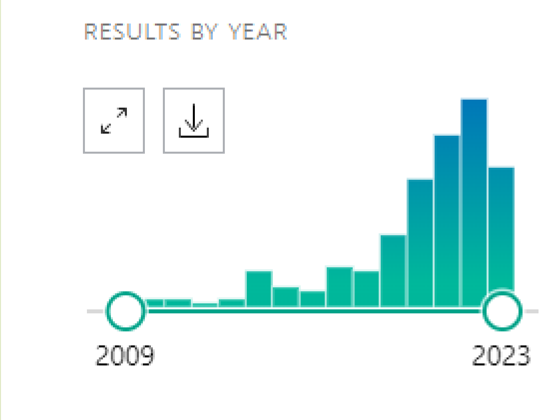
Exposome: a new field, a new journal

Gary W. Miller, Ph.D. [Editor-in-Chief]

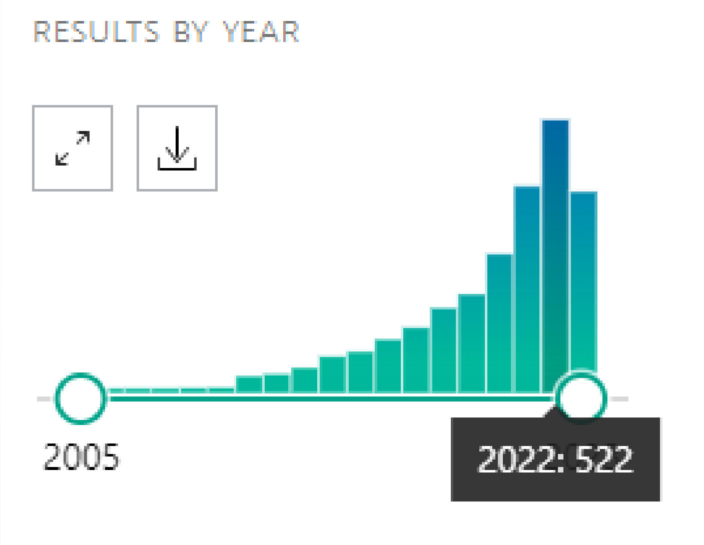
Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, U.S.A.

"I would like to suggest that there is need for an 'exposome' to match the genome…"

Christopher Wild (Wild, 2005).



