

*Acute air pollution and respiratory
infections, including COVID-19*

Francesco Forastiere

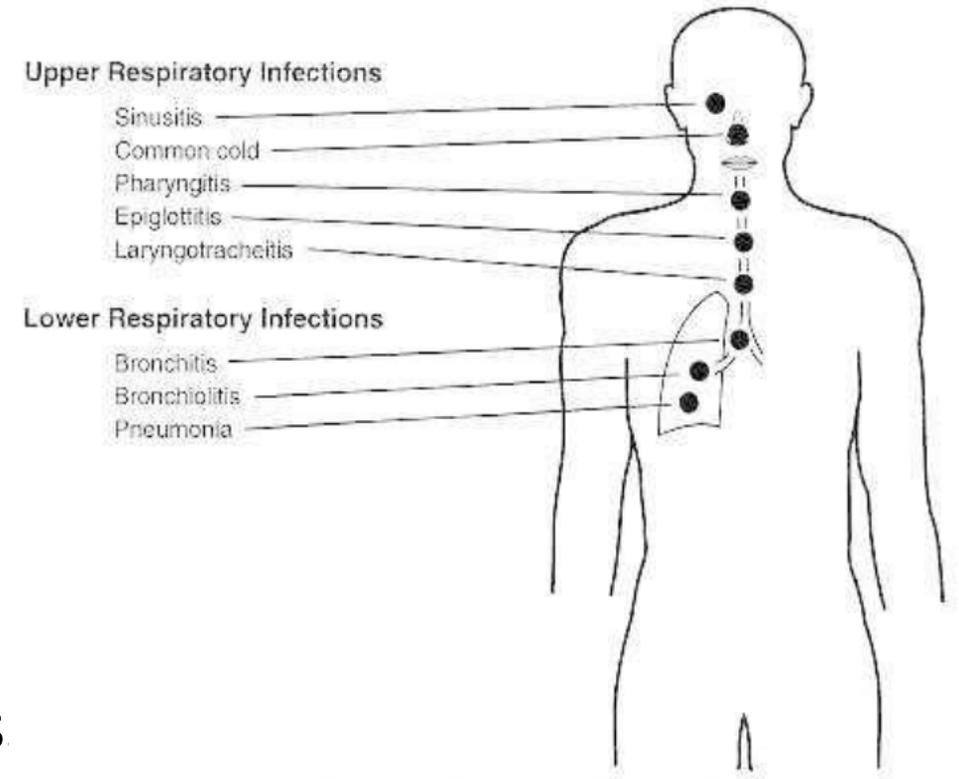
Irib-CNR, Rome, Italy

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Background

- Acute lower respiratory infections (ALRI) include pneumonia (infection of the lung alveoli), as well as infections affecting the lower airways such as acute bronchitis and bronchiolitis (infants and young children).
- These conditions are a leading cause of illness and death in children and adults/elderly across the world.

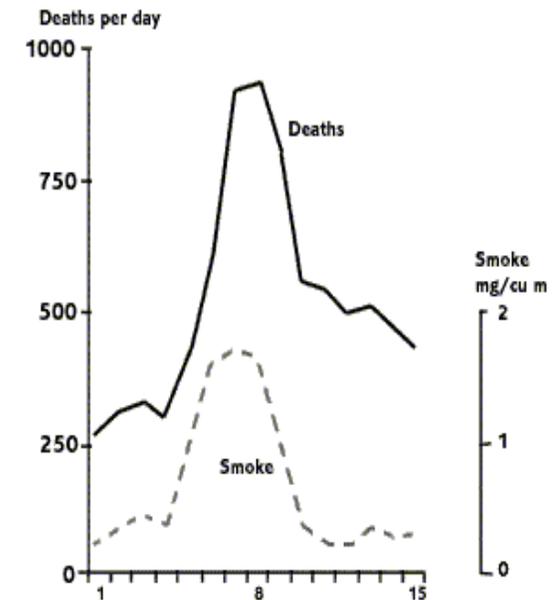


Lower respiratory infections

- Respiratory infection is usually caused by **viruses** (e.g. rhinovirus, respiratory syncytial virus (RSV); influenza; parainfluenza; and adenovirus) and **bacteria**. The most commonly identified pathogen for pneumonia is *Streptococcus pneumoniae* followed by *Haemophilus influenzae*, *Staphylococcus aureus*, and *Chlamydia pneumoniae*
- There is an **equilibrium** between the **virome/microbiome** (viruses and bacteria) and **host-related factors**; alterations of the **immune system** can subsequently increase susceptibility to viral infection and disease
- **Chronic mucus hypersecretion** is an important host factor that favors respiratory infections, this is the reason why **viral infections** are the major precipitants of acute exacerbations of **asthma** and **COPD**
- **Viruses promote** a pro-inflammatory mucosal response that accelerates the **growth** of potential **pathogens** such as *S pneumoniae* and *Haemophilus influenzae*
- Bronchitis and **bacterial pneumonia** occur commonly as **secondary to viral infections**

The London Smog, December 1952

Deaths from pneumonia increased threefold (very young and the elderly). Notifications for pneumonia increased 1.4-fold during the smog event, and 2.4- to 2.7-fold in the subsequent 2 weeks (compared same weeks 1947–1951).



Logan WP. Mortality in the London fog incident, 1952. *Lancet* 1953;1: 336–338.



Further Observations on London Fog, Waller & Lawther, BMJ 1957

FURTHER OBSERVATIONS ON
LONDON FOG

BY

ROBERT E. WALLER, B.Sc.

AND

PATRICK J. LAWTHOR, M.B., B.S., M.R.C.P.
Medical Research Council Group for Research on
Atmospheric Pollution, St. Bartholomew's Hospital, London

The first panel study:

- Daily measurement of smoke at St. Bartolomew's hospital
- Daily diary of respiratory conditions to 180 patients with chronic bronchitis (or COPD, as we call it today).

