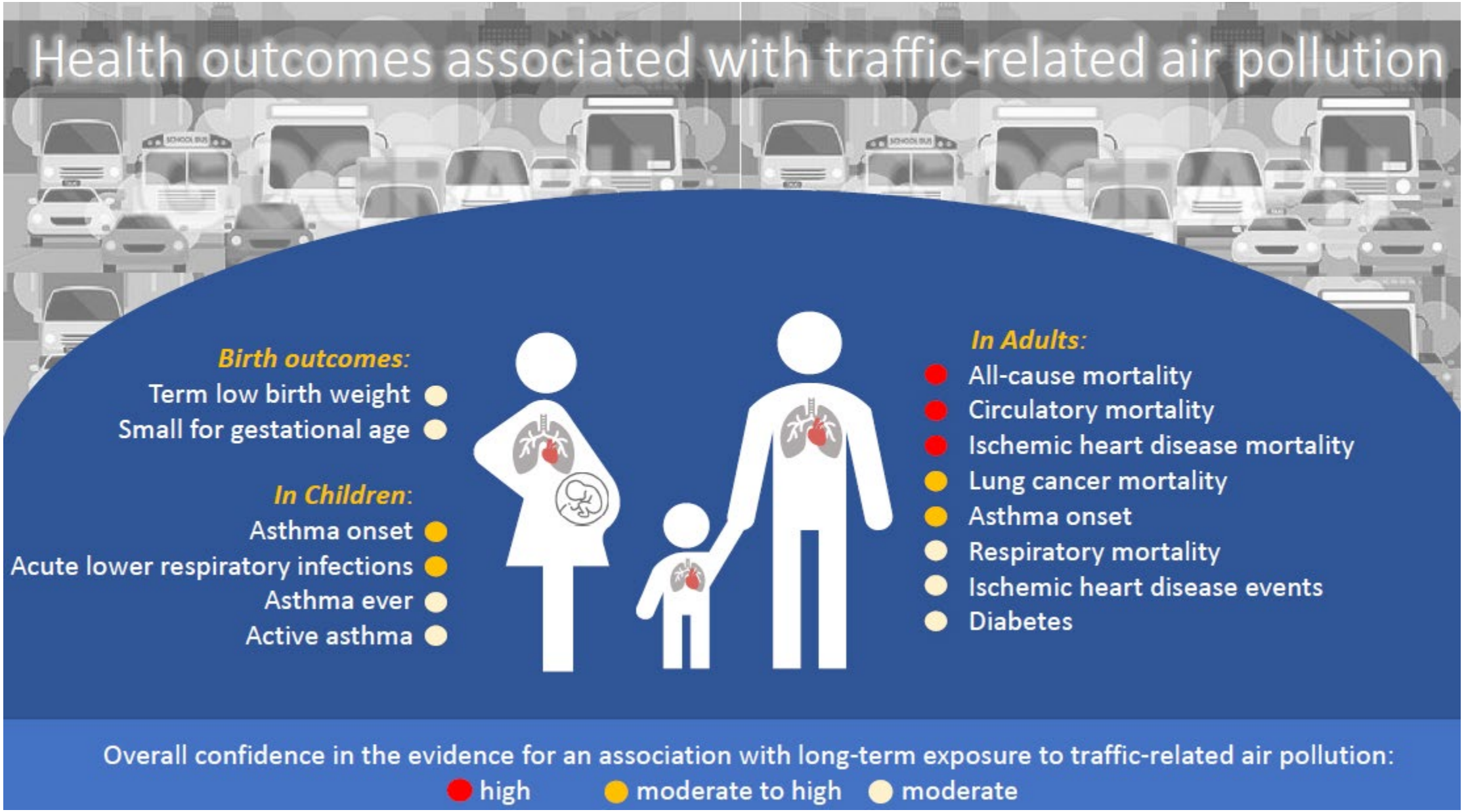
Current knowledge on adverse effects of traffic-related air pollution: have we filled the gap? What more do we need to know?

Francesco Forastiere
National Research Council, Italy
Imperial College, London, UK

Fran.Forastiere@gmail.com



Footnote: health outcomes for which the overall confidence in the evidence was low-to-moderate, low or very low are not in the picture.

Overall summary

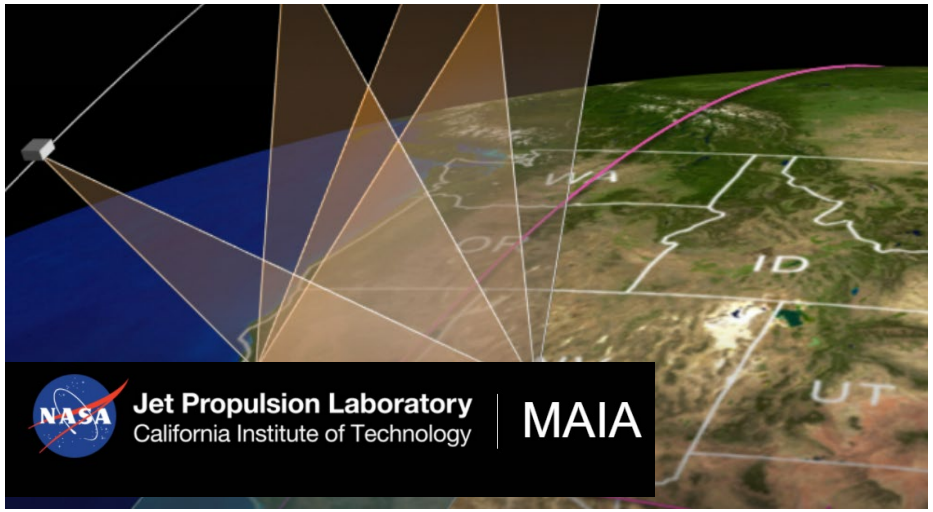
- The findings have provided an overall **high or moderate-to-high** level of confidence in an association between long-term exposure to traffic-related air pollution and the adverse health outcomes:

  all-cause, circulatory and ischemic heart disease mortality, lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children.

