Dose response relationships

Francesco Forastiere

Trieste, 25 April 2018

Contents

- What is a dose response function?
- ERF versus LOEL / bench mark dose
- Which ERFs to quantify
- How do I get ERFs for a HIA?
- Local versus generic ERFs
- Double counting
- Shape of exposure response function

Terminology

- http://www.epa.gov/risk_assessment/glossary.htm
- **Dose-response assessment** examines the relationship between exposure and effects.
- **No-observed-adverse-effect level (NOAEL):** The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

Terminology

- **Lowest-observed-adverse-effect level (LOAEL):** The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

- **Benchmark Dose (BMD) or Concentration (BMC):** A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

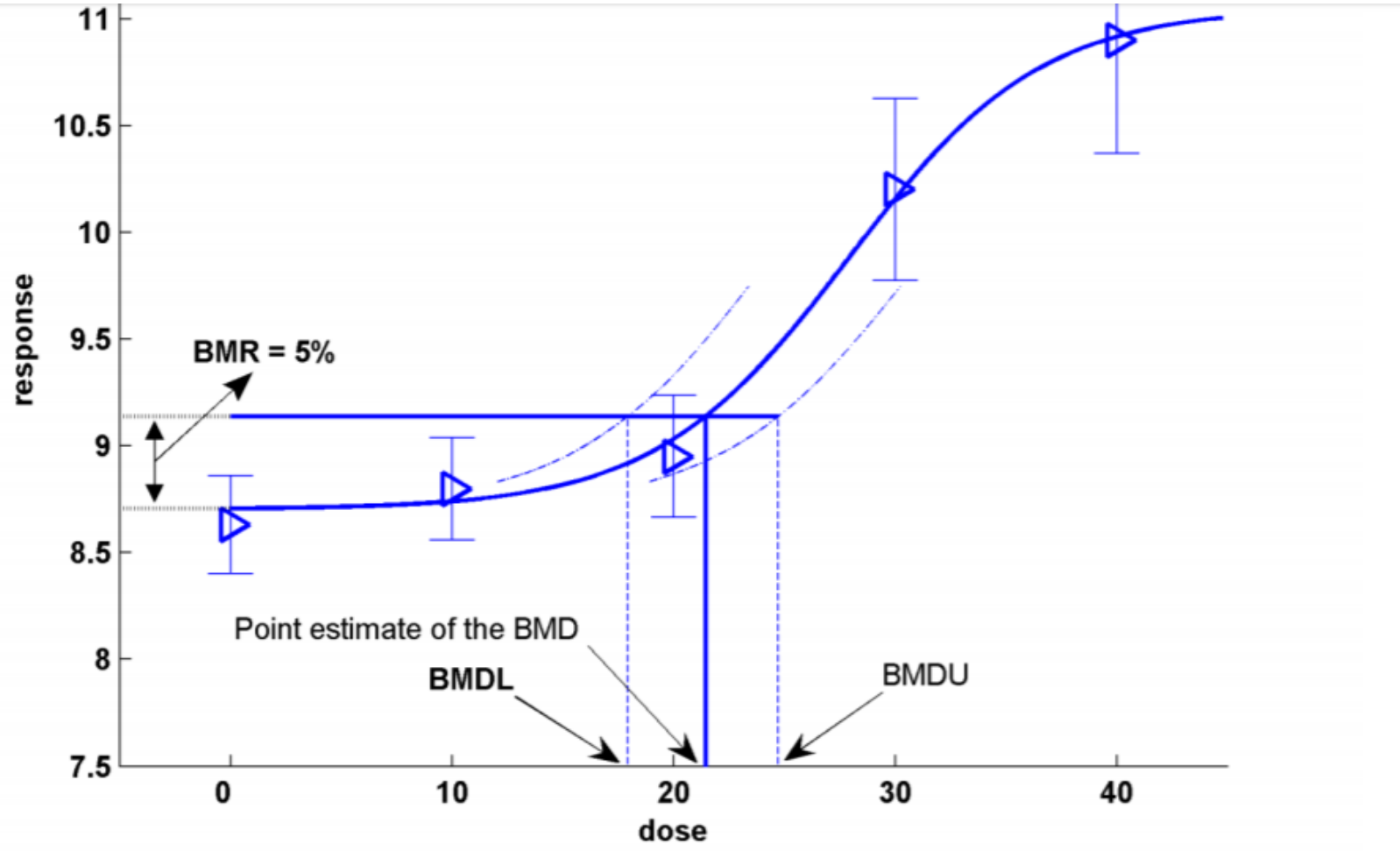


Figure 1: Key concepts for the BMD approach, illustrated by using hypothetical continuous data.

The observed mean responses (triangles) are plotted, together with their confidence intervals. The solid curve is a fitted dose-response model. This curve determines the point estimate of the BMD, which is generally defined as a dose that corresponds to a low but measurable change in response, denoted the benchmark response (BMR). The dashed curves represent respectively the upper and lower 95%-confidence bounds (one sided)[4] for the effect size as a function of dose. Their intersections with the horizontal line are at the lower and upper bounds of the BMD, denoted BMDL and BMDU, respectively.

Terminology

- These concepts very much based on Toxicology, animal experiments and the desire to derive a (legal) guideline
- In HIA, we need to know how much a health effects changes with a change of exposure related to a policy
- Air pollution ERF are based primarily on epidemiological studies

What is an ERF?

- ERFs may be reported as a slope of a regression line with the health response as the dependent variable and the stressor as the independent variable.
- ERFs from epidemiology and/or toxicology
- Uncertainty of the central estimate should be available, e.g. as a confidence interval

Long-Term Exposure to Urban Air Pollution and Mortality in a Cohort of More than a Million Adults in Rome

Giulia Cesaroni,[1] Chiara Badaloni,[1] Claudio Gariazzo,[2] Massimo Stafoggia,[1] Roberto Sozzi,[3] Marina Davoli,[1] and Francesco Forastiere[1]

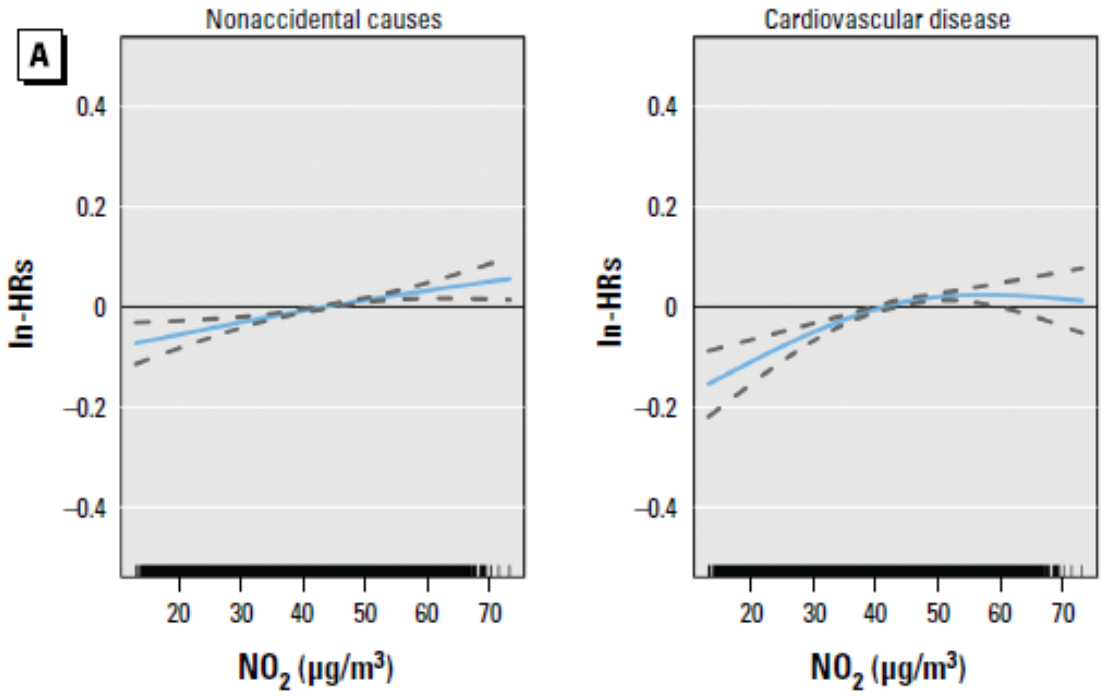


Figure 2. Estimated concentration–response curves (solid lines) and 95% CIs (dashed lines) for nonaccidental causes, cardiovascular disease, IHD, and lung cancer for NO_2 (*A*) and $PM_{2.5}$ (*B*). Cox models adjusted for sex, marital status, place of birth, education, occupation, and area-based socioeconomic position on a 20% sample of the cohort.

Different terms for Exposure in ERFs

Pollutant discharge

▼

Concentration in environment

▼

Exposure

▼

Internal **dose**

▼

Biologically effective dose

▼

Biological effect

ERF in air pollution HIA

- Typically concentration response functions
- Outdoor air concentration as exposure metric
- Due to design of epidemiological studies

- Issue of transferability or portability to variable populations

Which ERF to quantify?