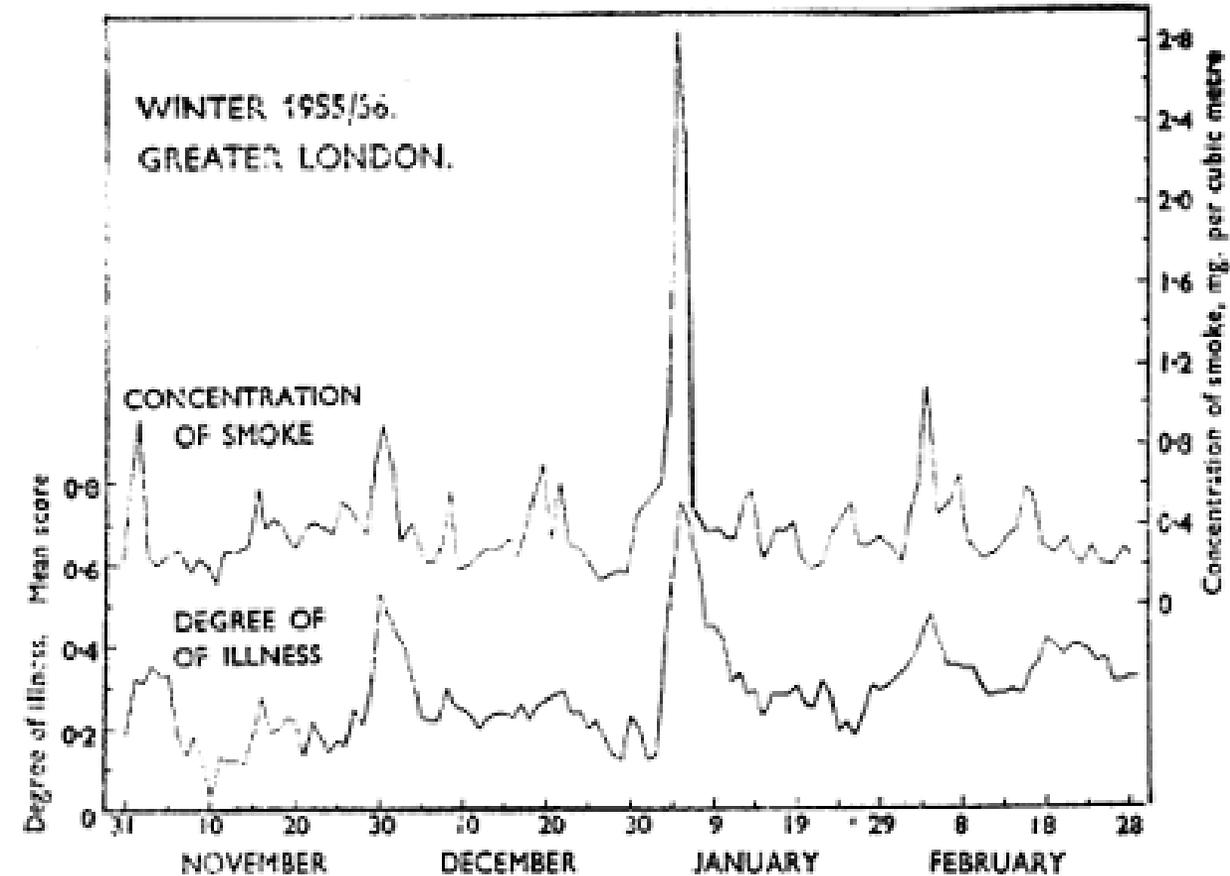
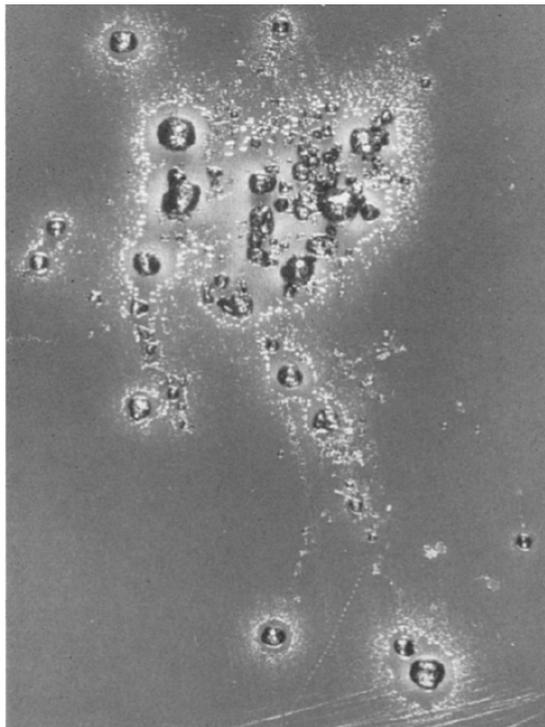


FIG. 1—Degree of illness of a group of 180 chronic bronchitic patients and concentration of smoke in London, November, 1955, to February, 1956.

Haemophilus Influenzae: Growth Stimulation by Atmospheric Pollutants

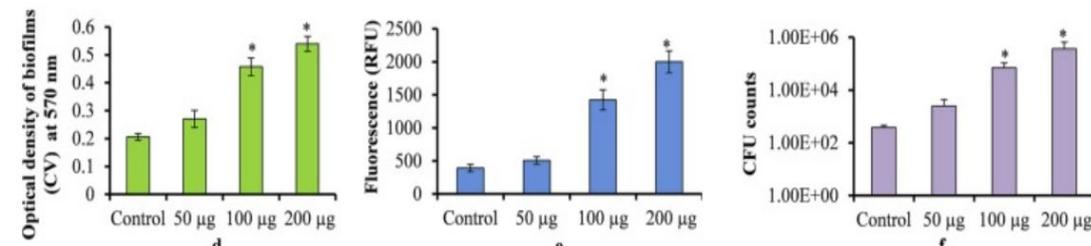
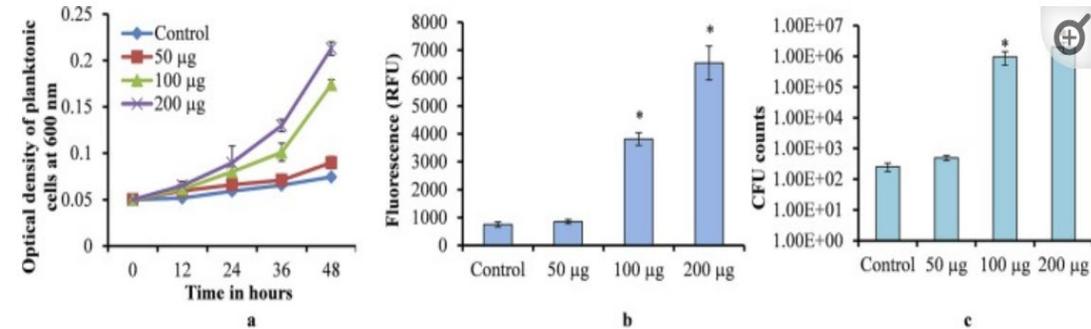
P. J. LAWATHER, T. R. EMERSON AND F. W. O'GRADY

Medical Research Council Air Pollution Research Unit
and Department of Bacteriology,
St Bartholomew's Hospital, London EC1



Stimulatory effect of sprinkled pollutant on the growth of *H. influenzae* on blood agar.

Urban Particles Elevated *Streptococcus pneumoniae* Biofilms, Colonization of the Human Middle Ear Epithelial Cells, Mouse Nasopharynx and Transit to the Middle Ear and Lungs