- The Panel's confidence in the evidence was considered moderate, low or very low for the other selected outcomes.
- In light of the large number of people exposed, the results indicate that traffic-related air pollution remain an important public health concern.
- Several future research opportunities emerged from this report.

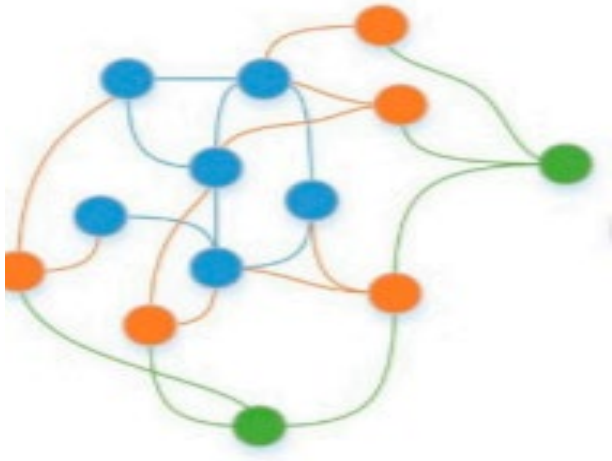
1.Beyond LUR: improve exposure assessment

Satellites: Size and shape of the particles

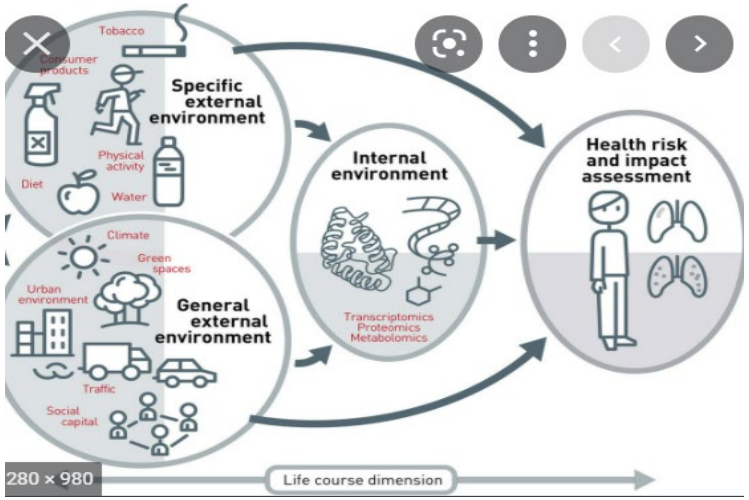


Sensors: personal exposures to gases and particles

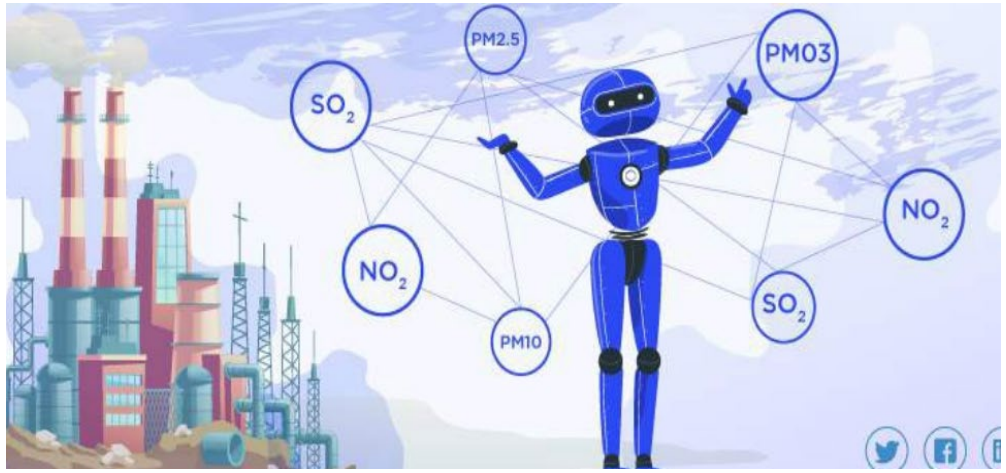
Social media: Time- activity patterns



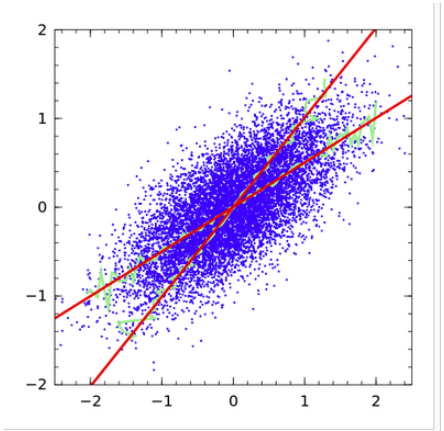
Exposome: markers of exposure



Machine learning: non-linear relations



Apply **Regression Calibration** to address measurement error



2. Conduct long-term health studies on UFP and non-tailpipe PM

A case for UFP

- ✓ Exposures to ultrafine and fine particles differ in space and time
- ✓ Experimental and epidemiological studies suggest independent short-term health effects
- ✓ Studies on long-term health effects of UFP are limited

A case for non-tailpipe PM components (e.g., Cu, Fe)

- ✓ No great progress in the last two decades but need to continue to address the issue and search for better evidence

3. The NO_2 dilemma: per se… or not per se

Gain a better understanding of whether the epidemiological associations found for TRAP are due to direct effects of NO_2, to another component of TRAP, or to the broader mixture of correlated components indicative of TRAP.