- List potential relationships between stressors and health
- Some but not all to be quantified
- Criteria for quantifying relationships:
  - level of evidence (causality)
  - severity of the health response
  - number of people affected
  - *stakeholder views*

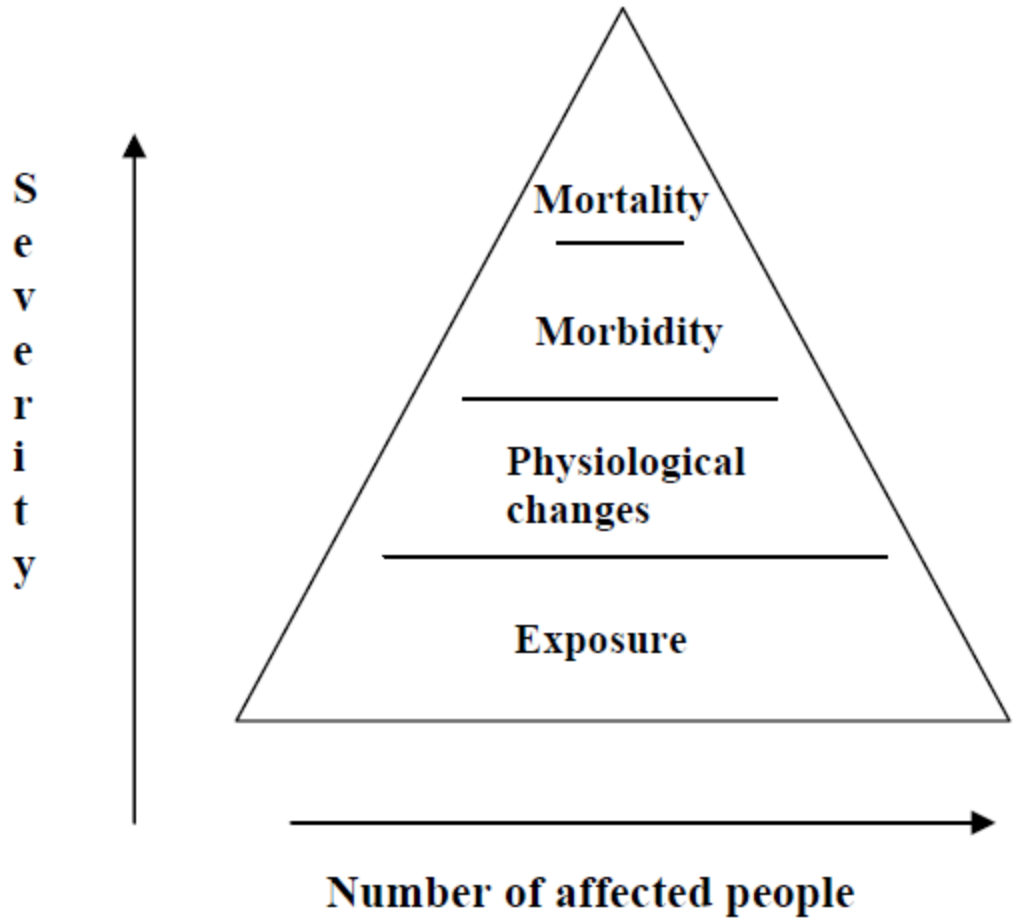


Figure 5 Health effect pyramid

Deriving an ERF

- Published and up-to-date ERF, preferably from an authoritative organisation, e.g. WHO
- Develop your own systematic review and meta-analysis *(Appropriate for epidemiological and toxicological data)*
- Formal methods of expert panel

New versus existing ERF

- Drawback new: time consuming
- Therefore modified methods are:

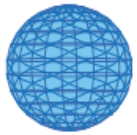
  - ERF used in previous HIAs;

  - results of a previously published good-quality meta-analysis;

  - using a key multi-centre study or a core (non-exhaustive) set of studies;

Systematic review:
January 2013

Hoek *et al. Environmental Health* 2013, **12**:43
http://www.ehjournal.net/content/12/1/43



ENVIRONMENTAL HEALTH

REVIEW **Open Access**

Long-term air pollution exposure and cardio- respiratory mortality: a review

Gerard Hoek[1*], Ranjini M Krishnan[2], Rob Beelen[1], Annette Peters[3], Bart Ostro[4], Bert Brunekreef[1,5] and Joel D Kaufman[2]

Long-term air pollution exposure and cardio- respiratory mortality: a review

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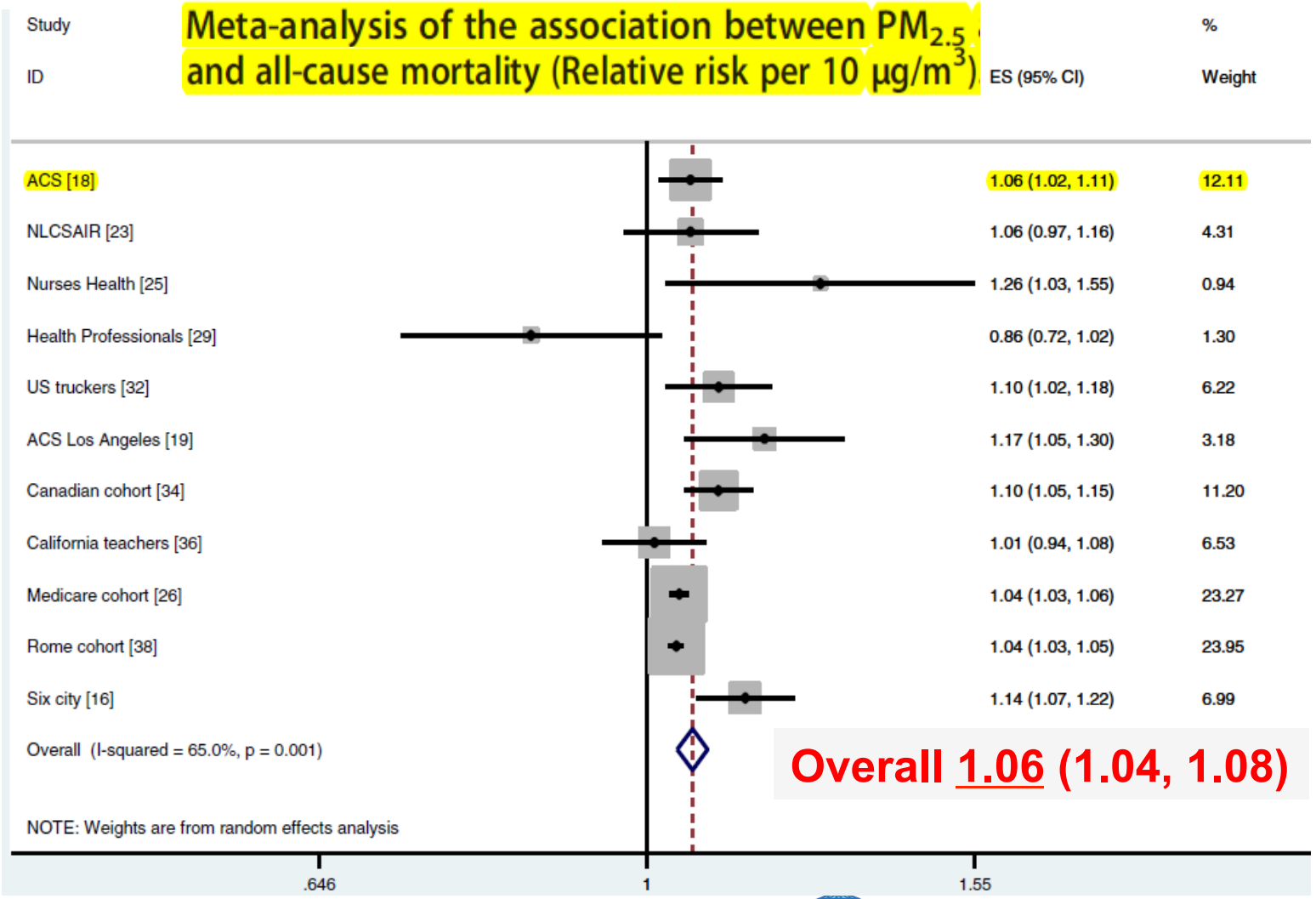


World Health Organization

REGIONAL OFFICE FOR Europe

Health risks of air pollution in Europe – HRAPIE project

Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide

Table 1. CRFs recommended by the HRAPIE project

PM, long-term exposure						
Pollutant metric	**Health outcome**	**Group**	**RR (95% CI) per 10 µg/m³**	**Range of concentration**	**Source of background health data**	**Source of CRF**
$PM_{2.5}$, annual mean	Mortality, all-cause (natural), age 30+ years	A*	1.062 (1.040–1.083)	All	European mortality database (MDB) (WHO, 2013c), rates for deaths from all natural causes (International Classification of Diseases, tenth revision (ICD-10) chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	Meta-analysis of 13 cohort studies with results: Hoek et al. (2013)
$PM_{2.5}$, annual mean	Mortality, cerebrovascular disease (includes stroke), ischaemic heart disease, chronic obstructive pulmonary disease (COPD) and trachea, bronchus and lung cancer, age 30+ years	A	Global Burden of Disease (GBD) 2010 study (IHME, 2013), supra-linear exponential decay saturation model (age-specific), linearized by the $PM_{2.5}$ expected in 2020 under the current legislation scenario	All	European detailed mortality database (WHO, 2013d), ICD-10 codes cerebrovascular: I60–I63, I65–I67, I69.0–I69.3; ischaemic heart disease: I20–I25; COPD: J40–J44, J47; trachea, bronchus and lung cancer: C33–C34, D02.1–D02.2, D38.1	CRFs used in the GBD 2010 study
PM_{10}, annual mean	Postneonatal (age 1–12 months) infant mortality, all-cause	B*	1.04 (1.02, 1.07)	All	European Health for All database (WHO, 2013e) and United Nations projections	Woodruff, Grillo and Schoendorf (1997), based on 4 million infants in the United States

NO_2, long-term exposure						
Pollutant metric	**Health outcome**	**Group**	**RR (95% CI) per 10 µg/m³**	**Range of concentration**	**Source of background health data**	**Source of CRF**
NO_2, annual mean	Mortality, all (natural) causes, age 30+ years	B*	1.055 (1.031–1.080)	>20 µg/m³	MDB (WHO, 2013c), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 WHO Regional Office for Europe countries, latest available data	Meta-analysis of all (11) cohort studies published before January 2013 by Hoek et al. (2013); RR based on single-pollutant models