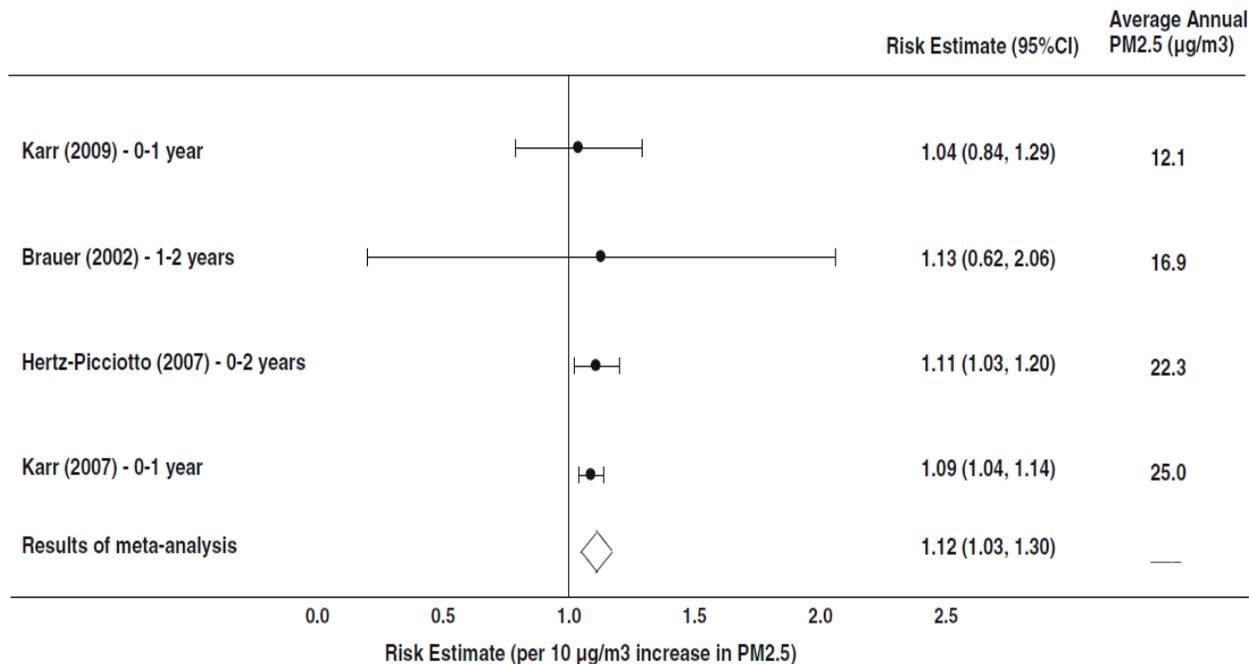


How air pollution could work?

- **Bacteria/virus:**
 - enhances bacterial growth and colonization
- **Airways:**
 - causes pulmonary oxidative damage and inflammation
 - damages the mucociliary system
 - suppresses alveolar macrophage uptake
 - impairs microbial clearance
 - enhance pneumococcal adherence to airway epithelial cells
- **Immune system:**
 - increases susceptibility to both viral and bacterial infections via dysregulation of immune tolerance and antimicrobial responses

Pneumonia children, long-term exposure

PM_{2.5} Systematic review,
Metha et al 2013



ELAPSE study, 10 EU
birth cohorts
MacIntyre et al, 2014

Pollutant	RR pneumonia
NO ₂	1.30 (1.02, 1.65)*
NO _x	1.26 (1.04, 1.52)*
PM _{2.5}	2.58 (0.91, 7.27)
PM _{2.5} absorbance	1.99 (1.44, 2.75)*
PM ₁₀	1.76 (1.00, 3.09)*

Fig. 2 Risk estimates from longer-term studies of PM_{2.5} and ALRI in children below 5 years of age, ordered by average annual PM_{2.5} concentration

HEI Traffic Review: Long-term exposure to TRAP and Acute Lower Respiratory Infections in children

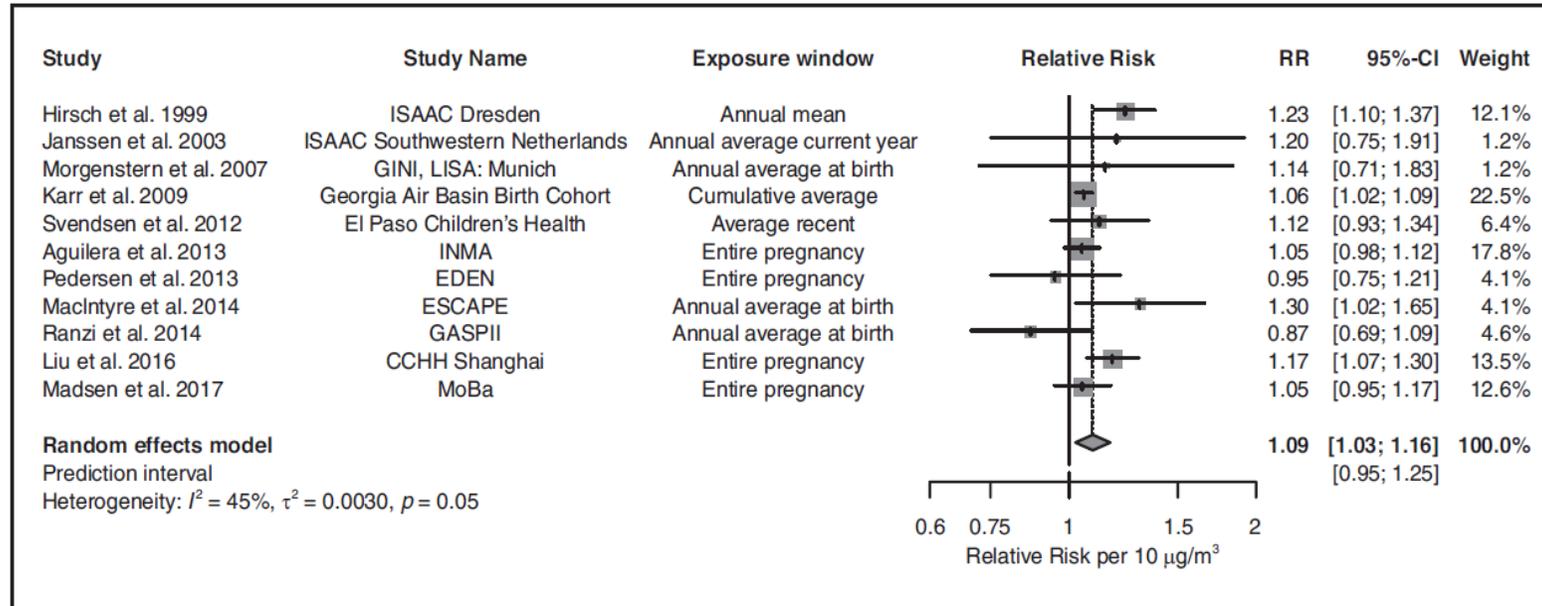


Figure 9.20. Association between NO₂ and ALRI in children: meta-analysis.

Metanalysis of long-term NO₂ exposure and ALRI in children

Strenght of the evidence: moderate to high

Based on NO₂ metanalysis and supporting evidence from EC and studies based on indirect measures of TRAP