Despite:

- ✓ Two Integrated Science Assessment (USA EPA 2016; Health Canada 2016)
- ✓ One critical assessment, COMEAP 2018 (not all conclusions were unanimous)
- ✓ Seven systematic reviews

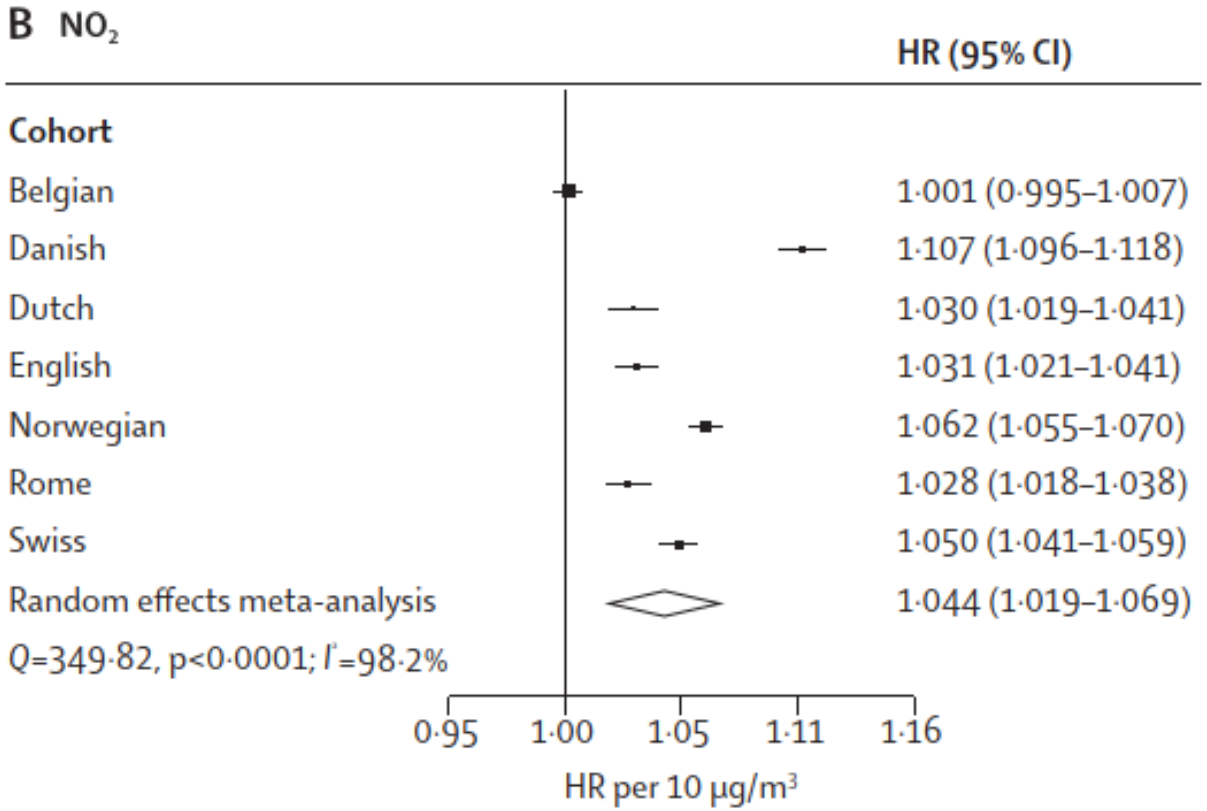
NO_2 and all-cause mortality

Reference	Number of studies	Summary estimate (95% CI) per 10 ug/m^3
HEI traffic review 2022	11	1.041 (1.015-1.068)
Stieb 2021	39	1.034 (1.018-1.050)
Stieb 2021*	32*	1.025 (1.012-1.038)
Huang 2021	28	1.032 (1.021-1.043)
Huangfue 2020 (WHO)	24	1.020 (1.005-1.036)
Atkinson 2018	20	1.020 (1.010-1.030)
Faustini 2014	12	1.042 (1.019-1.076)
Hoek 2013	12	1.056 (1.031-1.083)

* After excluding studies with probably high or high risk of bias in confounding domain

Long-term NO_2 and mortality: ELAPSE administrative cohorts

Results are robust against adjustments for other pollutants



	Adjusted	Percent increase (95% CI) per 10 ug/m^3
NO_2	-	4.4% (1.9-6.9%)
NO_2	$PM_{2.5}$	4.2% (2.0-6.5%)
NO_2	BC	4.1% (0.9-7.3%)
NO_2	O_3	4.0% (1.2-6.9%)

Stafoggia et al. Lancet Planetary Health (2022)

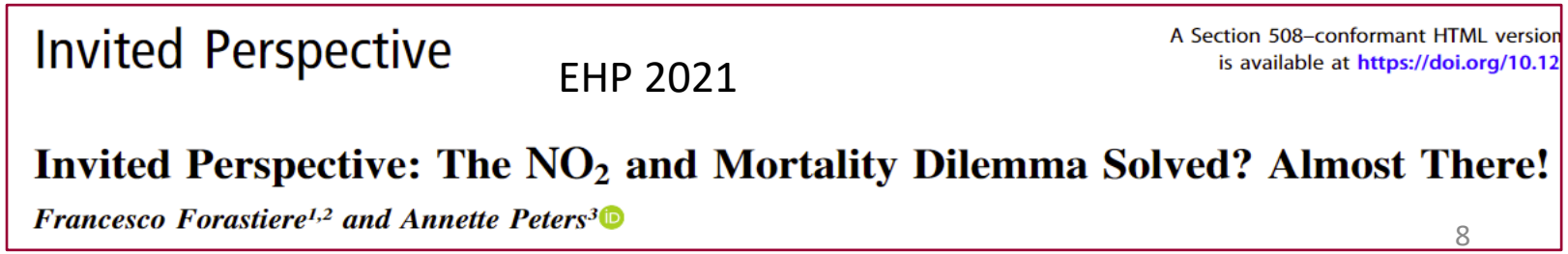
3. The NO_2 dilemma: need to triangulate evidence capitalizing on experimental studies

- ✓ Capacity of NO_2 to induce bronchial hyperresponsiveness and responses to inhaled allergen in patients with asthma

  Particle Depletion Does Not Remediate Acute Effects of Traffic-related Air Pollution and Allergen. A Randomized, Double-Blind Crossover Study. Wooding et al. AJRCCM 2019