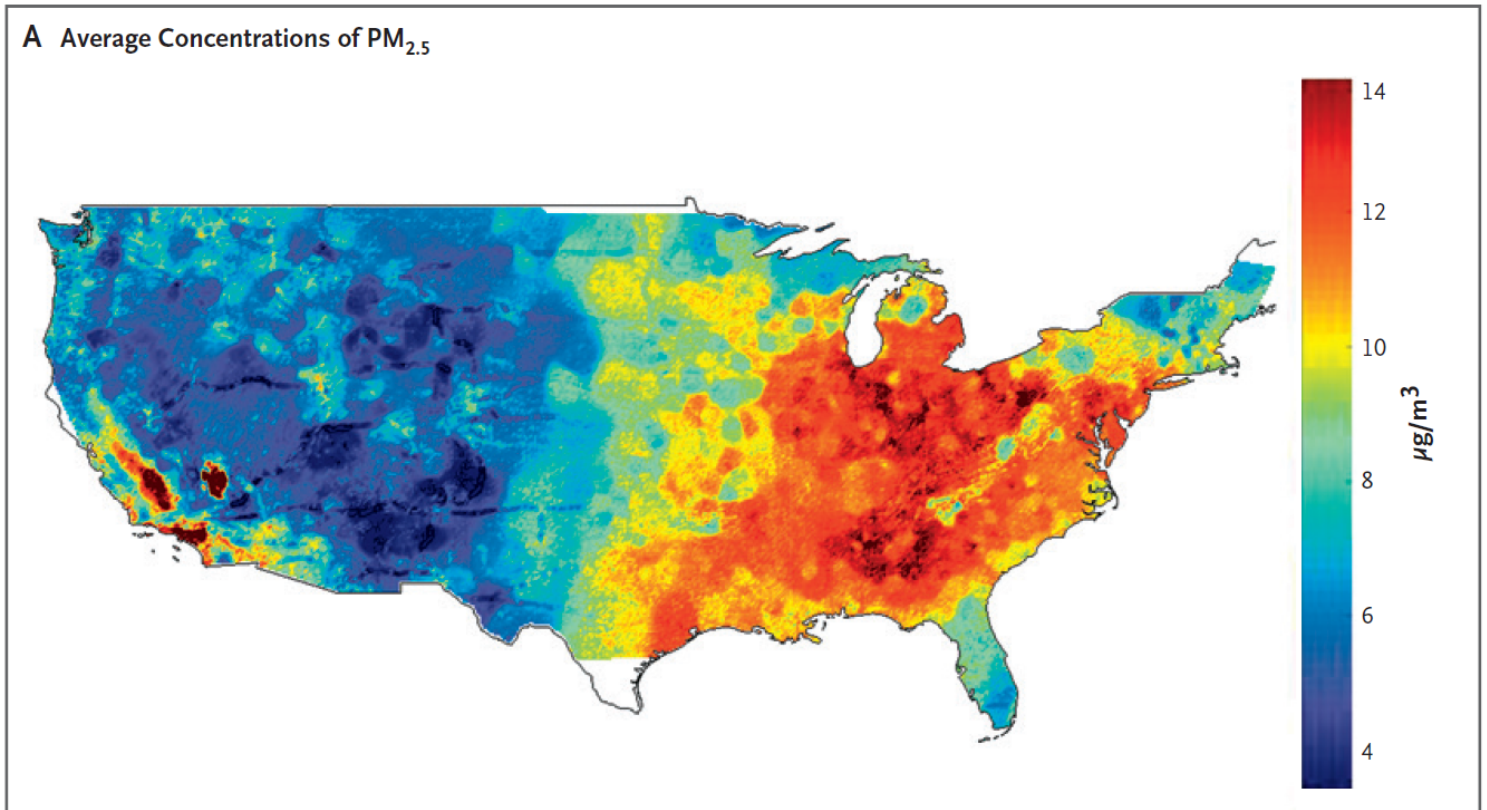
Comments
Some of the long-term NO_2 effects may overlap with effects from long-term $PM_{2.5}$ (up to 33%); this is therefore recommended for quantification under Group B to avoid double counting in Group A analysis

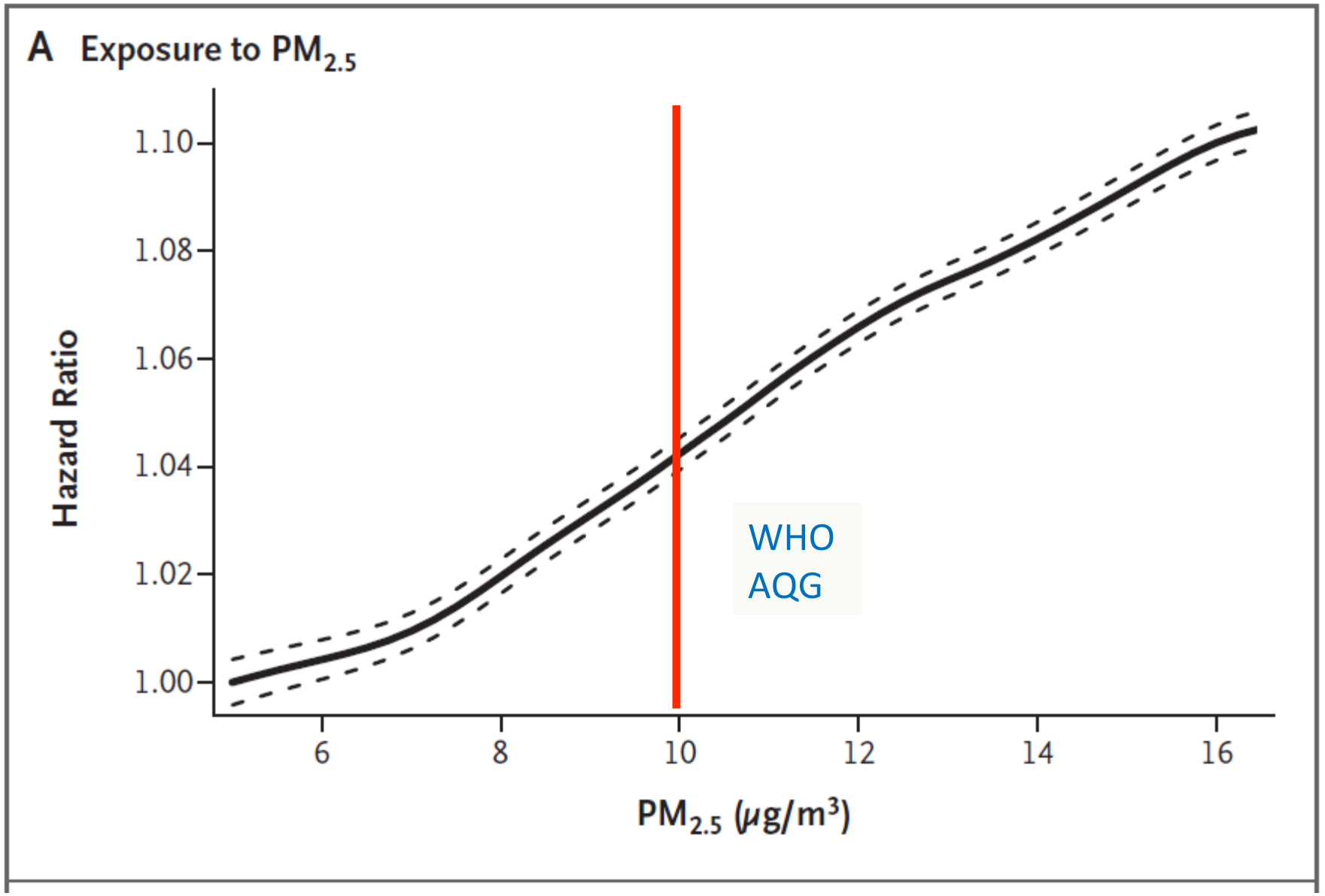
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 29, 2017 VOL. 376 NO. 26

Air Pollution and Mortality in the Medicare Population

Qian Di, M.S., Yan Wang, M.S., Antonella Zanobetti, Ph.D., Yun Wang, Ph.D., Petros Koutrakis, Ph.D., Christine Choirat, Ph.D., Francesca Dominici, Ph.D., and Joel D. Schwartz, Ph.D.




A Exposure to $PM_{2.5}$
Hazard Ratio
1.10
1.08
1.06
1.04
1.02
1.00
6
8
10
12
14
16
$PM_{2.5}$ ($\mu g/m^3$)
WHO
AQG

Methods

- Systematical search of PubMed, Web of Science, Embase for studies up until the 10th of September 2017 using specific keywords.
- Meta-analysis using random effects methods of DerSimonian and Laird (1986).
- Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