Pneumonia adults, long-term exposure

Few studies on hospitalizations,
e.g. Medicare

Danesh Yazdi et al, 2019

Neupane et al, 2010

Case-control in Ontario

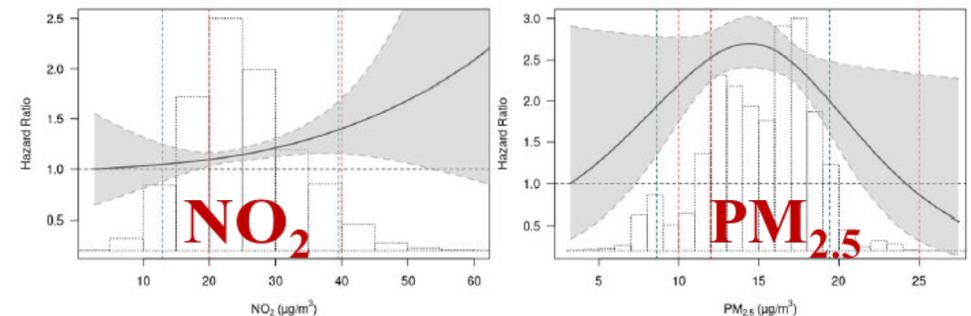
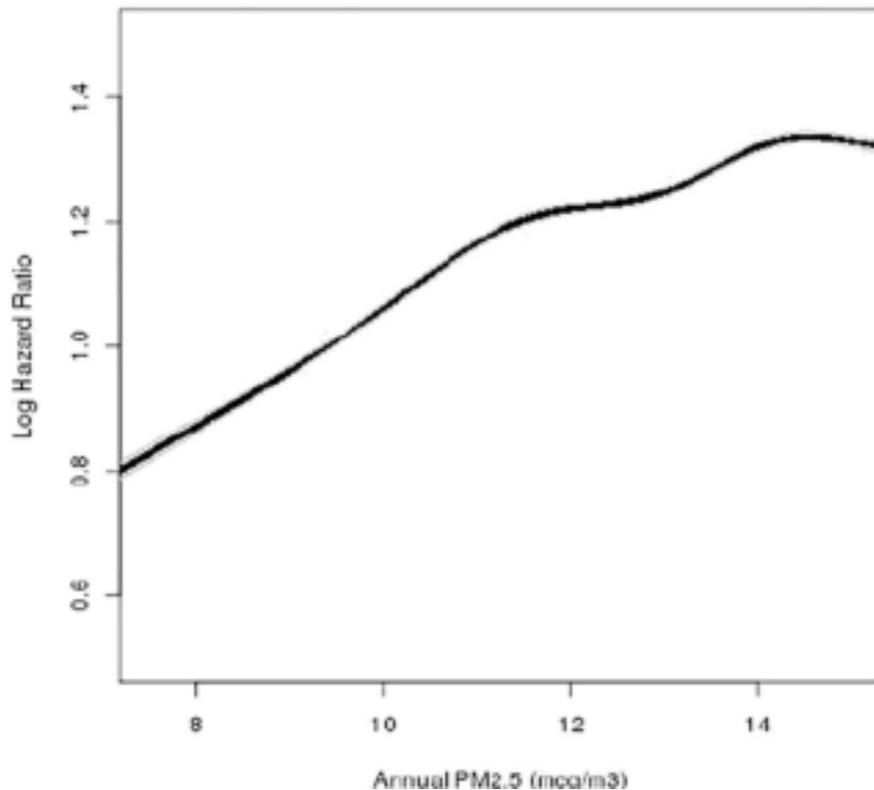
TABLE 3. ADJUSTED ESTIMATES OF ASSOCIATIONS OF AIR POLLUTION VARIABLES* WITH HOSPITALIZATION WITH COMMUNITY-ACQUIRED PNEUMONIA

Air Pollution Variables [†]	OR [‡]	95% CI [‡]	P Value
NO ₂ , ppb (IDW)	2.30	1.25, 4.21	0.007
NO ₂ , ppb (SPL)	2.19	1.25, 3.83	0.006
NO ₂ , ppb (LUR)	1.70	1.00 - 2.89	0.049
SO ₂ , ppb (IDW)	0.97	0.59, 1.61	0.918
SO ₂ , ppb (SPL)	1.09	0.63, 1.89	0.766
PM _{2.5} , ppb (IDW)	2.26	1.20, 4.24	0.012
PM _{2.5} , ppb (SPL)	1.70	0.99, 2.92	0.053

Liu et al, 2022

ELAPSE pneumonia mortality

PM2.5 vs. First Admission for Pneumonia





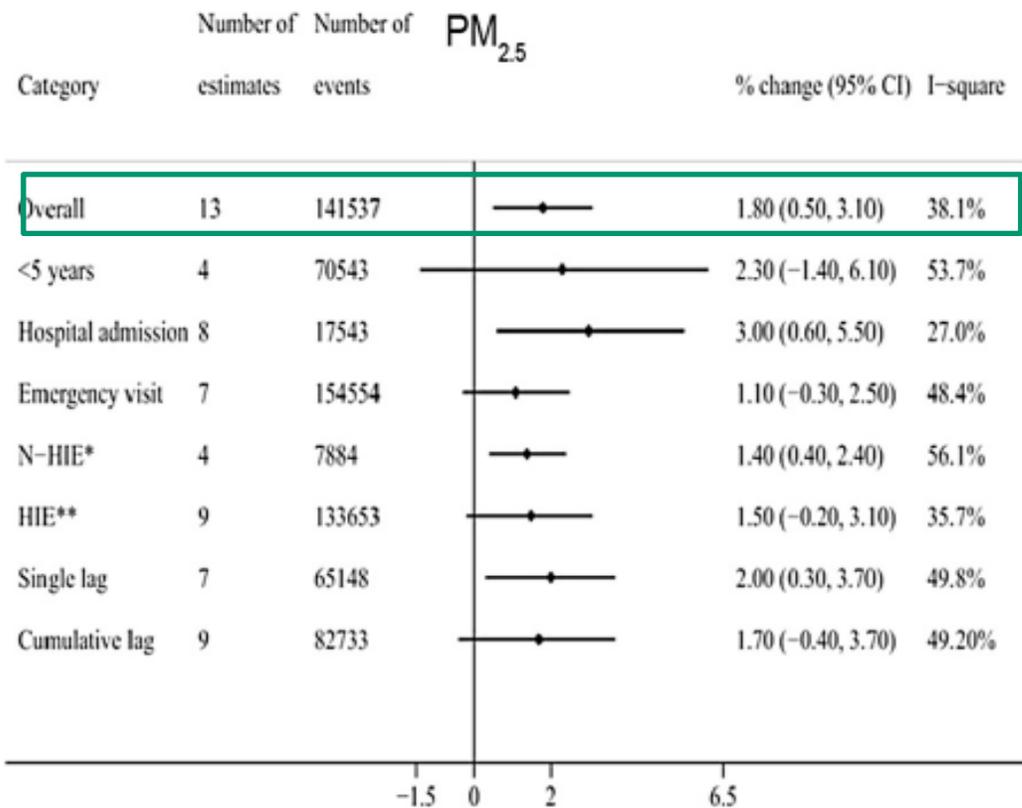
Pneumonia children, Short-term exposure

Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies[☆]