  - ✓ Controlled chamber exposure experiments in allergen-sensitized individuals
  - ✓ Nasal instillation of allergen and diesel exhaust exposure > exhaust particles enhanced both sensitization to neoallergen and the allergen response
  - ✓ Filtering out the particles (NO_2 increased) provided no protection

- ✓ This strongly implicates NO_2 associated with diesel exhaust as an important adjuvant factor enhancing allergen sensitization (Bosson et al. AJRCCM 2019)


Invited Perspective

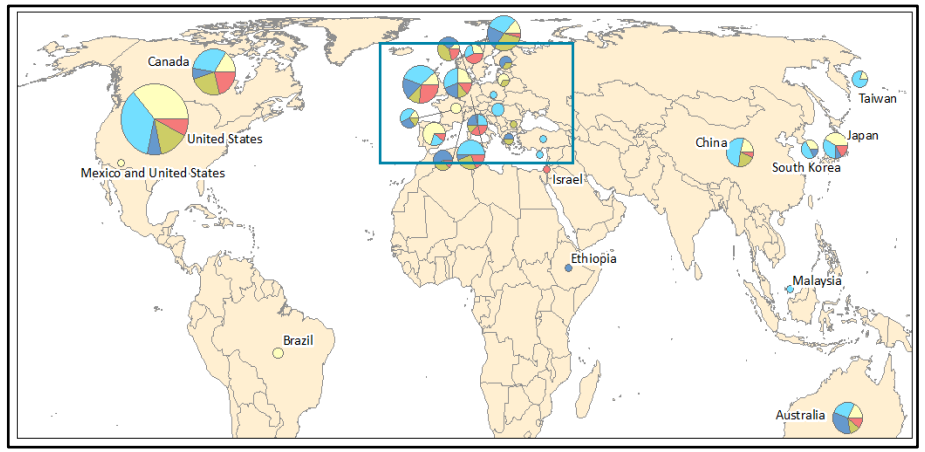
EHP 2021

A Section 508–conformant HTML version is available at https://doi.org/10.12

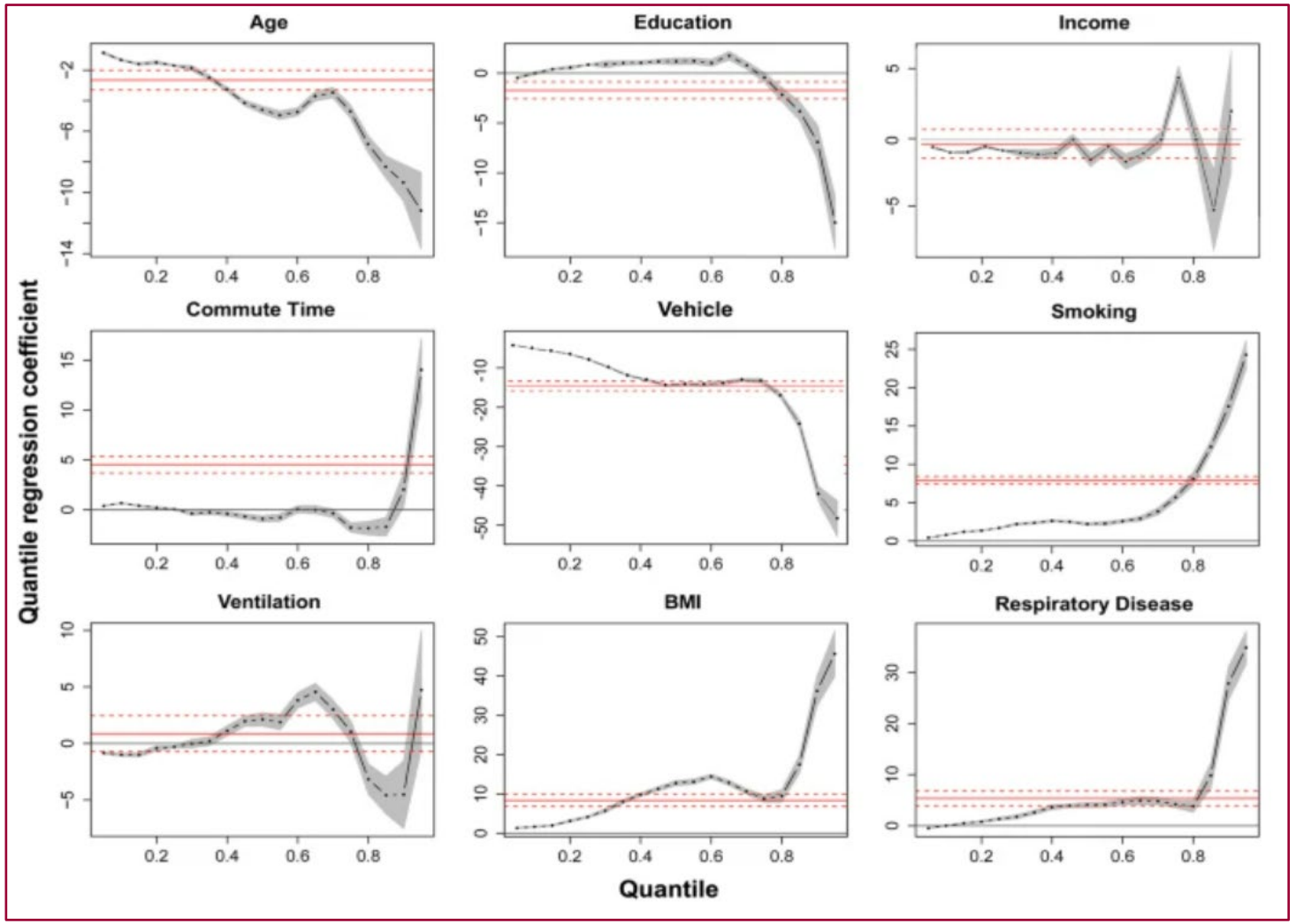
Invited Perspective: The NO_2 and Mortality Dilemma Solved? Almost There!