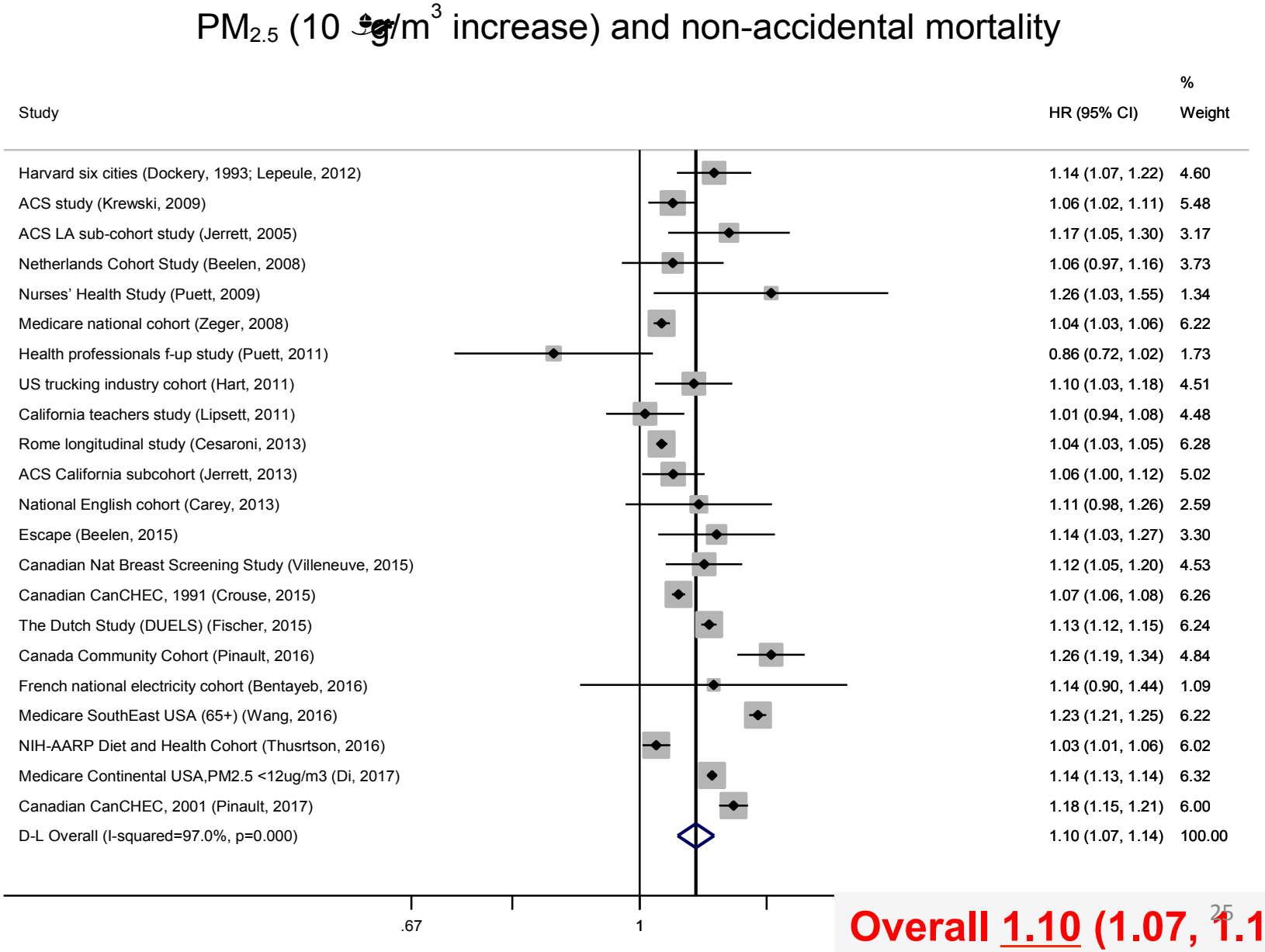
Studies after Hoek 2013

- **ACS California subcohort (Jerrett, 2013)**
  73,711 subjects living in California, 1982 – 2000
- **National English cohort (Carey, 2013)**
  835,607 patients from general practice, 2003-2007
- **Escape (Beelen, 2014)**
  367,251 participants from 22 European cohorts 1985-2008
- **Canadian Nat Breast Screening Study (Villeneuve, 2015)**
  89,248 women enrolled in the Canadian National Breast Screening Study
- **Canadian national cohort (Crouse, 2015)**
  2.5 million residents in Canada in 1991
- **The Dutch Study (DUELS) (Fischer, 2015)**
  7.1 millions from the Dutch Environmental Longitudinal Study (DUELS)
- **Canada Community Cohort (Pinault, 2016)**
  299,500 respondents to the Canada Comunity Health Survey
- **French national electricity cohort (Bentayeb, 2016)**
  20,327 adults working at the French national electricity and gas company
- **Medicare (65+) (Wang, 2016)**
  13.1 million Medicare beneficiaries (age ≥65) in seven southeastern US states
- **NIH-AARP Diet and Health Cohort (Thusrtson, 2016)**
  517,041 men and women in the National Institutes of Health-AARP cohort.
- **Medicare Continental USA, PM2.5 <12ug/m3 (Di, 2017)**
  28 million Medicare beneficiaries (age ≥65) with exposure below 12 ug/m3 in the USA
- **Canadian CanCHEC, 2001 (Pinault, 2017)**
  2.4 millions residents in Canada in 2001

Cohort studies conducted in North America and Europe until 2016 reporting associations between long-term exposure to PM2.5 and all-cause (or natural-cause) mortality. % Increase Risk (IR) per 10 ug/m3

N.	Study	Conc. (range) ($\mu g/m^3$)	% IR	95% CI	
1	Harvard six cities (Dockery, 1993)	16 (11-24)	14	7	22
2	ACS study (Krewski, 2009)	18 (10-26)	6	2	11
3	ACS LA sub-cohort study (Jerrett, 2005)	18 (~9-27)	17	5	30
4	Netherlands Cohort Study (Beelen, 2008)	28 (23-37)	6	-3	16
5	Nurses' Health Study (Puett, 2009)	14 (6-28)	26	2	54
6	Medicare national cohort (Zeger, 2008)	13 (7-19)	4	3	6
7	Health professionals f-up study (Puett, 2011)	18 (12-24)	-14	-28	2
8	US trucking industry cohort (Hart, 2011)	14 (6-22)	10	3	18
9	California teachers study (Lipsett, 2011)	16 (3-28)	1	-5	9
10	Rome longitudinal study (Cesaroni, 2013)	23 (7-32)	4	3	5
11	ACS California subcohort (Jerrett, 2013)	14 (4-25)	6	0	12
12	National English cohort (Carey, 2013)	13 (10-16)	11	-2	26
13	Escape (Beelen, 2015)	19 (6-31)	14	3	27
14	Canadian Nat Breast Screening Study (Villeneuve, 2015)	9 (1-18)	12	4	19
15	Canadian national cohort (Crouse, 2015)	9 (1-18)	7	6	8
16	The Dutch Study (DUELS) (Fischer, 2015)	19 (16-21)	13	11	14
17	Canada Community Cohort (Pinault, 2016)	6 (1-13)	26	19	34
18	French national electricity cohort (Bentayeb, 2016)	15 (6-24)	14	-10	44
19	Medicare (65+) (Wang, 2016)	11 (6-21)	23	21	25
20	NIH-AARP Diet and Health Cohort (Thusrtson, 2016)	12 (6-19)	3	0	5
21	Medicare Continental USA, PM2.5 <12ug/m3 (Di, 2017)	10 (6-12)	14	13	14
22	Canadian CanCHEC, 2001 (Pinault, 2017)	7 (2-13)	18	15	21

Metanalysis, all studies included (September 2017)

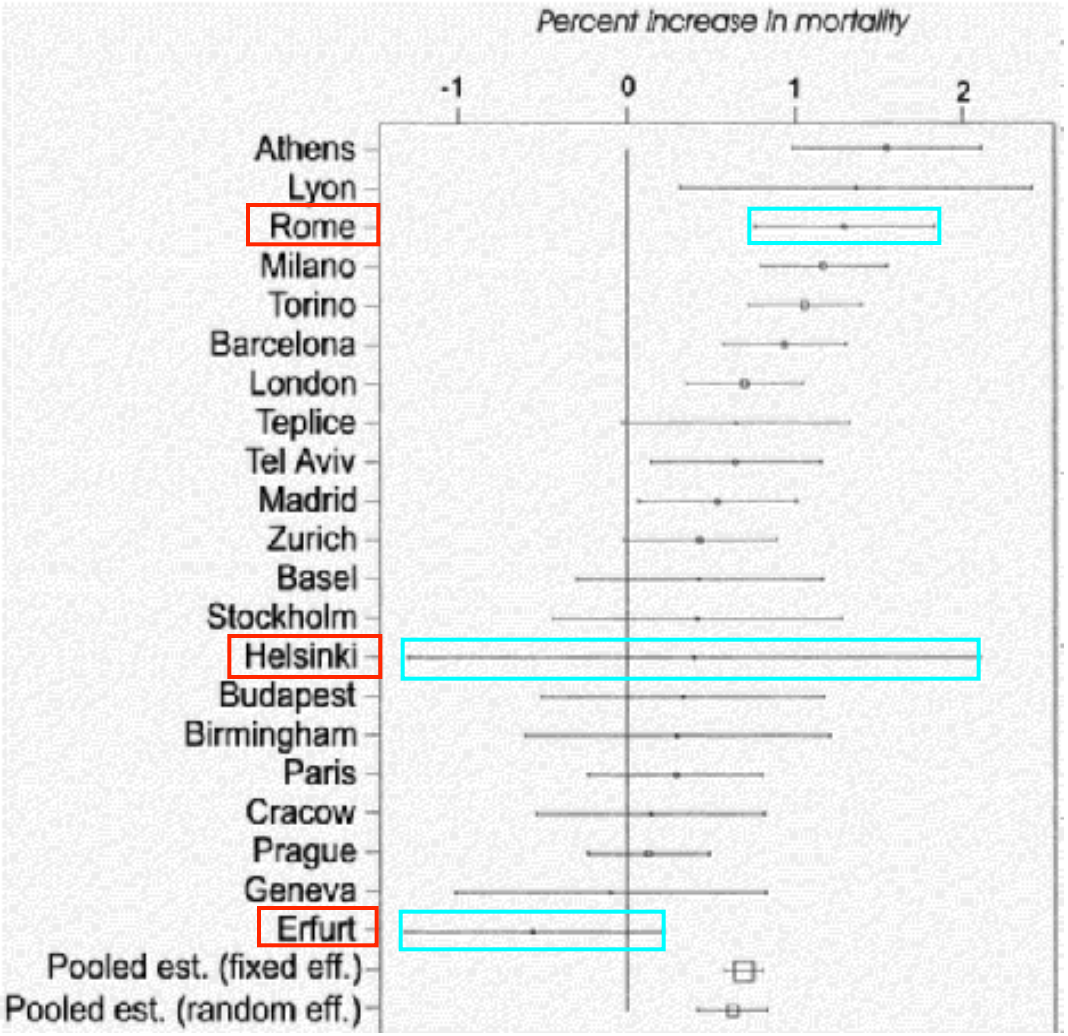


Overall 1.10 (1.07, 1.14)

Transferability between locations

- Question: WHICH ERF IS MOST APPROPRIATE?

- Assume that you want to estimate the increase in mortality due to air pollution in the following cities for HIA purposes:
- Rome
- Helsinki
- Erfurt



Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 2001;12(5):521-31.

Different options

- Choose the city specific estimates
- Choose the pooled estimate
- Investigate why city-specific estimates differ from each other (heterogeneity)
- Calculate a weighted mean of the local-city value and the pooled estimate (shrunken estimate)

Heterogeneity of PM10 Relative Risk per 10 μg/m3 : APHEA-2

Effect modifier	25th percentile effect modifier	75th percentile effect modifier
NO2	0.19	0.80
Temperature	0.29	0.82
Northwest/East	0.73	0.22

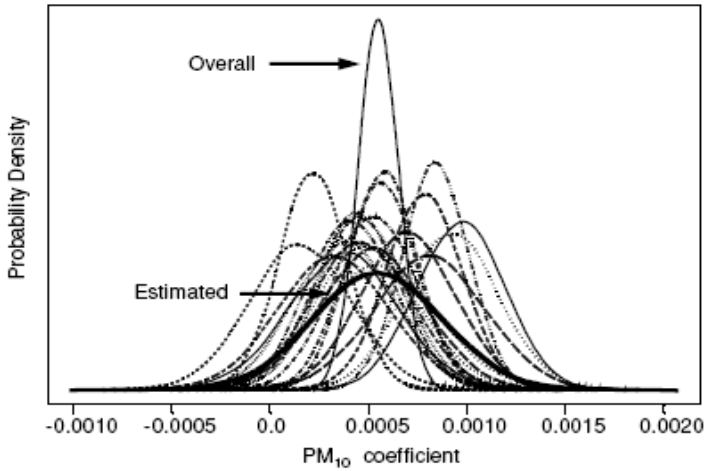
Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 2001;12(5):521-31.