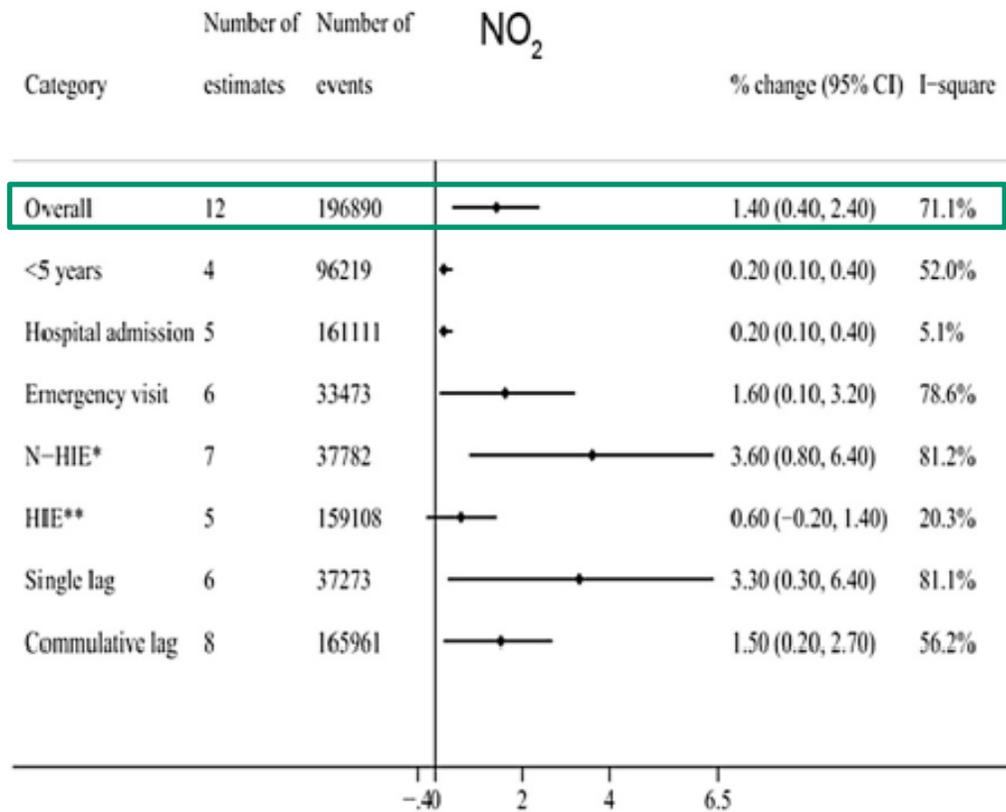


Nguyen Thi Trang Nhung^{a, b, c, *}, Heresh Amini^{a, b}, Christian Schindler^{a, b}, Meltem Kutlar Joss^{a, b}, Tran Minh Dien^d, Nicole Probst-Hensch^{a, b}, Laura Perez^{a, b, 1}, Nino Künzli^{a, b}

PM_{2.5}



NO₂



Pnumonia adults, Short-term exposure

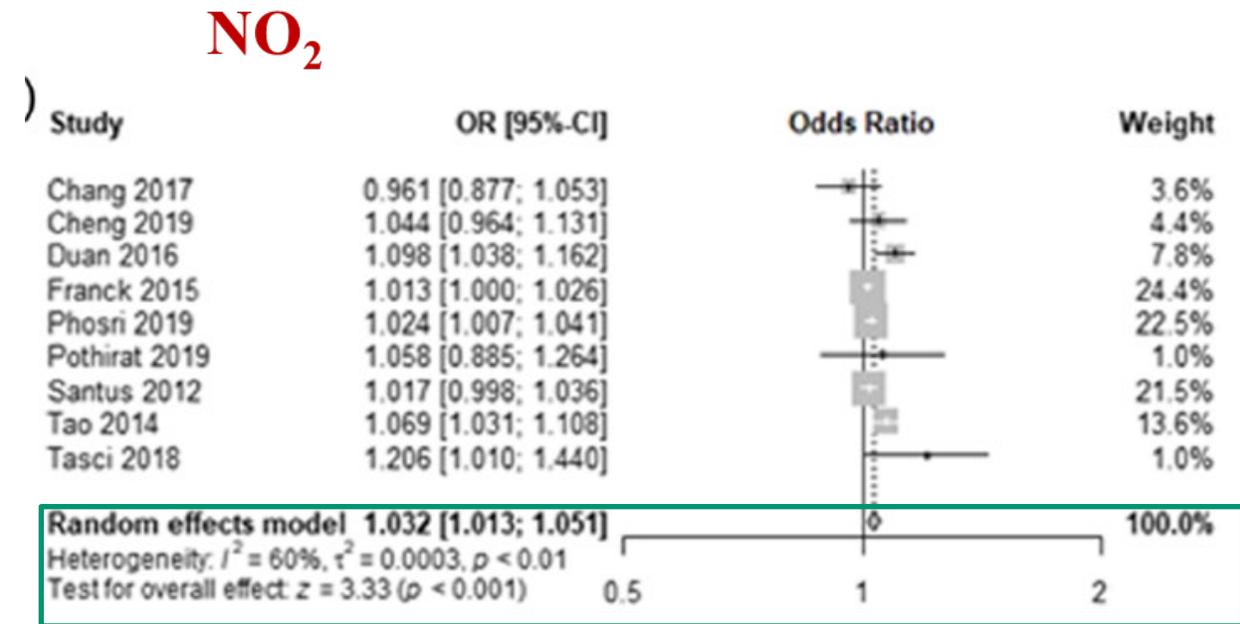
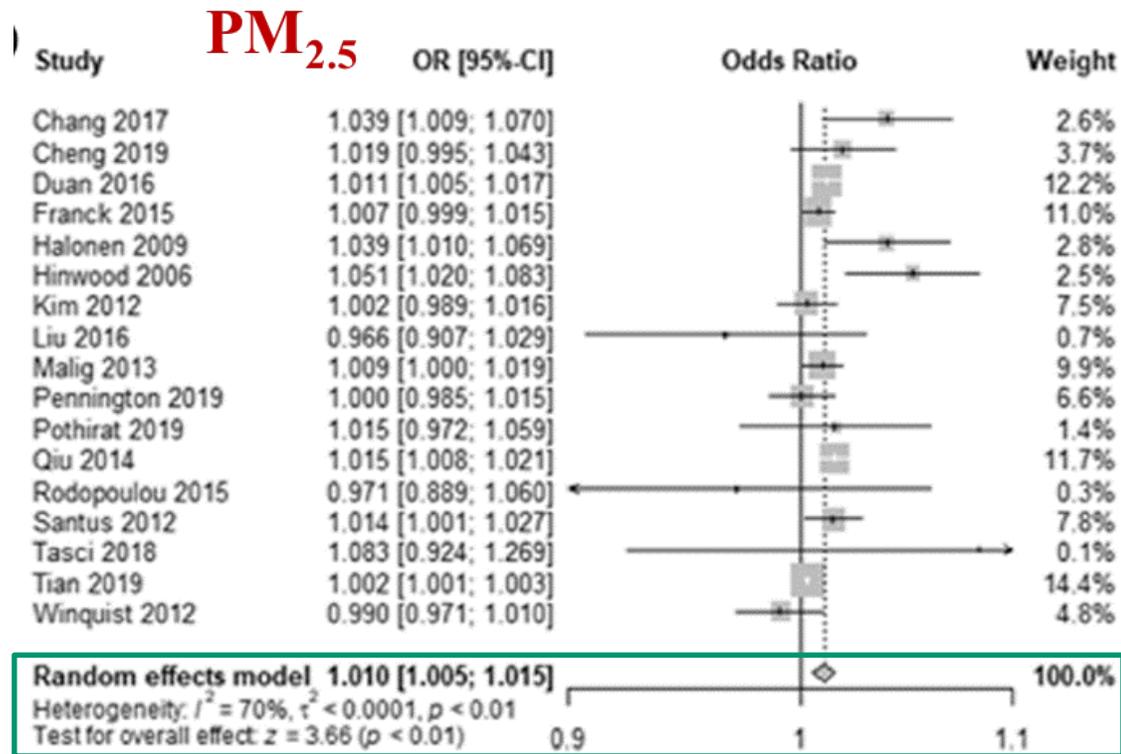
REVIEW

Open Access



Short-term exposure to air pollution and hospital admission for pneumonia: a systematic review and meta-analysis

Jeong Yee^{1†}, Young Ah Cho^{2,3†}, Hee Jeong Yoo^{1,4}, Hyunseo Yun⁵ and Hye Sun Gwak^{1*}