Francesco Forastiere[1,2] and Annette Peters[3]

4. Conduct health studies in areas outside North America and Europe



Geographical location of the studies in the HEI systematic review



The effects of sociodemographic, travel behavior, living conditions, and health status on personal PM2.5 exposure in Beijing.
Liang et al, BMC Public Health 2019

5. Conduct additional research on outcomes for which there are suggestions of an association with TRAP, but for which the **evidence is still limited**

- ✓ Critical windows of exposure in birth outcome studies, and for asthma onset in children
- ✓ TRAP and COVID-19 incidence, hospitalization and mortality, especially after vaccination and new variants
- ✓ Additional long-term TRAP studies are needed for:

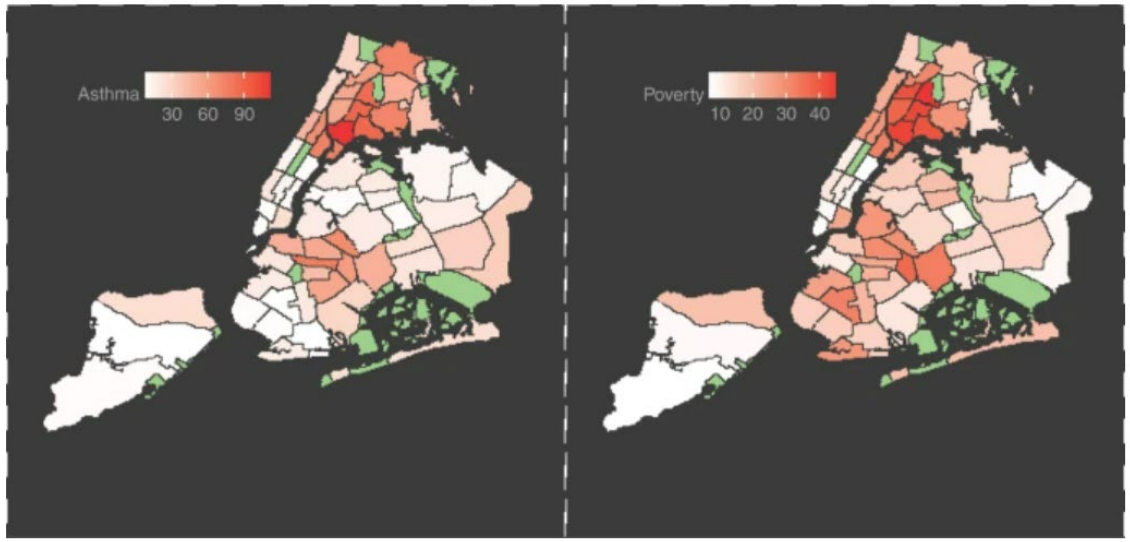
  COPD and ALRI in adults

  Cardiometabolic outcomes

  COPD, stroke, and ALRI mortality

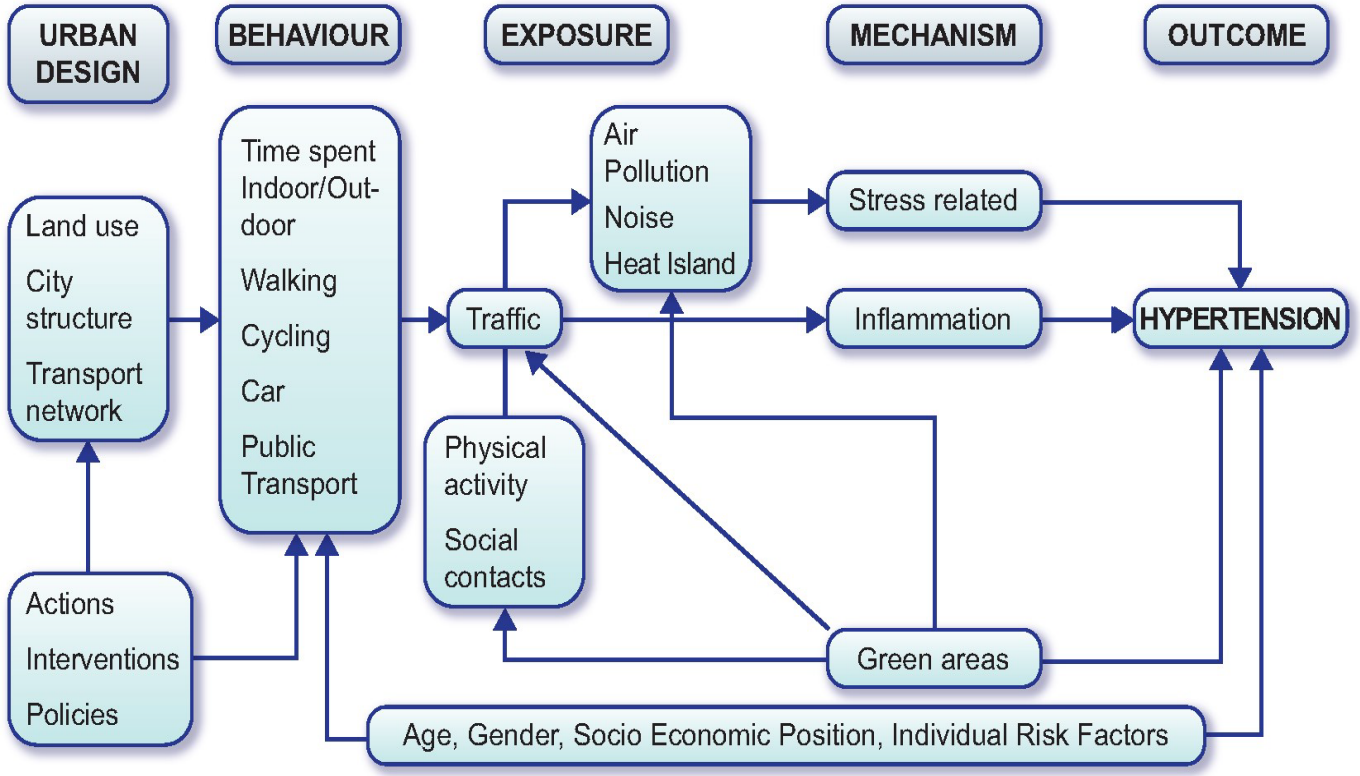
6. Consider spatially correlated factors like **poverty, traffic noise**, and factors related to the built environment, such as presence of **green space**