Shrunken estimate (Bayesian estimate)

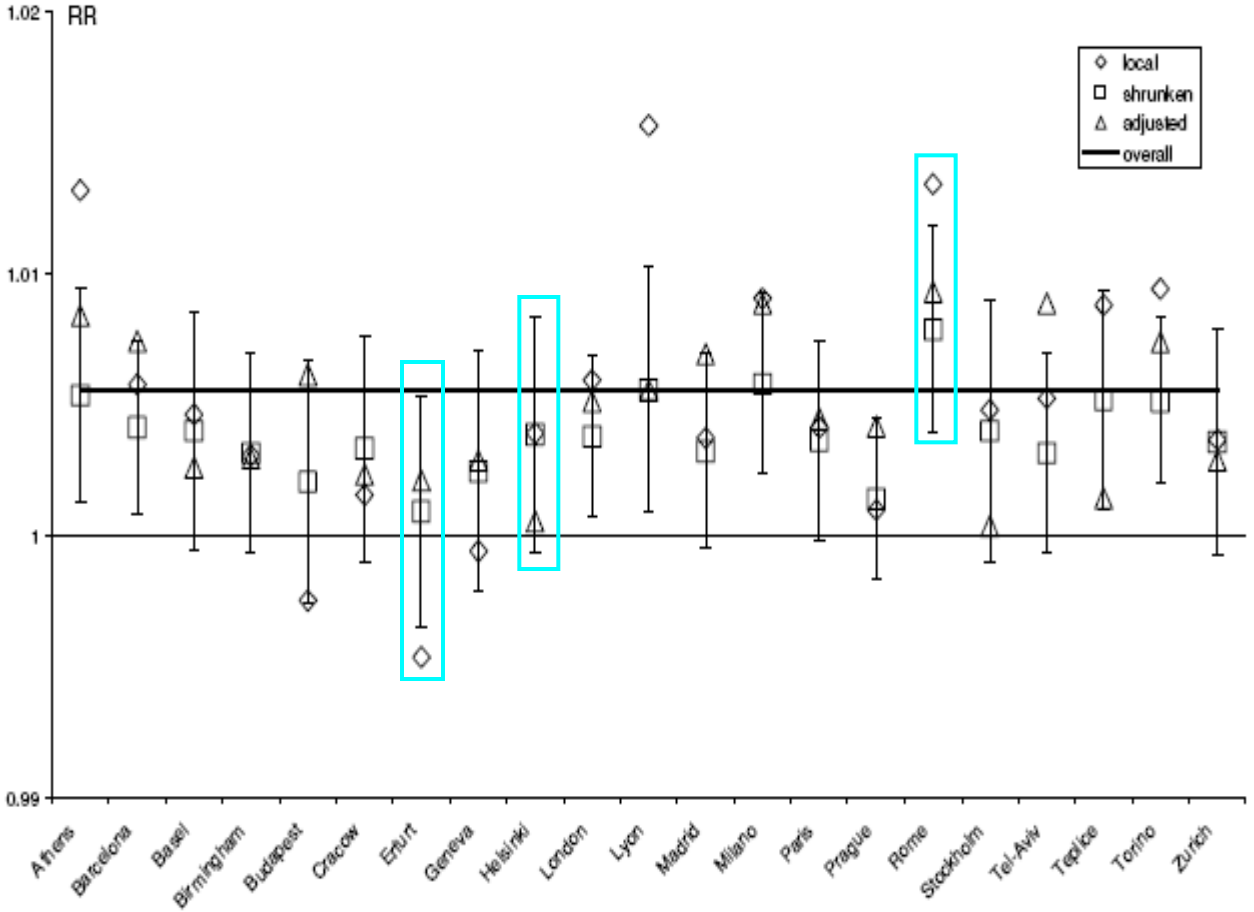
- To calculate a shrunken estimate you use information of the pooled estimate and the city specific (local) estimate

$$\hat{\beta}^{c}_{p,Shr} = E\left(\mu^{c}_{p} \mid \hat{\beta}^{c}_{p}; \bar{\beta}, \sigma^{2}_{B}, \sigma^{2}_{W,c}\right)$$

$$= \bar{\beta} + \frac{\sigma^{2}_{B}}{\sigma^{2}_{B} + \sigma^{2}_{W,c}}\left(\hat{\beta}^{c}_{p} - \bar{\beta}\right)$$



Le Tertre A, Schwartz J, Touloumi G. Empirical Bayes and adjusted estimates approach to estimating the relation of mortality to exposure of PM(10). Risk Anal 2005;25(3):711-8.



Le Tertre A, Schwartz J, Touloumi G. Empirical Bayes and adjusted estimates approach to estimating the relation of mortality to exposure of PM(10). Risk Anal 2005;25(3):711-8.

Double counting (or undercounting?)

- Air pollution is a complex mixture of many gaseous and particulate components
- These components may interact
- In HIA usually a few components are selected e.g. those for which a ERF is available
- PM2.5 often component of choice, e.g recent WHO meetings

Double counting (or undercounting?)

- Use of a single pollutant may underestimate effect of the mixture
- PM2.5 may underestimate effect local traffic policies
- Adding health effects from two or more pollutants may however overestimate effects if
  - Derived from same studies
  - Single pollutant estimates are used
  - Pollutants are correlated highly

Estimates at high concentration

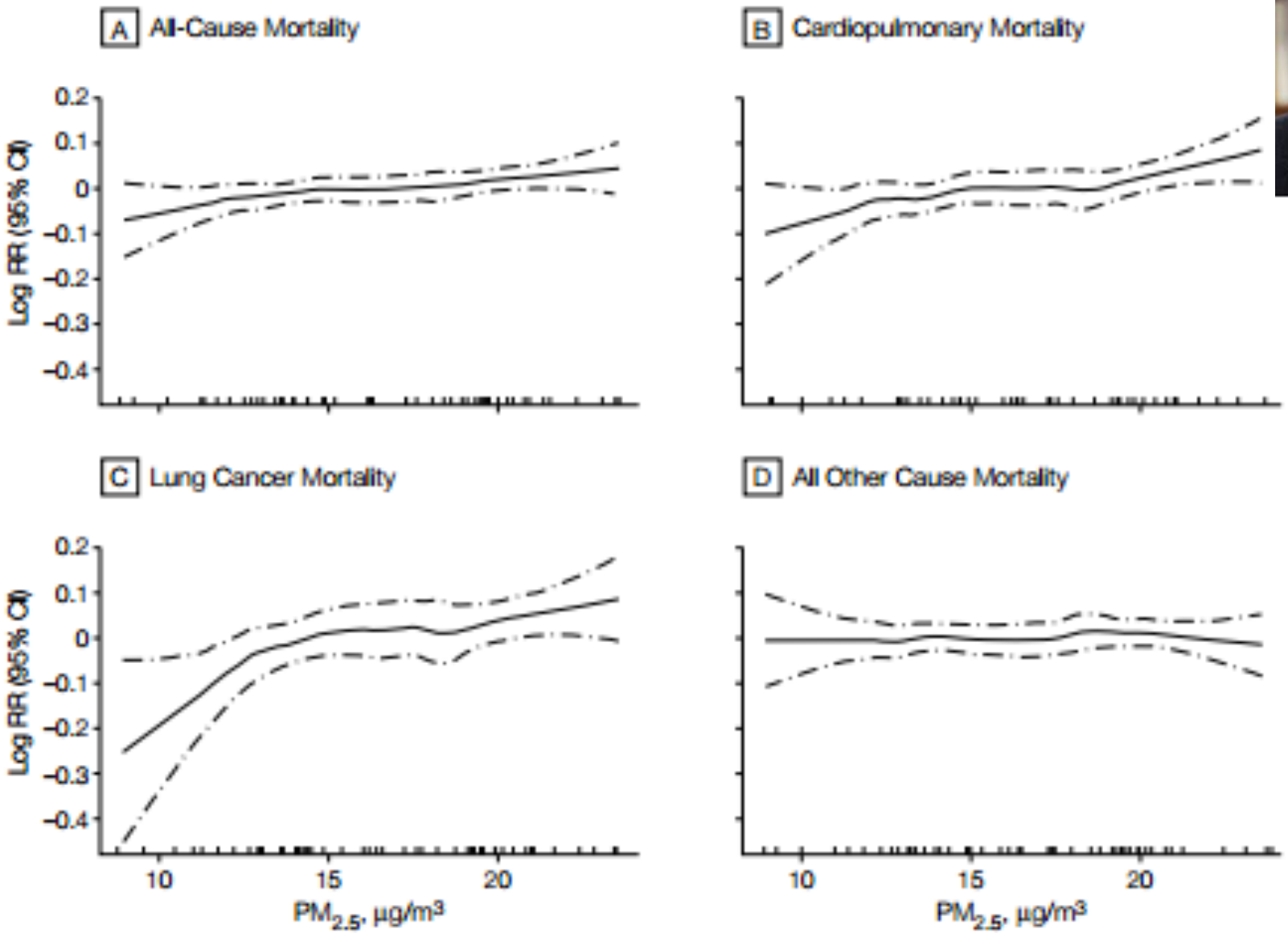
2004, first WHO Global Burden of Disease