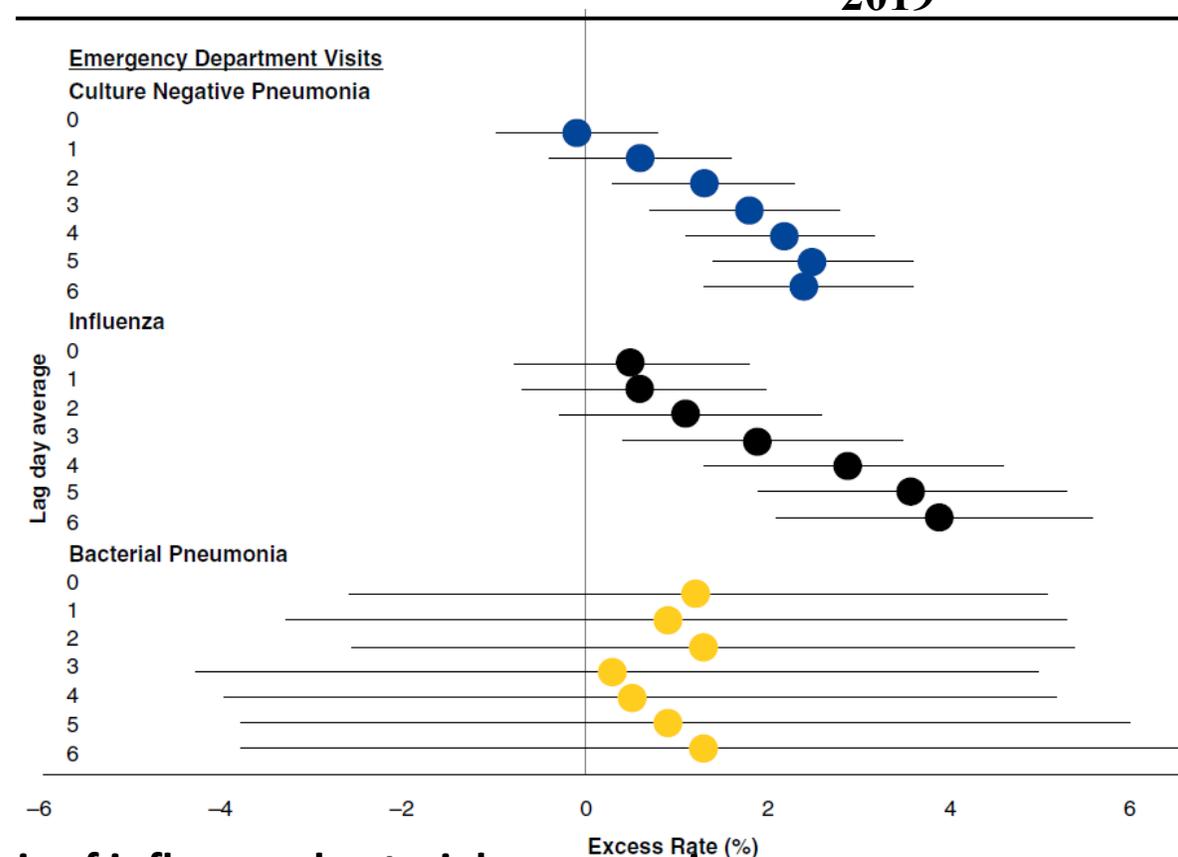
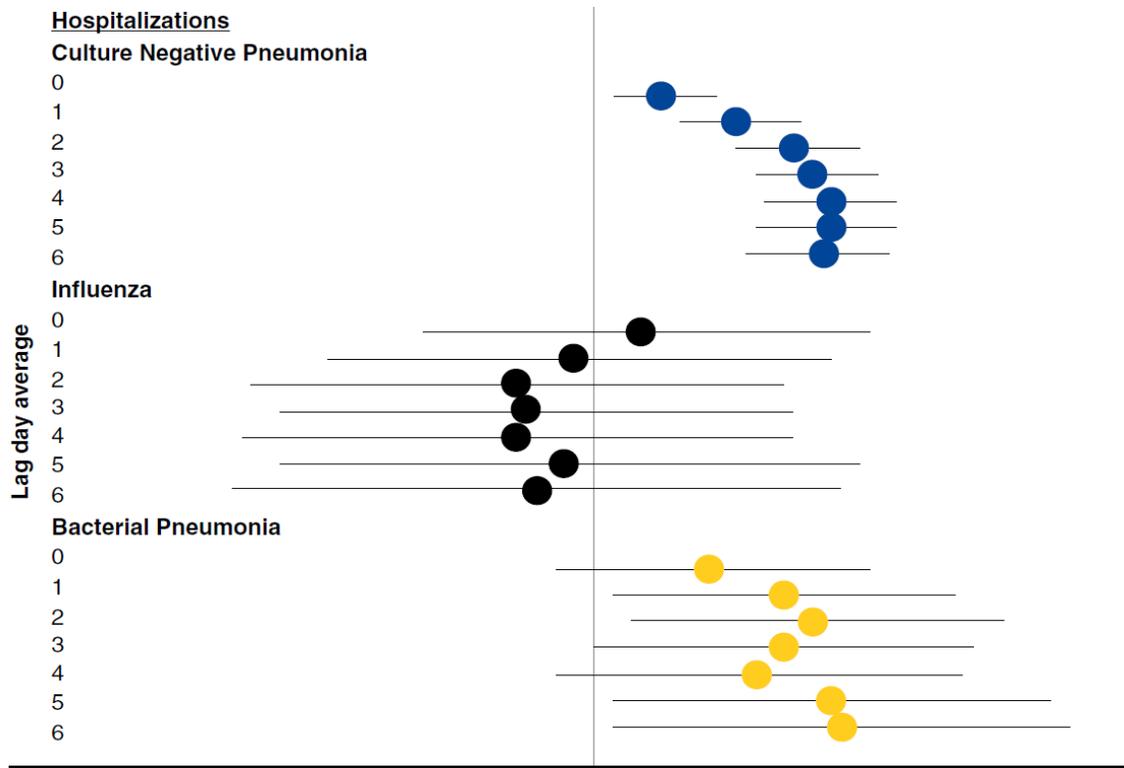


The lag time of the effect

The Association between Respiratory Infection and Air Pollution in the Setting of Air Quality Policy and Economic Change

Daniel P. Croft¹, Wangjian Zhang², Shao Lin², Sally W. Thurston³, Philip K. Hopke^{4,5}, Mauro Masiol^{4,5}, Stefania Squizzato^{4,5}, Edwin van Wijngaarden^{4,6}, Mark J. Utell^{1,6}, and David Q. Rich^{1,4,6}