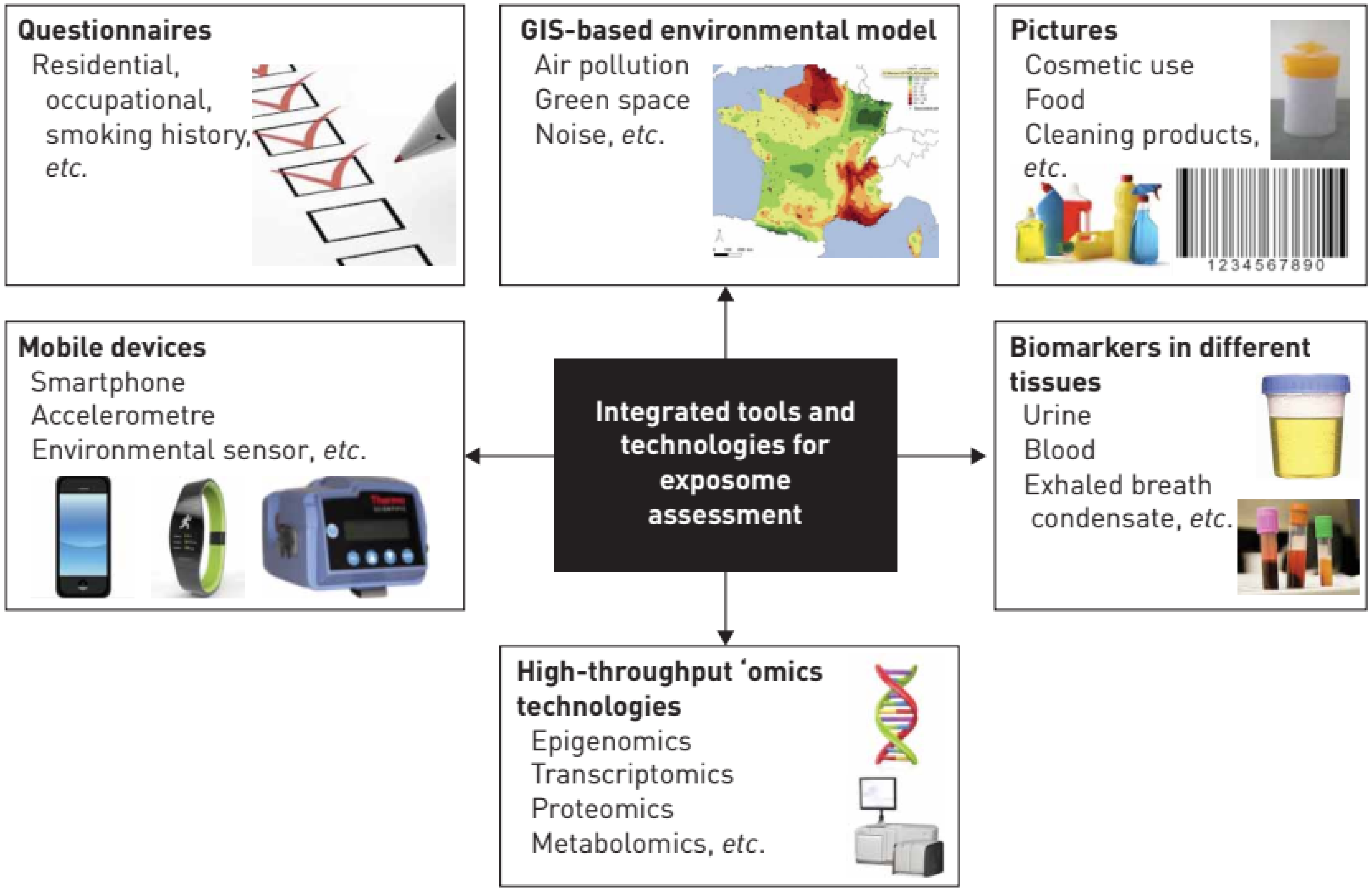
192 results on « "exposome" AND "(respiratory disease OR asthma OR COPD OR cystic Fibrosis OR fibrosis)"



2030 results sur « exposome »
With 70 studies….

The exposome concept: a challenge and a potential driver for environmental health research

Valérie Siroux[1,2,3], Lydiane Agier[1,2,3] and Rémy Slama[1,2,3]



Challenges

- Consideration of ALL exposures
- ON THE WHOLE OF THE PERSON'S LIFE
- Exposure = a different impact according to each stage of life (birth, childhood, adolescence, adult, elderly, diseases, treatments....!)
  - So different approaches possible
  - Large and complex databases... therefore complex analysis methods
    - Often taken into account factors successively by univariate analysis (Exposome Wide Association Study, ExWAS) and then multivariate (adjusted for co-exposures) (e.g. Deletion-Substitution-Addition (DSA) algorithm) regression-based models
    - Good for assessing many exposures for many pathologies and their fate
      - No consideration of the interaction/addition effects of the different effects.
    - Others approaches =
      - Analysis based of clusters to identifya specific profile of a risk-exposition to a disease
      - Analysis with intermediate biological factors
  - Many different methods so studies with non-comparable results

What have we already learned?