Chapter 17

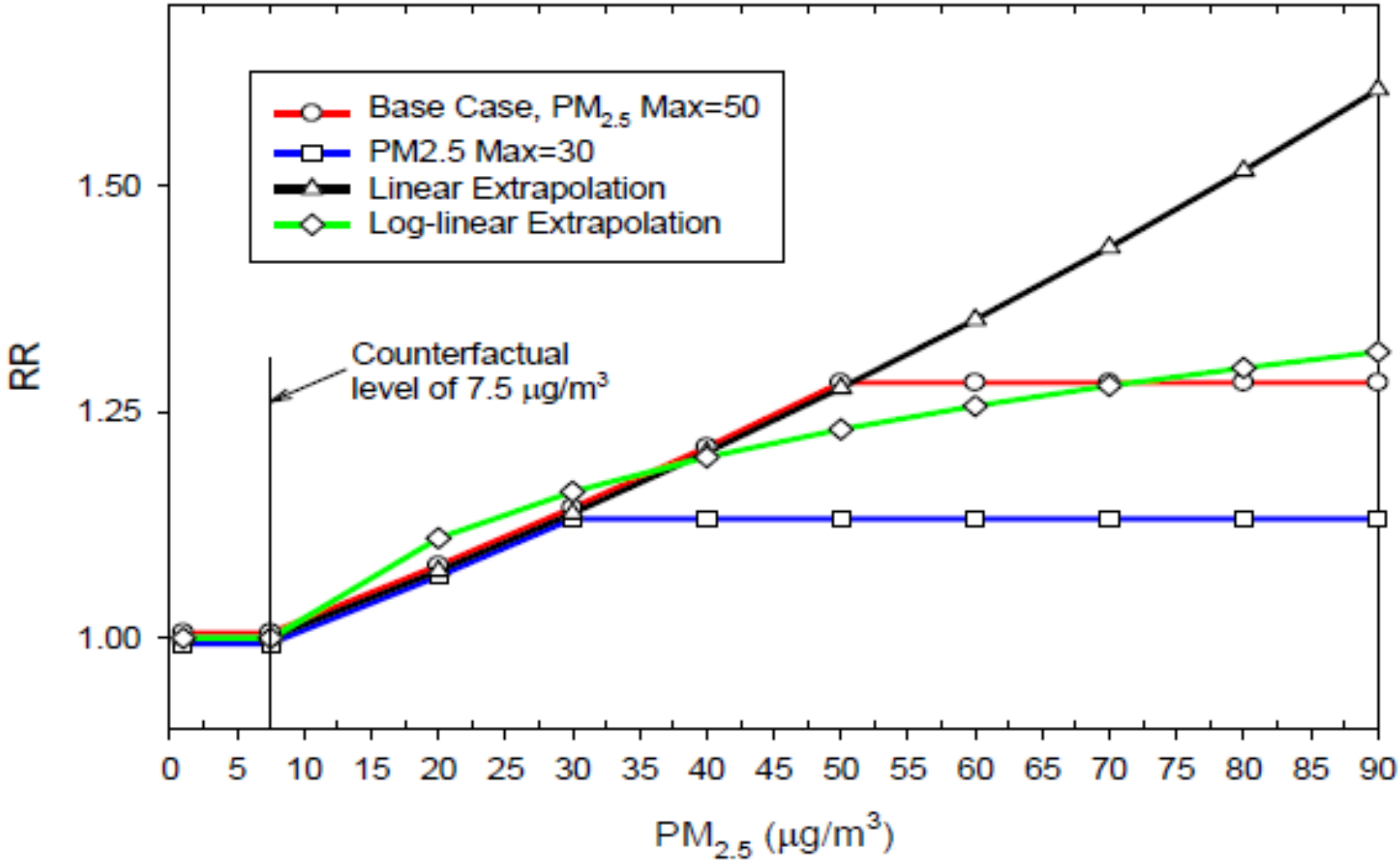
URBAN AIR POLLUTION

AARON J. COHEN, H. ROSS ANDERSON, BART OSTRO,
KIRAN DEV PANDEY, MICHAL KRZYZANOWSKI,
NINO KÜNZLI, KERSTEN GUTSCHMIDT,
C. ARDEN POPE III, ISABELLE ROMIEU,
JONATHAN M. SAMET AND KIRK R. SMITH

Figure 2. Nonparametric Smoothed Exposure Response Relationship



Exposure-response function: long-term PM2.5 and mortality, ACS. Pope et al, 2002



Alternative concentration-response curves for cardiopulmonary deaths. From Cohen et al. (2004).

Cardiovascular Mortality and Exposure to Airborne Fine Particulate Matter and Cigarette Smoke

Shape of the Exposure-Response Relationship

C. Arden Pope III, PhD; Richard T. Burnett, PhD; Daniel Krewski, PhD; Michael Jerre
Yuanli Shi, MD; Eugenia E. Calle, PhD; Michael J. Thun, MD

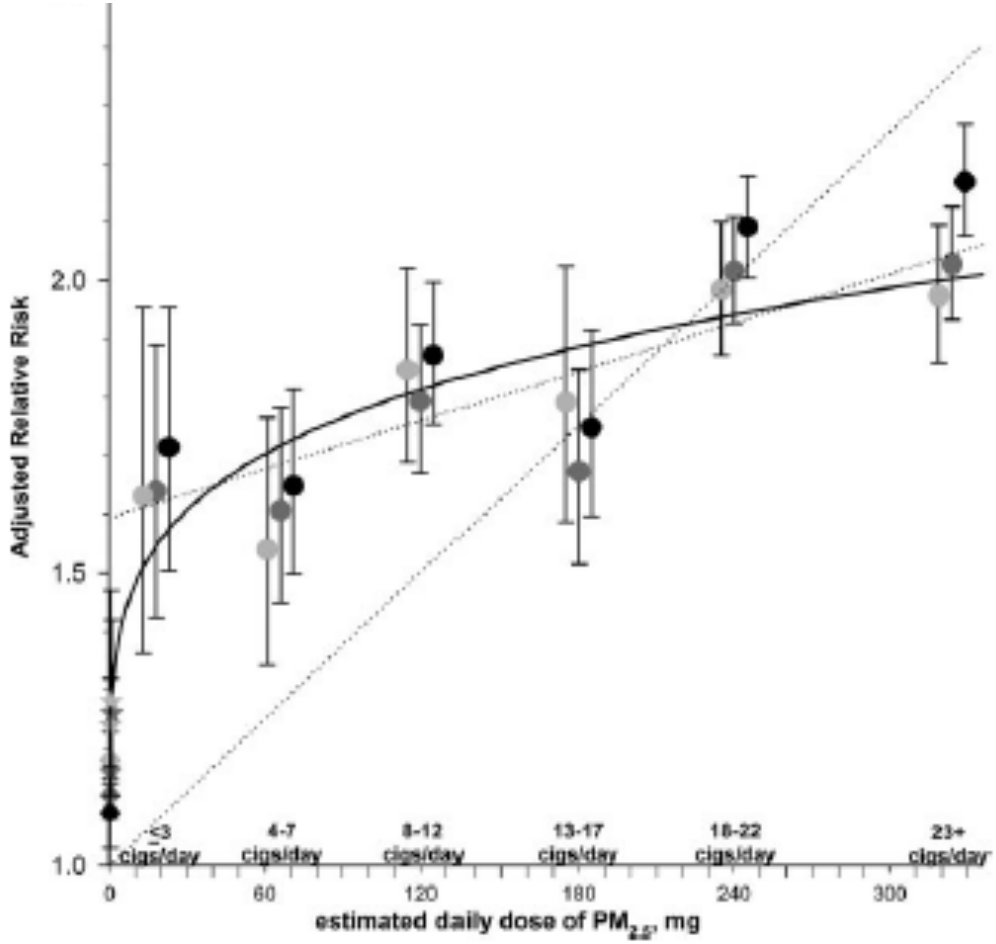


Figure 1. Adjusted relative risks (and 95% CIs) of ischemic heart disease (light gray), cardiovascular disease (dark gray), and cardiopulmonary disease (black) mortality plotted over baseline estimated daily dose of $PM_{2.5}$ from different increments of current cigarette (cigs) smoking (relative to never smokers). Diamonds represent comparable mortality risk estimates for $PM_{2.5}$ from air pollution. Stars represent comparable pooled relative risk estimates associated with SHS exposure from the 2006 Surgeon General's report and from the INTERHEART study. The solid and dotted lines are fitted linear and nonlinear lines illustrating alternative monotonic exposure-response relationships.

2009

An Integrated Risk Function for Estimating the Global Burden of Disease Attributable to Ambient Fine Particulate Matter Exposure

Richard T. Burnett,[1] C. Arden Pope III,[2] Majid Ezzati,[3] Casey Olives,[4] Stephen S. Lim,[5] Sumi Mehta,[6] Hwashin H. Shin,[1] Gitanjali Singh,[7] Bryan Hubbell,[8] Michael Brauer,[9] H. Ross Anderson,[10] Kirk John R. Balmes,[12,13] Nigel G. Bruce,[14] Haidong Kan,[15] Francine Laden,[16] Annette Prüss-Ustün, Michelle C. Turner,[18] Susan M. Gapstur,[19] W. Ryan Diver,[19] and Aaron Cohen[20]

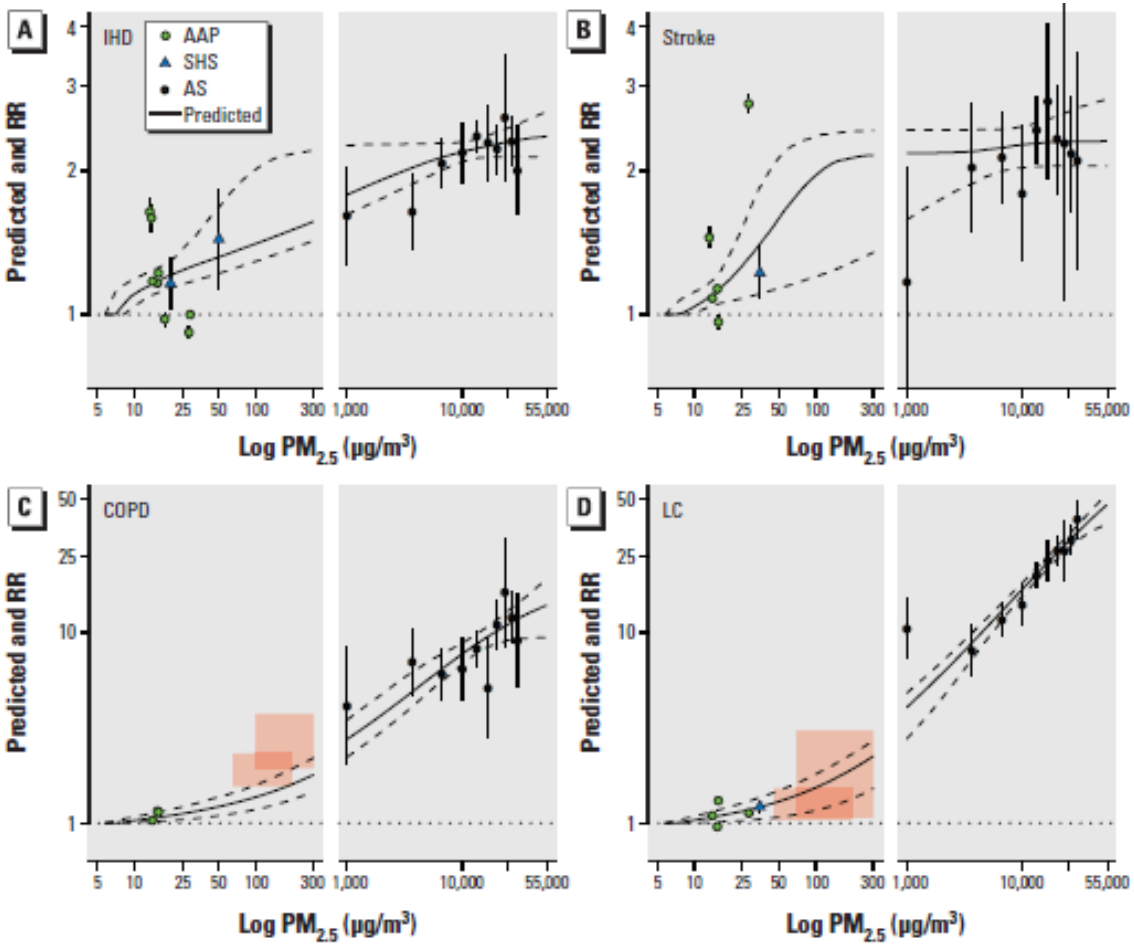


Figure 1. Predicted values of IER model (solid line) and 95% CIs (dashed line) and type-specific RRs (points) and 95% CIs (error bars) for IHD (*A*), stroke (*B*), COPD (*C*), and LC (*D*) mortality. Shaded boxes for COPD and LC mortality represent uncertainty (height) and exposure contrast (width) of RR HAP estimates for males (smaller boxes) and females (larger boxes) separately.