Asthma and poverty in NYC, Caplin et al. 2019



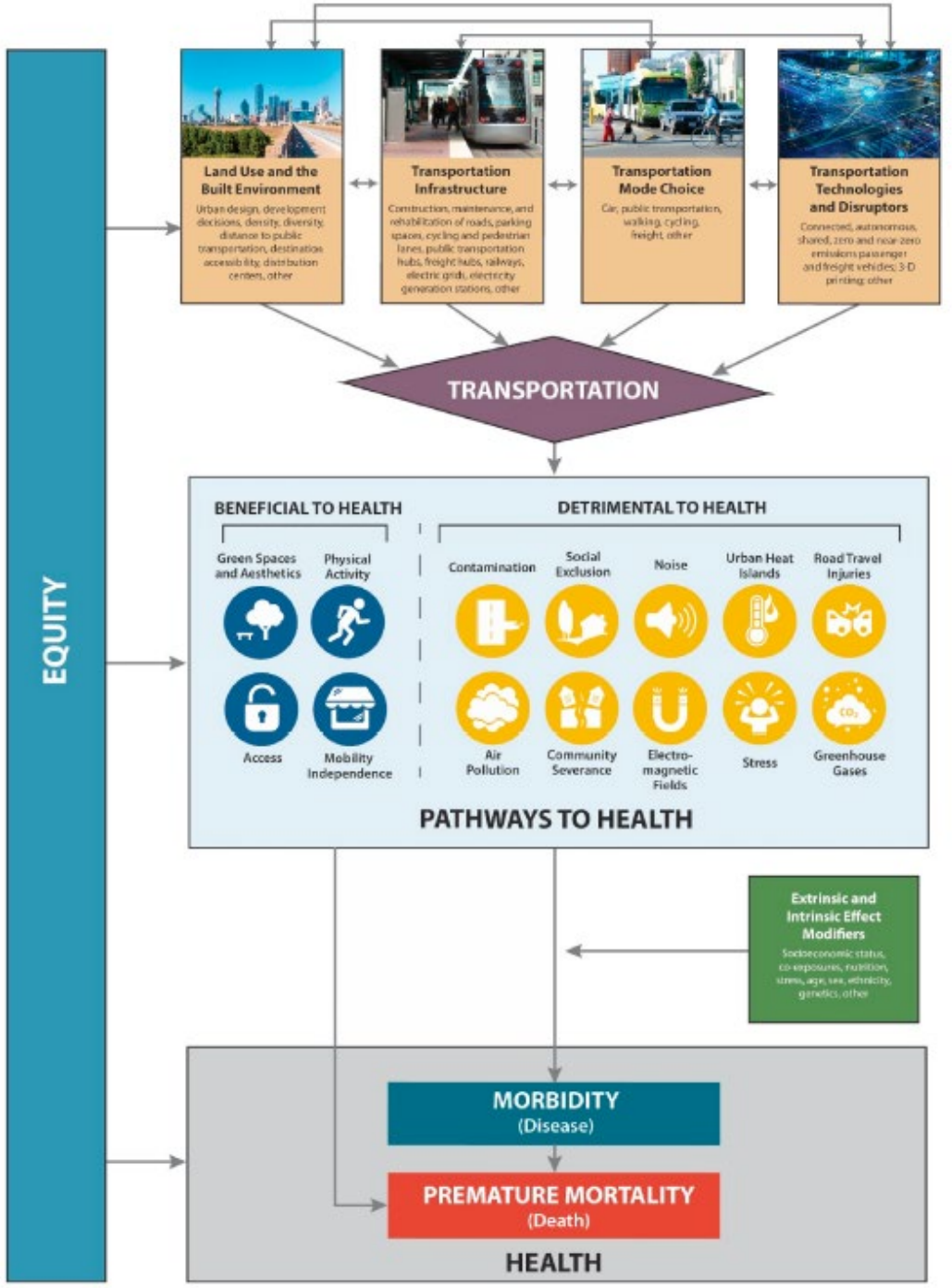
NYC 2014 Community District Data for: (left) Children's Asthma Admissions per 10,000 persons; and, (right) percent poverty in the same period. Green shaded areas represent parks, airports, etc.

Conceptual framework of the relationship between hypertension and urban and transport planning, traffic ...Mannucci &Ancona, EHJ, 2021



7. Evaluate the fuller range of potential impacts of transportation and (new) mobility on public health

This includes the opportunities for physical activity and active transport to mitigate the adverse health effects of TRAP



Glazener et al. 2021. Fourteen pathways between urban transportation and health: A conceptual model and literature review. Journal of Transport & Health

8. Evaluate the mechanisms behind the association of TRAP with the selected outcomes by studying markers and subclinical outcomes

"Meet-in-the-middle" approach (Chadeau-Hyam et al. 2011)