Ann Am
Thorac Soc,
2019



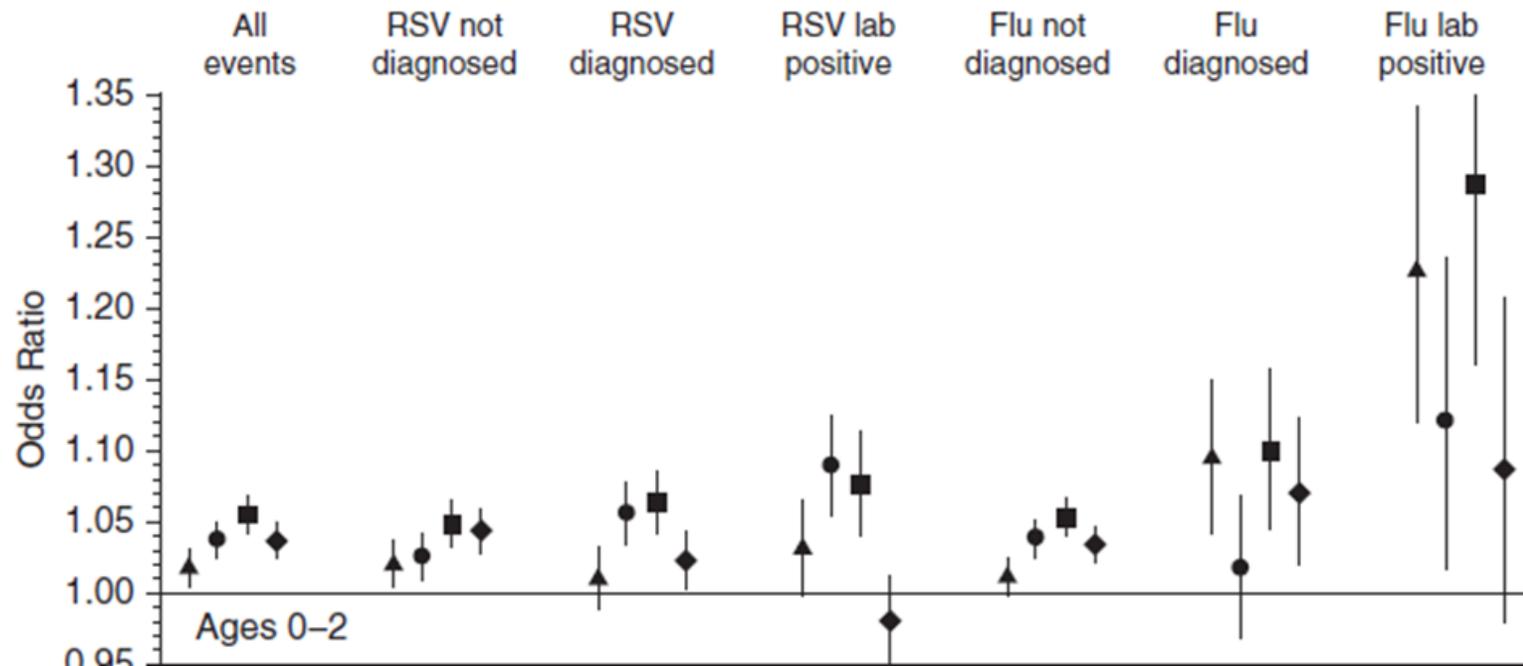
498,118 adult New York State residents with a primary diagnosis of influenza, bacterial pneumonia, or culture-negative pneumonia upon hospitalization or emergency department (ED) visit (2005–2016).

Risk modification by air pollutants on viral mediated ALRI (bronchiolitis) risk

- Case-cross over in Utah, (n = 112,467 0-2 years).
- Triangles, circles, squares, and diamonds are odds ratios for PM_{2.5} 0–6, 7–13, 14–20, and 21–27 days before the day of event

- Largest effect at 14-20 days lag
- Incubation period for RSV is 5 days
- Air pollution exposure precedes RSV infection

(Horne et al, AJRCCM 2018)

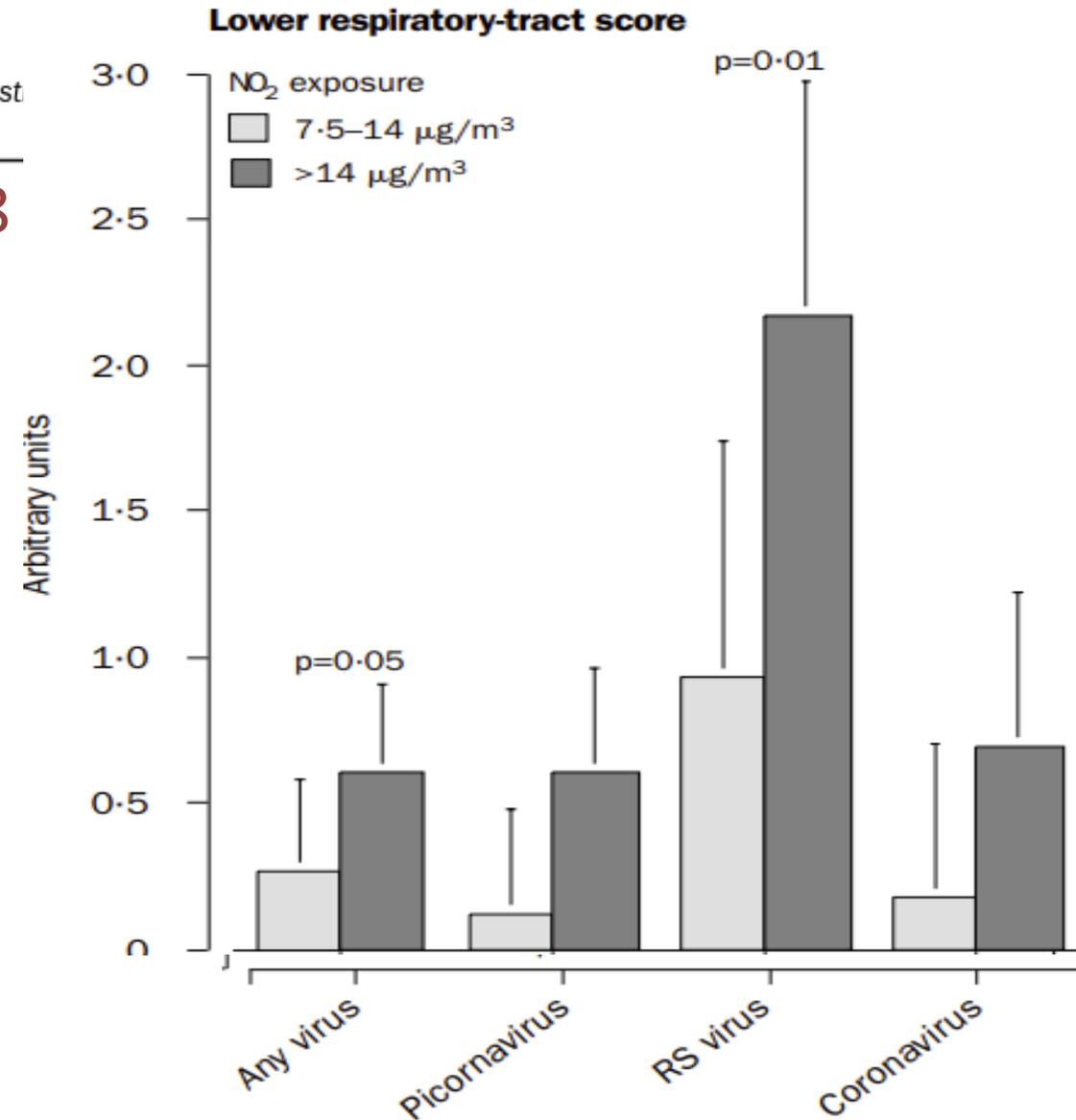


Personal exposure to nitrogen dioxide (NO₂) and the severity of virus-induced asthma in children

The Lancet.
2003

A J Chauhan, Hazel M Inskip, Catherine H Linaker, Sandra Smith, Jacqueline Schreiber, Sebastien T Holgate

- A cohort of 114 asthmatic children (8 and 11 years) with daily upper and lower respiratory tract symptoms, peak expiratory flow (PEF), and measured personal NO₂ exposures every week for up to 13 months.
- Nasal aspirates during reported episodes of upper respiratory-tract illness and test for infection (RT-PCR assays).