2014

The Lancet, May 2017

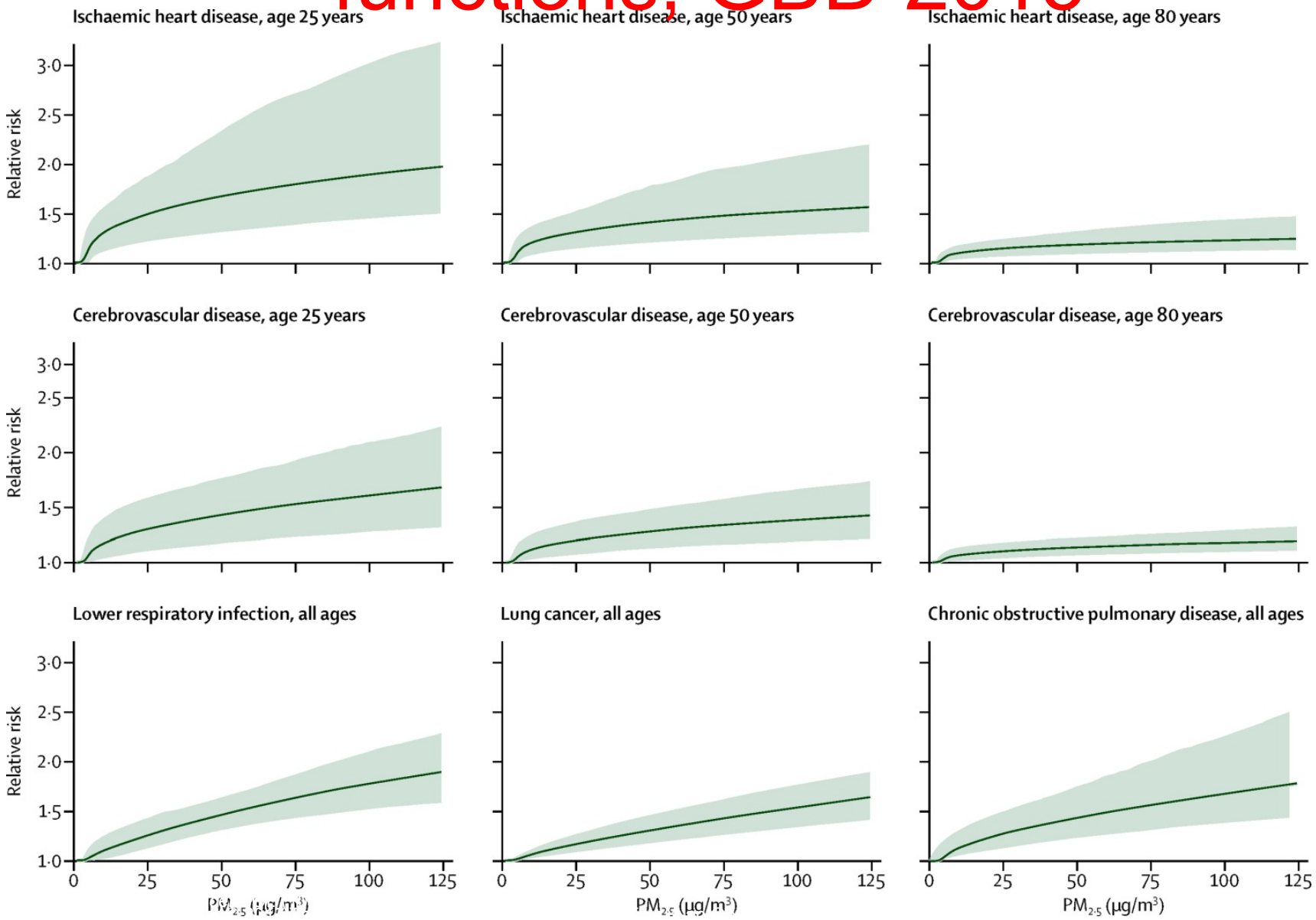
Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015

Aaron J Cohen*, Michael Brauer*, Richard Burnett, H Ross Anderson, Joseph Frostad, Kara Estep, Kalpana Balakrishnan, Bert Brunekreef, Lalit Dandona, Rakhi Dandona, Valery Feigin, Greg Freedman, Bryan Hubbell, Amelia Jobling, Haidong Kan, Luke Knibbs, Yang Liu, Randall Martin, Lidia Morawska, C Arden Pope III, Hwashin Shin, Kurt Straif, Gavin Shaddick, Matthew Thomas, Rita van Dingenen, Aaron van Donkelaar, Theo Vos, Christopher J L Murray, Mohammad H Forouzanfar†

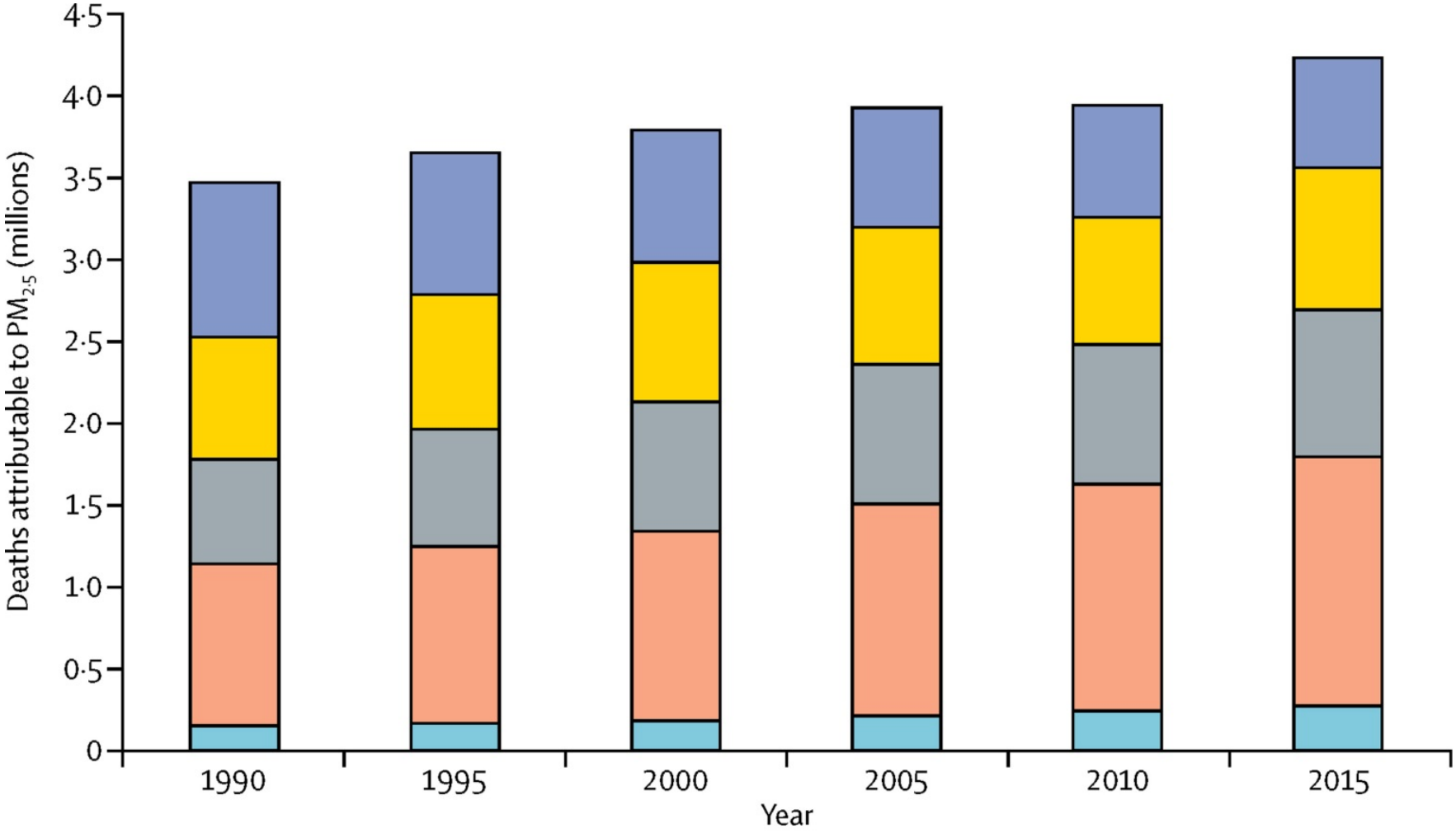
Findings Ambient $PM_{2.5}$ was the fifth-ranking mortality risk factor in 2015. Exposure to $PM_{2.5}$ caused 4·2 million (95% uncertainty interval [UI] 3·7 million to 4·8 million) deaths and 103·1 million (90·8 million 115·1 million) disability-adjusted life-years (DALYs) in 2015, representing 7·6% of total global deaths and 4·2% of global DALYs, 59% of these in east and south Asia. Deaths attributable to ambient $PM_{2.5}$ increased from 3·5 million (95% UI 3·0 million to 4·0 million) in 1990 to 4·2 million (3·7 million to 4·8 million) in 2015. Exposure to ozone caused an additional 254 000 (95% UI 97 000–422 000) deaths and a loss of 4·1 million (1·6 million to 6·8 million) DALYs from chronic obstructive pulmonary disease in 2015.