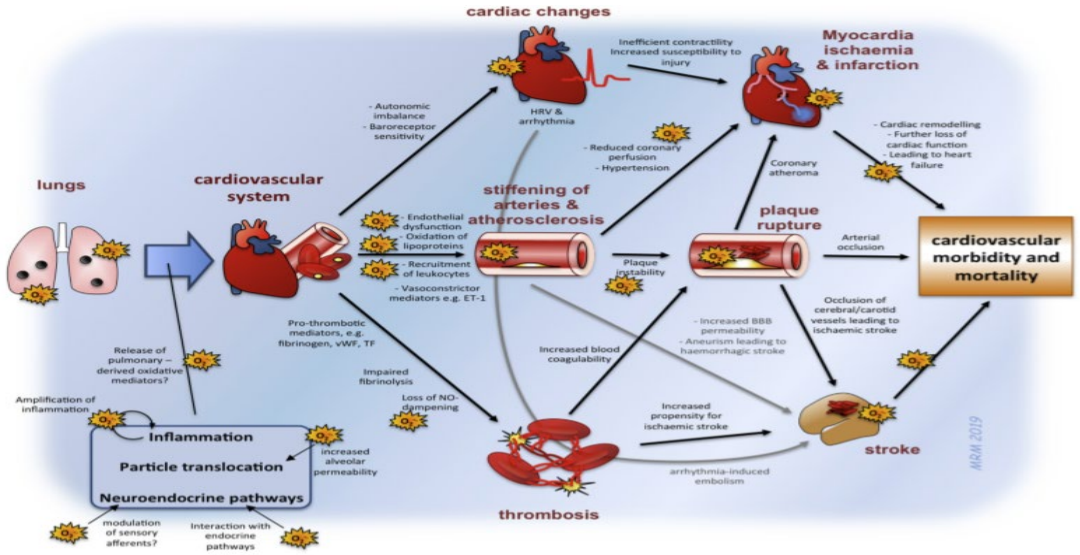


Fig. 8. Contribution of oxidative stress to the mechanisms by which inhaled PM induces cardiovascular dysfunction. A complex series of interconnecting mechanisms underlies the effects of inhaled PM on cardiovascular morbidity and mortality. O_2^- is used to represent places where oxidative stress is likely to play a direct role in exacerbating the disease process. While a direct action of oxidative stress is not always immediately apparent, it is worth noting that oxidative stress has been associated with most of the cardiovascular impairments shown on the diagram, and may indirectly contribute to other pathways by which PM has cardiovascular actions. Abbreviations: BBB = blood brain barrier; ET-1 = endothelin-1; HRV = heart rate variability; NO = nitric oxide; TF = tissue factor; vWF = von Willebrand Factor.

Oxidative stress and the cardiovascular effects of air pollution (Miller et al. 2020)

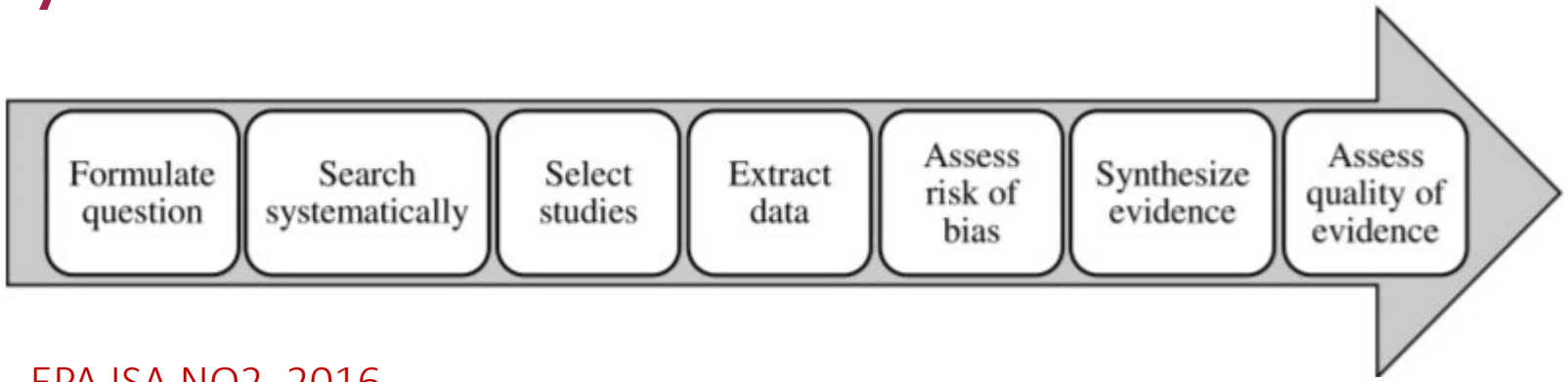
Meet-in-the middle approach consists of measuring intermediate biomarkers (often with an agnostic omic investigation) and relating them

(a) Retrospectively to measurements of external exposure and

(b) Prospectively to a health outcome (disease, or ageing, or other outcomes).

If the same set of markers is robustly associated with both ends of the exposure-to-disease continuum, this is a validation of a causal hypothesis according to the pathway perturbation paradigm. See Vineis et al. 2020.

9. Improve the methodological aspects related to the synthesis of the scientific evidence and its overall evaluation



GRADE

EPA ISA NO2, 2016

1. Steps of the systematic review process.

- **Causal relationship:** the consistency and coherence of evidence integrated across scientific disciplines and related health outcomes are sufficient to rule out chance, confounding, and other biases with reasonable confidence.
- **Likely to be a causal relationship:** there are studies where results are not explained by chance, confounding, or other biases, but uncertainties remain in the evidence overall. For example, the influence of other pollutants is difficult to address, or evidence among scientific disciplines may be limited or inconsistent.
- **Suggestive of, but not sufficient to infer, a causal relationship:** evidence is generally supportive but not entirely consistent or overall is limited. Chance, confounding, and other biases cannot be ruled out.
- **Inadequate to infer a causal relationship:** there is insufficient quantity, quality, consistency, or statistical power of results from studies.
- **Not likely to be a causal relationship:** several adequate studies, examining the full range of human exposure concentrations and potential at-risk populations and lifestages, consistently show no effect.

IDEAS AND OPINIONS 2016 Annals of Internal Medicine

GRADE Methods for Guideline Development: Time to Evolve?