Air Quality and COVID-19, 2021 Imperial Report

- Some plausibility that both long and short-term exposure could increase incidence and severity of Covid-19.
- Early ecological studies were useful to generate hypotheses, but had methodological limitations.
- Studies are unclear if air pollution increases the risk of infection with COVID-19
- Long-term exposure to air pollution pre-pandemic increases the risk of hospitalisation in people already infected with COVID-19



Recent individual studies on AP and COVID-19 severity

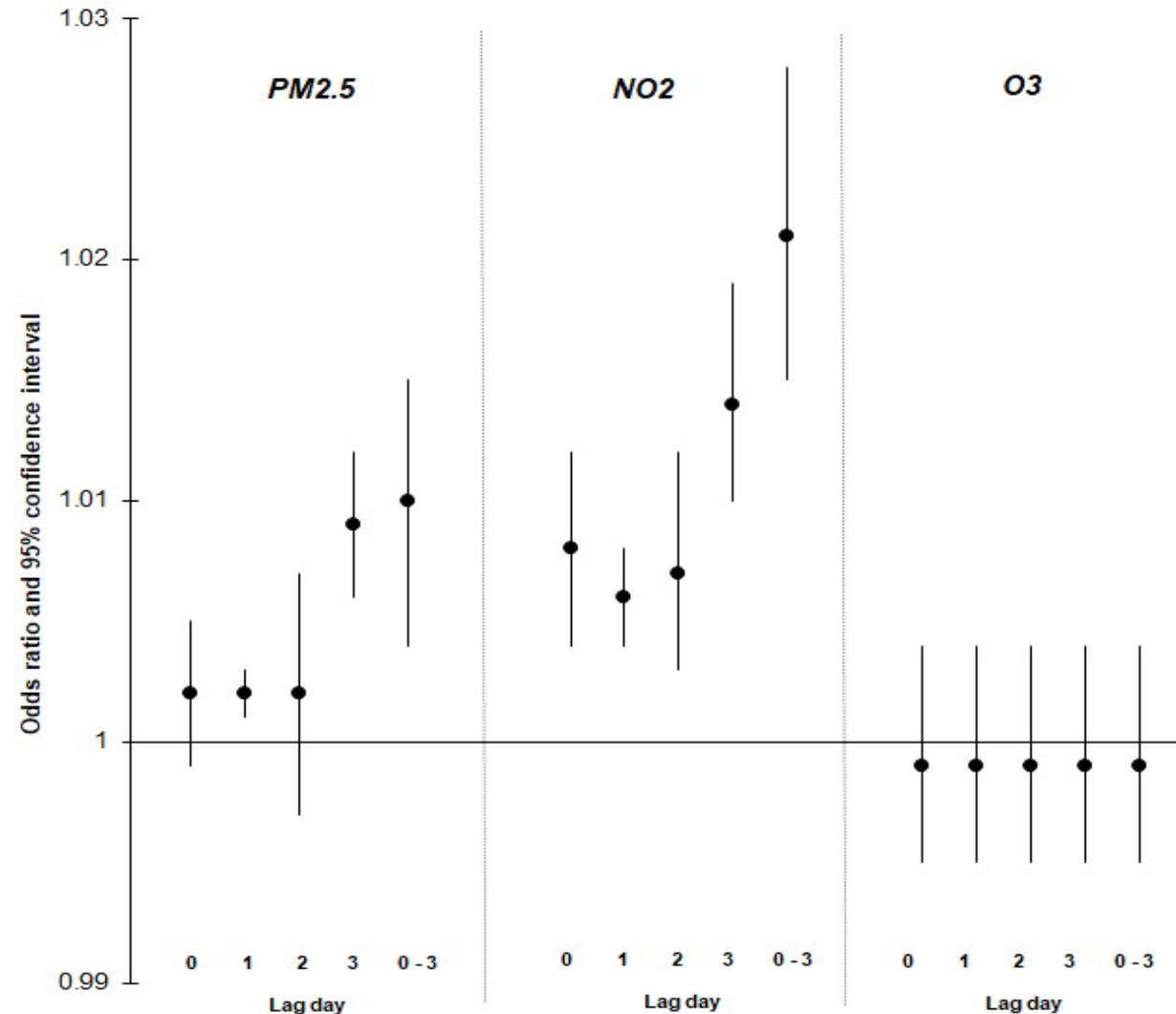
- *Long-term exposure*

- **Bowe et al, Env Int 2021**; 169,000 Covid-19 cases US Veterans. Annual 1.9 ug/m³ PM_{2.5} related to Covid-19 hospitalization, RR 1.10 (CI 1.08-1.12)
- **Kogevinas et al, EHP 2021**; 9000 subjects in Catalonia, annual 1.86 ug/m³ PM_{2.5} associated with antibody levels and more severe Covid-19, RR 1.51 (CI 1.06-2.16)
- **Bozack et al, AJRCCM 2021**; 6000 hospitalized subjects in NYC, annual 1.0 ug/m³ PM_{2.5}, RR 1.11 (CI 1.02-1.21) for mortality, RR 1.13 (CI 1.0-1.28) for ICU admission
- **Nobile et al, ERJ (in press)**; 1.5 million subjects from Rome, annual 1.0 ug/m³ PM_{2.5} was not related to Covid-19 incidence but to Covid-19 mortality, RR 1.08 (CI 1.03, 1.13).

Recent individual studies on AP and COVID-19 severity

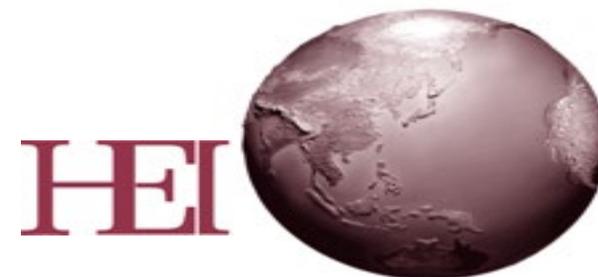
- Short-term exposure

- **Lavigne et al, Thorax 2022**; case-crossover study of 78,255 Covid-19 ED visits in Alberta and Ontario, Canada (March 2020 to March 2021). The association between $PM_{2.5}$ and ED visits was stronger among those hospitalised following an ED visit.



Summary

- **Strong evidence** that both long and short-term exposures to AP are associated with incidence of ALRI
- **Suggestive evidence** that both long and short term exposures to AP are associated with a severe Covid-19
- **Need** for human and animal studies on:
 - susceptibility to infection
 - severity of the resultant disease progression
 - impaired vaccine efficacy



The future in 2003

“While there is emerging evidence confirming that air pollutants are intimately related to infections, the challenges for epidemiologists and clinical scientists remain to go beyond the short-term triggering phenomena and consider how the increase in susceptibility to air pollutants reflects fundamental interactions with co-factors..... *The challenges remain to unravel the mechanisms that drive such effects of air pollution*”

Chauhan & Johnston, British Medical Bulletin, 2003

The future in 2022

- Combine chronic disease epidemiology approach with infectious disease epidemiology
- Set up large population cohort studies to detect infections
- Combine information from epidemiological and mechanistic studies on viruses/ pollutants interaction
- Lab data to assess the nature of the infection and the immune status of the population
- New designs to evaluate the effects on transmission, severity, and vaccine efficacy

Thanks

Contact: fran.forastiere@gmail.com