4.2 million deaths attributable to PM2.5 in 2015

Integrated exposure–response functions, GBD 2015



Deaths attributable to ambient particulate matter pollution by year and cause



Deaths attributable to ambient particulate matter pollution in 2015

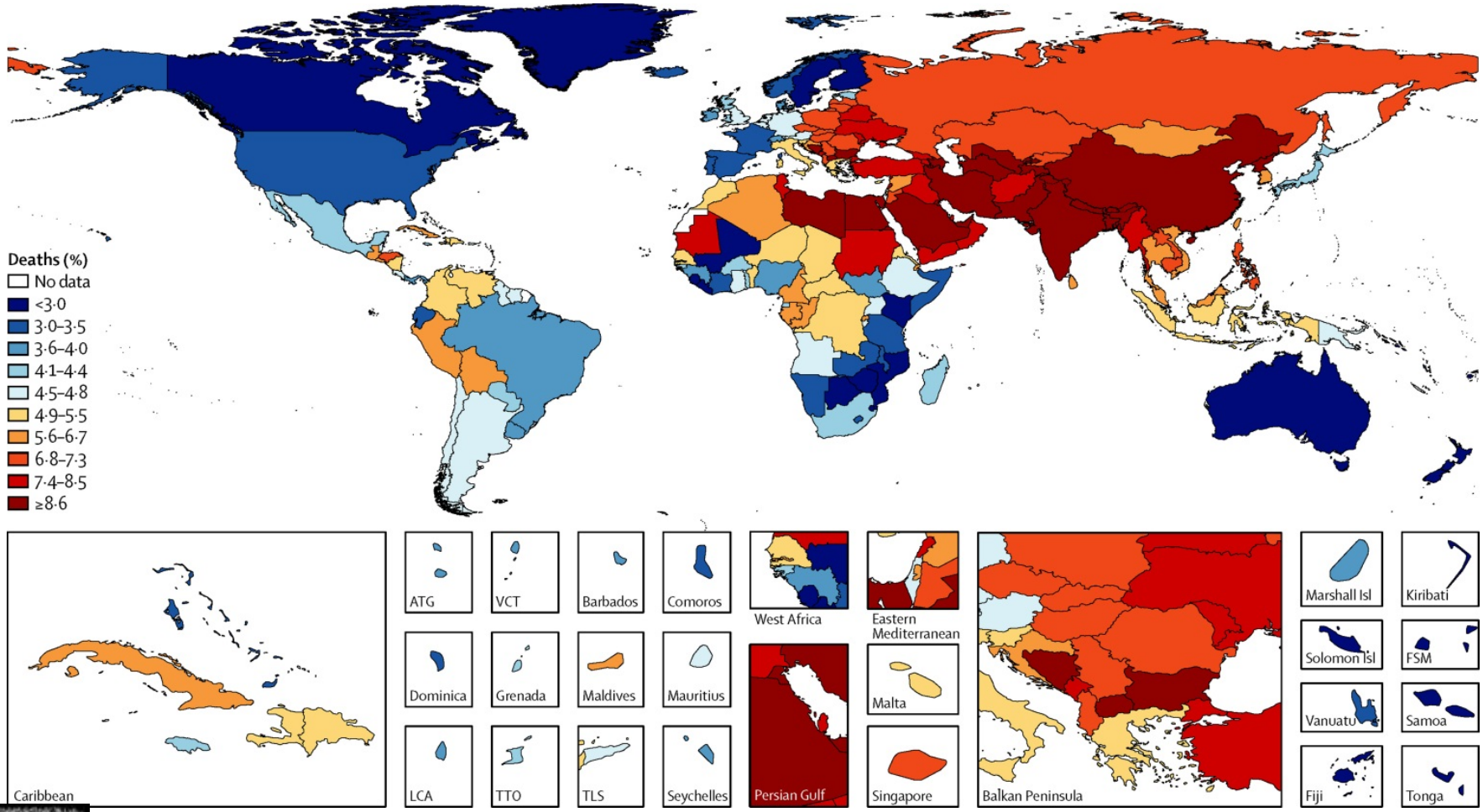
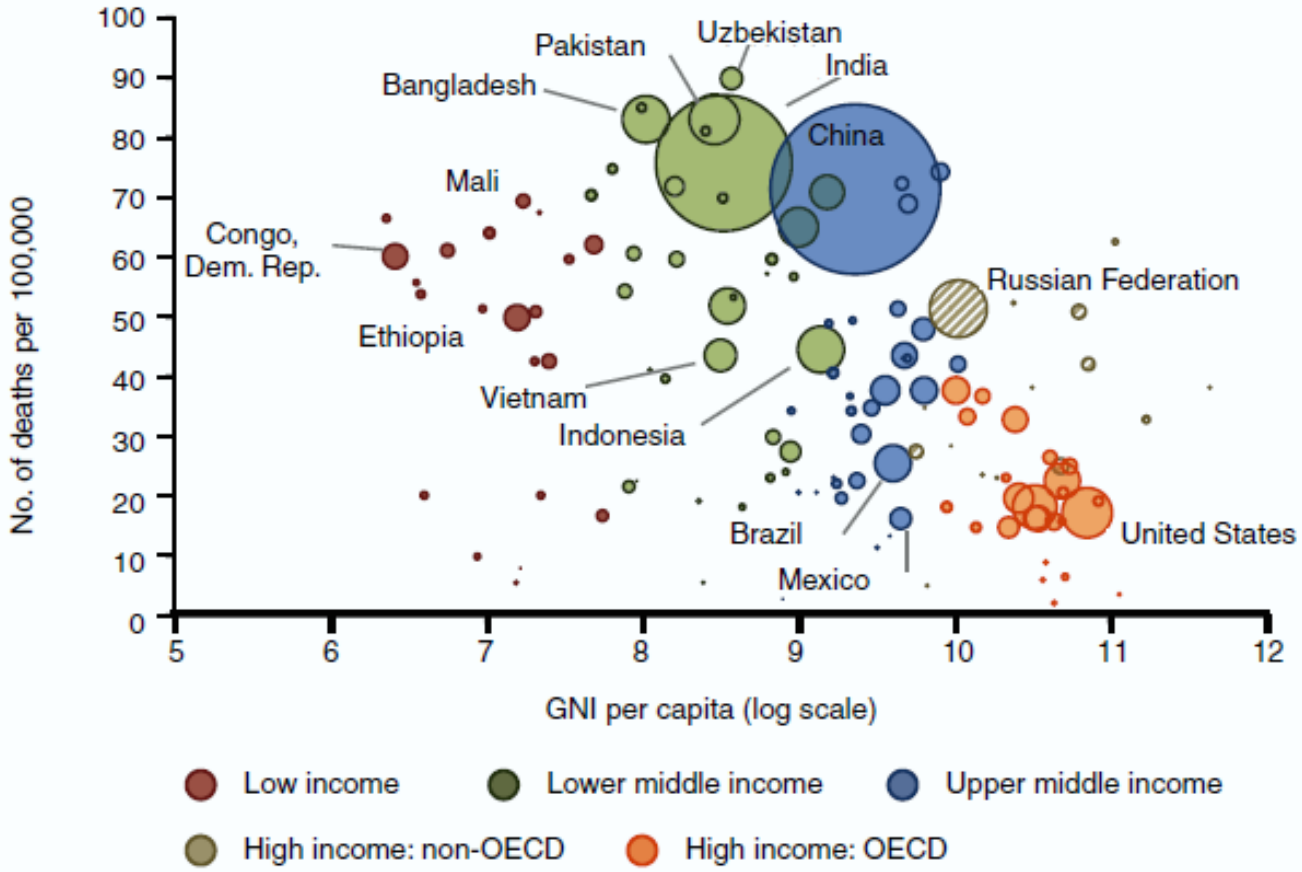


FIGURE 2.11 Ambient $PM_{2.5}$ Death Rate versus Income per Capita, 2013



Sources: World Bank and IHME.

Note: Size of bubble corresponds to total number of deaths. GNI = gross national income; OECD = Organisation for Economic Co-operation and Development.

Changes in mortality attributable to ambient particulate matter pollution according to population-level determinants by country from 1990 to 2015

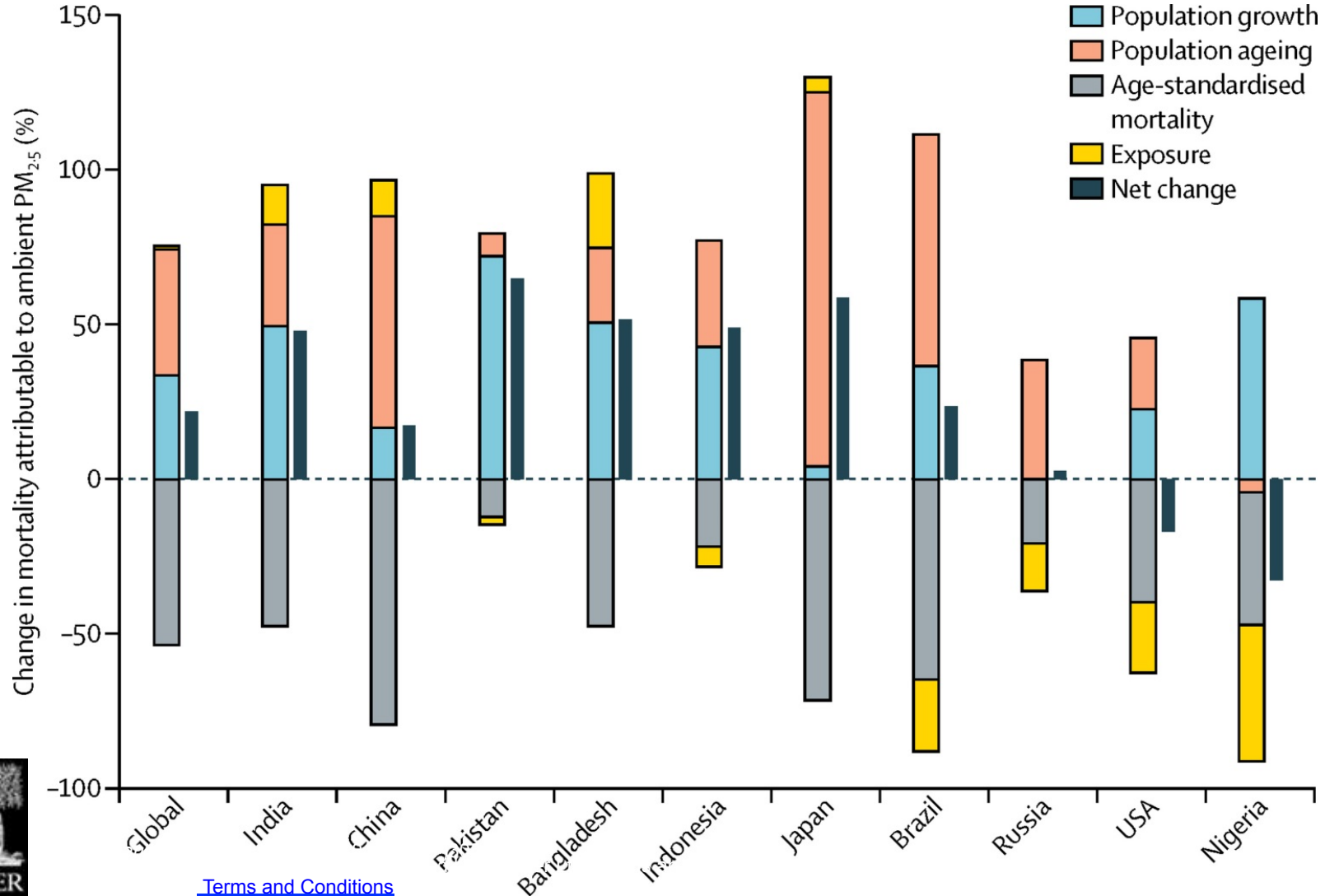


Figure 1. Global ranking of risk factors by total number of deaths from all causes for all ages and both sexes in 2016.