	Farmer, no. (%)		Nonfarmer, no. (%)		P value for difference
	No.	Percent	No.	Percent	
Population at birth	530	46.8	603	53.2	
Male sex	266	51.4	294	51.4	.988
Center					
Austria	105	47.7	115	52.3	.389
Switzerland	107	44.2	135	55.8	
France	94	46.3	109	53.7	
Germany	112	44.1	142	55.9	
Finland	112	52.3	102	47.7	
Education					
Low	116	21.9	86	14.3	<.001
Medium	234	44.2	253	42.0	
High	180	34.0	264	43.8	
Maternal history of asthma	38	7.2	61	10.1	.080
Maternal history of hay fever	108	20.4	196	32.5	<.001
Maternal farming exposure during pregnancy*					
Contact with stable	464	89.6	107	18.9	<.001
Contact with barn	362	70.0	65	11.5	<.001
Contact with >2 farm animals	208	39.2	64	10.7	<.001
Contact with cats and/or dogs	430	81.3	233	38.6	<.001
Farm milk consumption	406	76.6	98	16.3	<.001
Only boiled farm milk	94	17.8	27	4.5	<.001
Any unboiled farm milk	310	58.7	70	11.6	
Smoking	46	8.7	112	18.6	<.001
Child's farming exposure during first year of life*†					
Population at year 1	493	47.7	540	52.3	
Child living on a farm	486	98.6	10	1.9	<.001
Regular visit to farm	487	99.0	77	14.4	<.001
Regular stay in stable	332	71.7	40	7.6	<.001
Contact with cats and/or dogs	402	81.5	188	34.8	<.001
Farm milk consumption	283	57.8	51	9.5	<.001
Only boiled farm milk	141	28.8	27	5.1	<.001
Any unboiled farm milk	142	29.0	24	4.5	
Unboiled farm milk after month 10	78	16.0	15	2.8	<.001
Unboiled farm milk before month 10	60	12.3	8	1.5	
Early introduced solid food items (food score)					
0	51	10.3	102	18.9	<.001
1-3	191	38.7	214	39.6	
4-6	174	35.3	157	29.1	
7-11	77	15.6	67	12.4	
Smoking during breast-feeding	18	(3.8)	35	(6.8)	.034
Any breast-feeding					
>6 mo	240	48.7	285	52.8	.027
3-6 mo	118	23.9	96	17.8	
≤3 mo	89	18.1	120	22.2	
Never	46	9.3	39	7.2	
≥2 Siblings	235	47.7	111	20.6	<.001

Prenatal and early-life exposures alter expression of innate immunity genes: The PASTURE cohort study

	mRNA expression, GMR (95% CI)									
Exposure during pregnancy	*CD14*	*TLR1*	*TLR2*	*TLR4*	*TLR5*	*TLR6*	*TLR7*	*TLR8*	*TLR9*	P value of simple MANOVA
Farming			1.08† (1.00-1.16)		1.09† (1.00-1.18)		1.17† (1.04-1.31)	1.16‡ (1.06-1.28)		.041
Farm milk consumption										
No										.047
Only boiled farm milk										
Any unboiled farm milk					1.10† (1.01-1.20)			1.14† (1.03-1.26)		
Maternal farm work										.301
Contact with stable								1.11† (1.01-1.22)		.174
Contact with barn										.376
Contact with number of farm animals										
0										.206
1-2										
3-4										
Cats or dogs										.450
Smoking						0.85†,§ (0.75-0.97)		0.86† (0.74-0.99)		.279
Male sex		0.89†,§ (0.81-0.98)	0.90†,§ (0.85-0.98)							.002
Center										<.001

Environmental influences on childhood allergies and asthma — The Farm effect

Remo Frei[1,2] | Kristina Heye[3,2] | Caroline Roduit[2,3,4]

Exposure	Host
Farming intrauterin	TNF-alpha, IFN-gamma T_H1 Regulatory T cells
Farming school-age	T_H1 IL10, IL12, IFN-gamma
N-glycolylneuraminic acid	Regulatory T cells, IL-10
Arabinogalactan	Less co-stimulatory molecules Less proinflammatory cytokines
LPS/endotoxin	Less TNF-alpha, INF-gamma, IL-10, IL-12 TLR expression SOCS4, IRAK-2 IL-10, TGF-beta A20 mediated reduced cytokine secretion

Exposure	Host
Environmental microbes	MyD88 and Trif dependent inhibition of airway hyperreactivity and eosinophilia Less proinflammatory cytokines
Breast feeding	sIgA TGF-beta, IL-10
Food diversity	Colonization with butyrate-producing bacteria SCFA Regulatory T cells, IL-10
Farm-milk	Bovine serum albumin (BSA), α-lactalbumin, β-lactoglobulin Anti- β-lactoglobulin IgA and IgG TGF-beta ω-3 polyunsaturated fatty acids Regulatory T cells TLR4, TLR5, TLR6 Gene-environment CD14/-1721

Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort

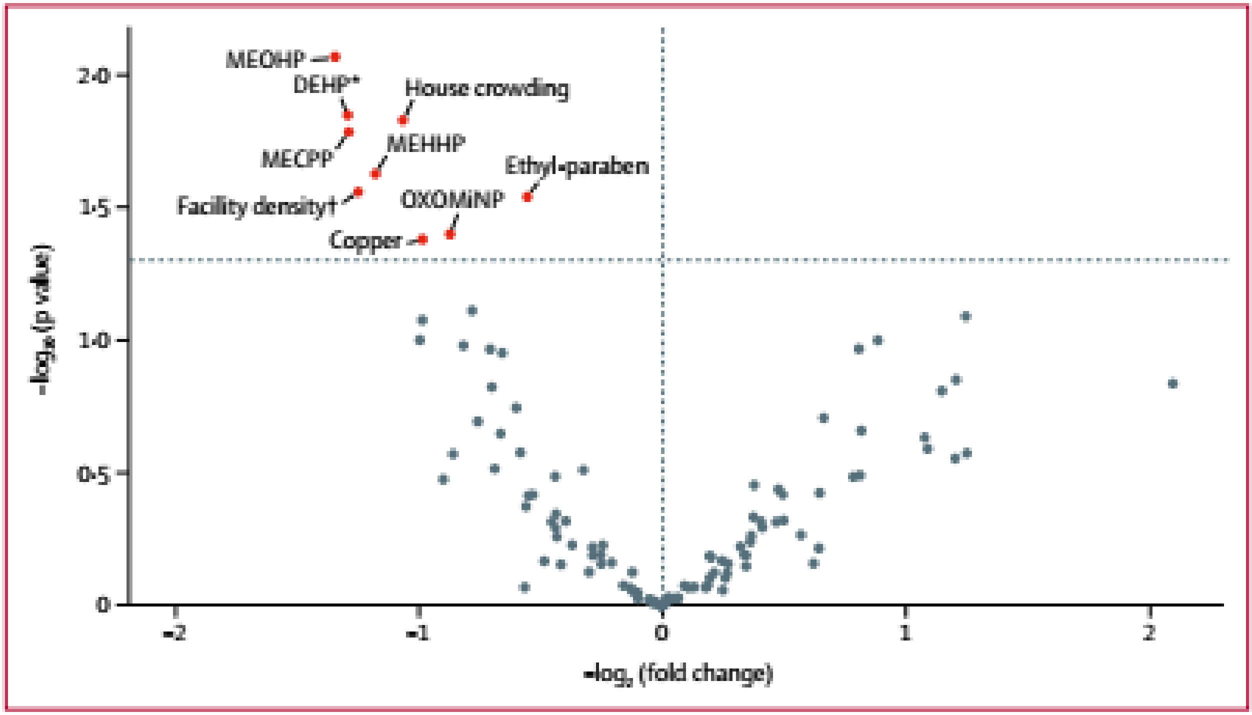
Lancet Planet Health 2019; 3: e81–92

	Description
Atmospheric pollutants	NO_2, $PM_{2.5}$, PM_{10}, PM_{abs}
UV	Ambient UV radiation levels
Surrounding natural space	Average Normalized Difference Vegetation Index within buffers of 100 m; presence of a major green space (ie, grass, trees, vegetation) or blue space (ie, visible water) within a distance of 300 m
Meteorology	Air temperature as measured by meteorological stations (mean, minimum, and maximum); humidity percentage as measured by meteorological stations; atmospheric pressure data from the ESCAPE project
Built environment	Population density: inhabitants per km²; building density: built area in m² of buildings per km² within a 300 m buffer; street connectivity: number of road intersections per km² within a 300 m buffer; accessibility: metres of bus public transport lines and number of bus public transport stops per km² within a 300 m buffer; facilities: facility richness index* and facility density index* within a 300 m buffer; land use evenness index†; walkability index‡ within a 300 m buffer
Traffic	Total traffic load of major roads within a 100 m buffer, total traffic load within a 100 m buffer, traffic density on nearest road, and inverse distance to nearest road
Road traffic noise	Night-time road noise levels, 24 h road noise levels
Organochlorine compounds	Blood concentrations of dichlorodiphenyldichloroethylene, dichlorodiphenyltrichloroethane, hexachlorobenzene, PCB-118, PCB-138, PCB-153, PCB-170, and PCB-180, with lipid adjustment
Brominated compounds	Blood concentrations of PBDE-47 and PBDE-153, with lipid adjustment
Perfluorinated alkylated substances	Blood concentrations of perfluorooctanoate, perfluorononanoate, perfluoroundecanoate, perfluorohexane sulphonate, and perfluorooctane sulphonate