Susan L. Norris, MD, MPH, MSc, and Lisa Bero, PhD

Environmental health and clinical medicine are two different disciplines

- Clinical medicine
- Environmental health

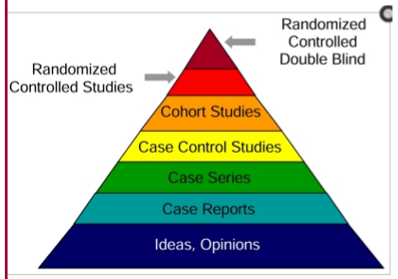


FIGURE 2-1 Evidentiary hierarchy of weighing evidence

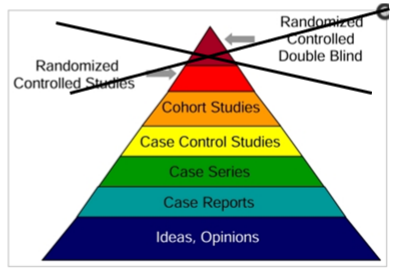


FIGURE 2-1 Evidentiary hierarchy of weighing evidence

HEI

Tension between two approaches

Grades of Recommendation Assessment, Development and Evaluation

GRADE

Cochrane Consumers and Communication

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide

www.gradeworkinggroup.org

2008 BMJ series

2011 JCE series

Triangulation in aetiological epidemiology

Debbie A. Lawlor,[1,2,*] Kate Tilling[1,2] and George Davey Smith[1,2]

[1]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK and [2]School of Social and Community Medicine, University of Bristol, Bristol, UK

The most famous shape in football: the triangle

Use of two approaches: narrative and modified OHAT

Separate assessments for confidence
in the quality of the body of evidence (modified OHAT) and
in the presence of an association (narrative)
(high, moderate, low, and very low)

For each exposure-outcome pair by study design → For each exposure-outcome pair → For each health outcome

↓

Overall confidence

9. Improve methods in evidence synthesis

The assessment of the evidence should be based on Bradford Hill criteria:

1.Strength (effect size)

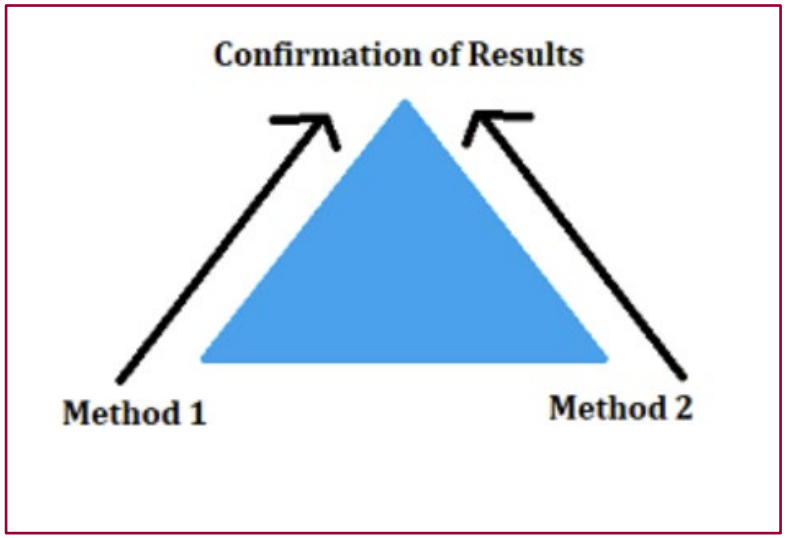
2.Consistency (reproducibility)

3.Temporality

4.Biological gradient (dose-response relationship)

5.Biological Plausibility

6.Coherence between epidemiological and laboratory findings



Triangulation is important and is very difficult in a GRADE-type framework

Some lessons learned regarding evidence synthesis of observational studies in environmental health

- ✓ To maximize what can be learned from observational studies in environmental health**, a "narrative" approach** is needed to complement the mechanistic up-and-downgrading of certain factors in evaluating the quality of a body of evidence.
- ✓ **Observational studies** can offer **high confidence** evidence in environmental health, where randomized controlled trials are generally not feasible.
- ✓ **All relevant studies should be included** in evidence synthesis, beyond the subset of evidence included in meta-analyses.
- ✓ **Consistency of associations** across study designs, populations, and exposure assessment methods provides additional confidence in the results.
- ✓ We call for **identifying and quantifying possible key biases**, their most likely direction, and their potential impacts on the results. (see Savitz, 2019 in Am J Epidemiol)

Conclusions: research opportunities

1. **Improve exposure assessment to TRAP** using novel methodologies
2. Additional epidemiological studies on an **array of traffic pollutants** including **UFP and non-tailpipe PM indicators**
3. **Evaluate direct effects of NO_2**, or to another component of TRAP, or to the broader mixture of correlated components indicative of TRAP
4. More health studies in areas **outside North America and Europe**
5. Conduct additional research on outcomes for which there are suggestions of an association with TRAP, but for which the **evidence is still limited**
6. Evaluate the **role of spatially correlated factors** that may either confound and/or modify the health effects of TRAP, most notably **poverty, traffic noise,** and factors related to the built environment, such as presence of **green space.**
7. Evaluate the **fuller range** of potential impacts of **transportation** and **(new) mobility** on public health
8. **Evaluate the mechanisms behind the association of TRAP with the** selected outcomes by studying **biomarkers** and **subclinical outcomes (**lung function, blood pressure,atherosclerosis, structure and function of the brain….)
9. **Improve methods** in systematic reviews and evidence synthesis

Thanks to the HEI Panel, Consultants, Contractors, external reviewers and HEI staff

Co-chairs:
Francesco Forastiere, *Imperial College London*
Frederick Lurmann, *Sonoma Technology*

Members:
Richard Atkinson, *University of London*
Jeffrey Brook, *University of Toronto; HEI Research Committee*
Howard Chang, *Emory University*
Gerard Hoek, *Utrecht University*
Barbara Hoffmann, *University of Düsseldorf; HEI Research Committee*
Sharon Sagiv, *University of California - Berkeley*
Evi Samoli, *University of Athens; HEI Research Committee*
Audrey Smargiassi, *University of Montreal*
Adam Szpiro, *University of Washington*
Danielle Vienneau, *Swiss Tropical and Public Health Institute*
Jennifer Weuve, *Boston University*

Consultants to the Panel:
Julia Fussell, *Imperial College London*
Frank Kelly, *Imperial College London*
Tim Nawrot, *University of Hasselt*
Gregory Wellenius, *Boston University; HEI Research Committee*

Contractor: Meltem Kutlar Joss and Ron Kappeler, *Swiss Tropical and Public Health Institute*

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