Metals and essential elements	Whole blood concentrations of arsenic, cadmium, ceasium, cobalt, copper, lead, manganese, mercury, molybdenum, and thallium
Phthalate metabolites	Urine concentrations of monoethyl phthalate, mono-iso-butyl phthalate, mono-n-butyl phthalate, mono benzyl phthalate, mono-2-ethylhexyl phthalate, mono-2-ethyl-5-hydroxyhexyl phthalate, mono-2-ethyl-5-oxohexyl phthalate, mono-2-ethyl 5-carboxypentyl phthalate, mono-4-methyl-7-hydroxyoctyl phthalate, mono-4-methyl-7-oxooctyl phthalate, with creatinine adjustment
Phenols	Urine concentrations of methyl-paraben, ethyl-paraben, bisphenol A, propyl-paraben, N-butyl-paraben, oxybenzone, and triclosan, with creatinine adjustment
Organophosphate pesticide metabolites	Urine concentrations of dimethyl phosphate, dimethyl thiophosphate, dimethyl dithiophosphate, diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate, with creatinine adjustment
Water disinfection by-products§	Total concentration of total trihalomethanes, chloroform, and total brominated trihalomethanes estimated in tap water from water company concentration and distribution data
Indoor air¶	Prediction models for indoor air concentrations of NO_2, $PM_{2.5}$, PM_{abs}, benzene, and TEX (toluene, ethylbenzene, xylene) using panel study data from indoor air samplers
Lifestyle	Diet, physical activity, sleep duration, pets in the home
Socioeconomic capital	Frequency of contact with family and friends, social participation, family affluence score, house crowding

- Study on 1033 mother-child couples from the "Human Early-Life Exposome" cohort from 6 birth cohort studies (France, Greece, Lithuania, Norway, Spain, UK between 2003 and 2009)
- Pulmonary function testing for children (6 -12 years)
- 85 pre-natal and 125 postnatal exhibitions (outdoor, indoor, lifestyle, etc.)

Results

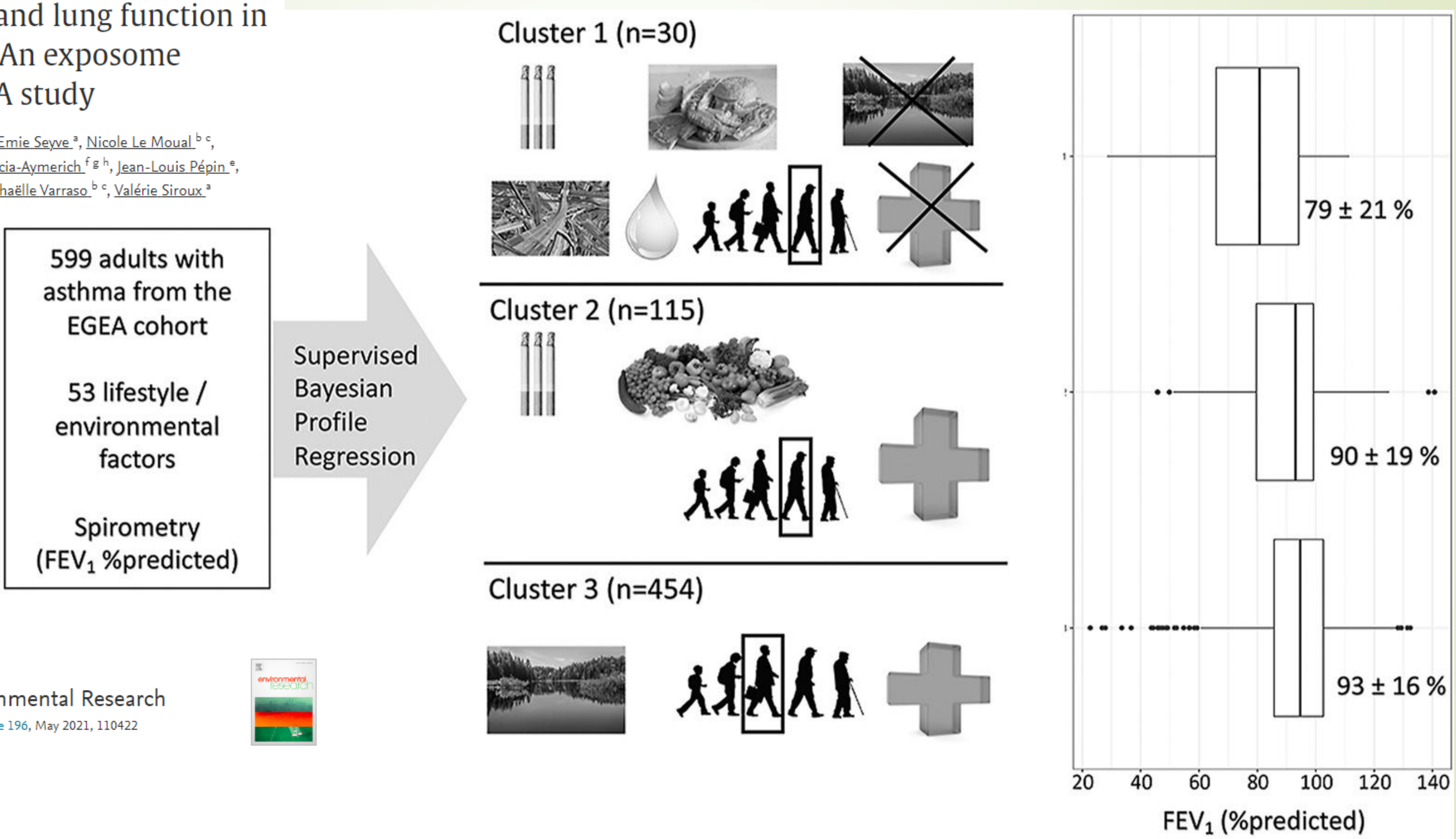
- 1033 children (median age 8.1 years)
- Average FEV1 98.8%
- Prenatal exposure to perfluoronenanoate (p=0.034) and perfluorooctanoate (p=0.030) associated with the lowest FEV1
- Correspondingly greater distance to the nearest route during pregnancy Inverse distance (p=0.030) associated with the highest FEV1
- 9 postnatal exposures: copper, ethyl-paraben, metabolites of phthalate metabolites, "overcrowded houses" and the density of buildings around schools



A french study the EGEA cohort

Profile of exposures and lung function in adults with asthma: An exposome approach in the EGEA study

Alicia Guillien [a], Johanna Lepeule [a], Emie Seyve [a], Nicole Le Moual [b c], Isabelle Pin [a d], Bruno Degano [e], Judith Garcia-Aymerich [f g h], Jean-Louis Pépin [e], Christophe Pison [i], Orianne Dumas [b c], Raphaëlle Varraso [b c], Valérie Siroux [a]



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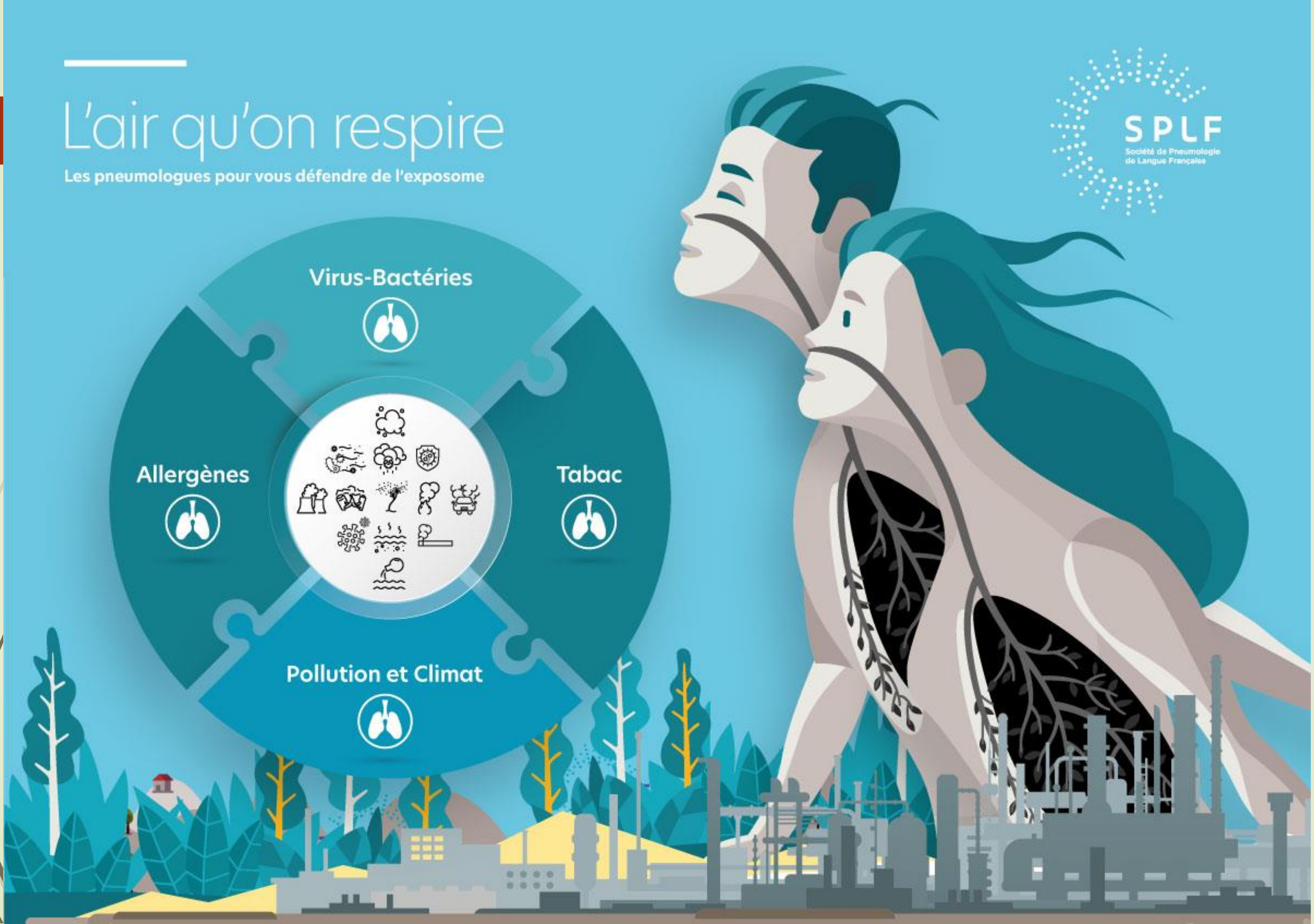
Environmental Research
Volume 196, May 2021, 110422

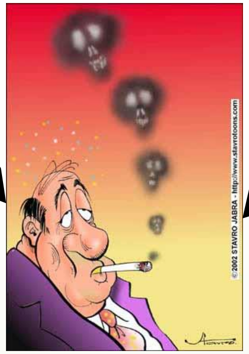

L'air qu'on respire
Les pneumologues pour vous défendre de l'exposome
SPLF
Société de Pneumologie de Langue Française
Virus-Bactéries
Allergènes
Tabac
Pollution et Climat

FHU RESPIRE

Environnment
- Microbiological
- Toxic
- Chemical

Emergence and re-emergence of respiratory pathogens

Integrated Approach to Respiratory Health



Take home messages

- Chronic respiratory diseases = public health issue
- UNDERDIAGNOSED!!! Screening!
- The lung in permanent interaction with its environment
  - To develop a healthy microbiota
- Microbiota subjected to various exposures
- Importance of the Exposome... Every exposition counts... from conception to death...
  - And in the exposition we count the behaviors: diet, urban or rural lifestyle, physical activity.....
  - Interest in knowing patient profiles for prevention or early diagnosis!
- Interest in taking care of our environment