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# Quantification methods for health effects of $NO_2$

**2nd July 2015**

# Outline

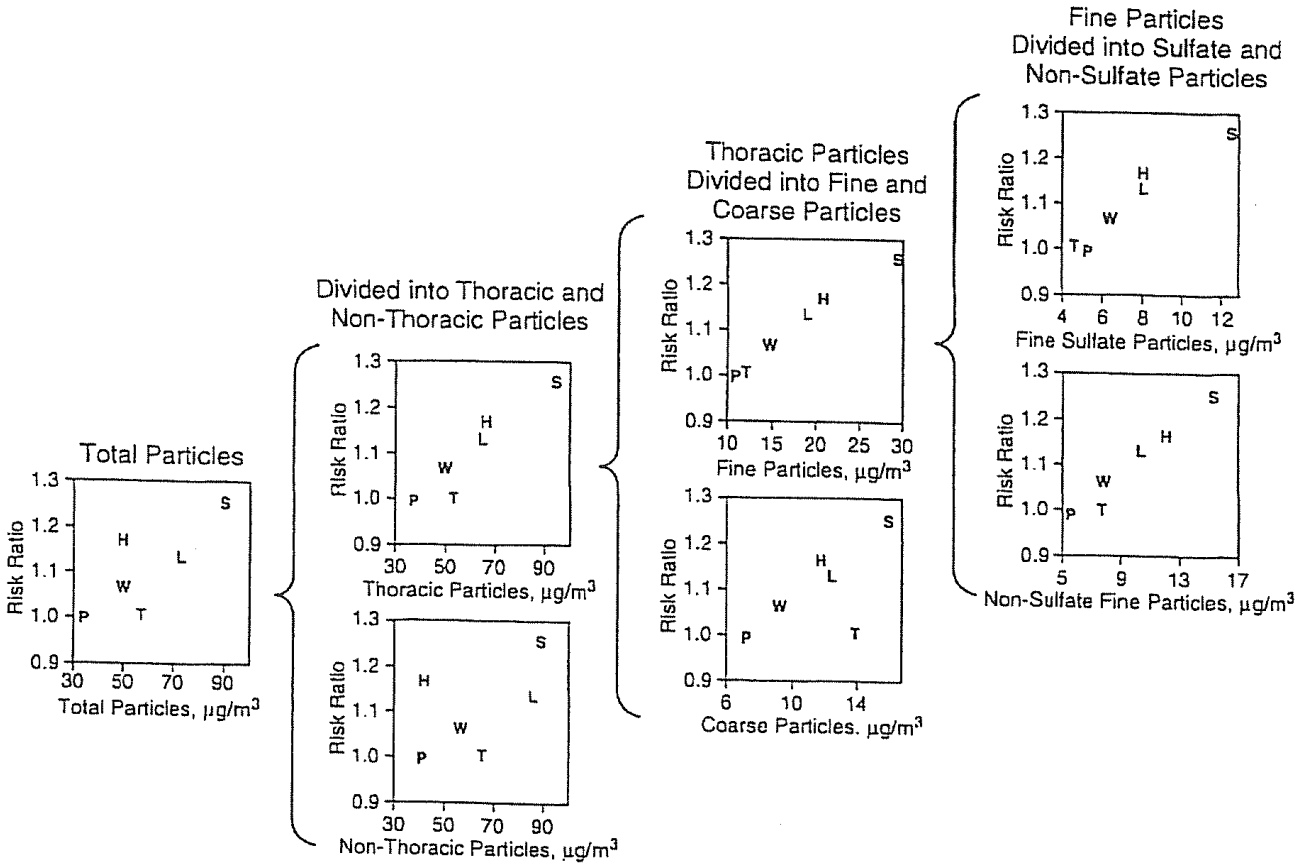
*(Focussing on long-term exposure and mortality)*

- Long term exposure studies on $PM_{2.5}$ and $NO_2$
- WHO discussions on causality
- WHO discussions on concentration-response functions
- Counterfactuals (baselines), cessation lags, scale of modelling
- Different approaches for different types of exposure assessment

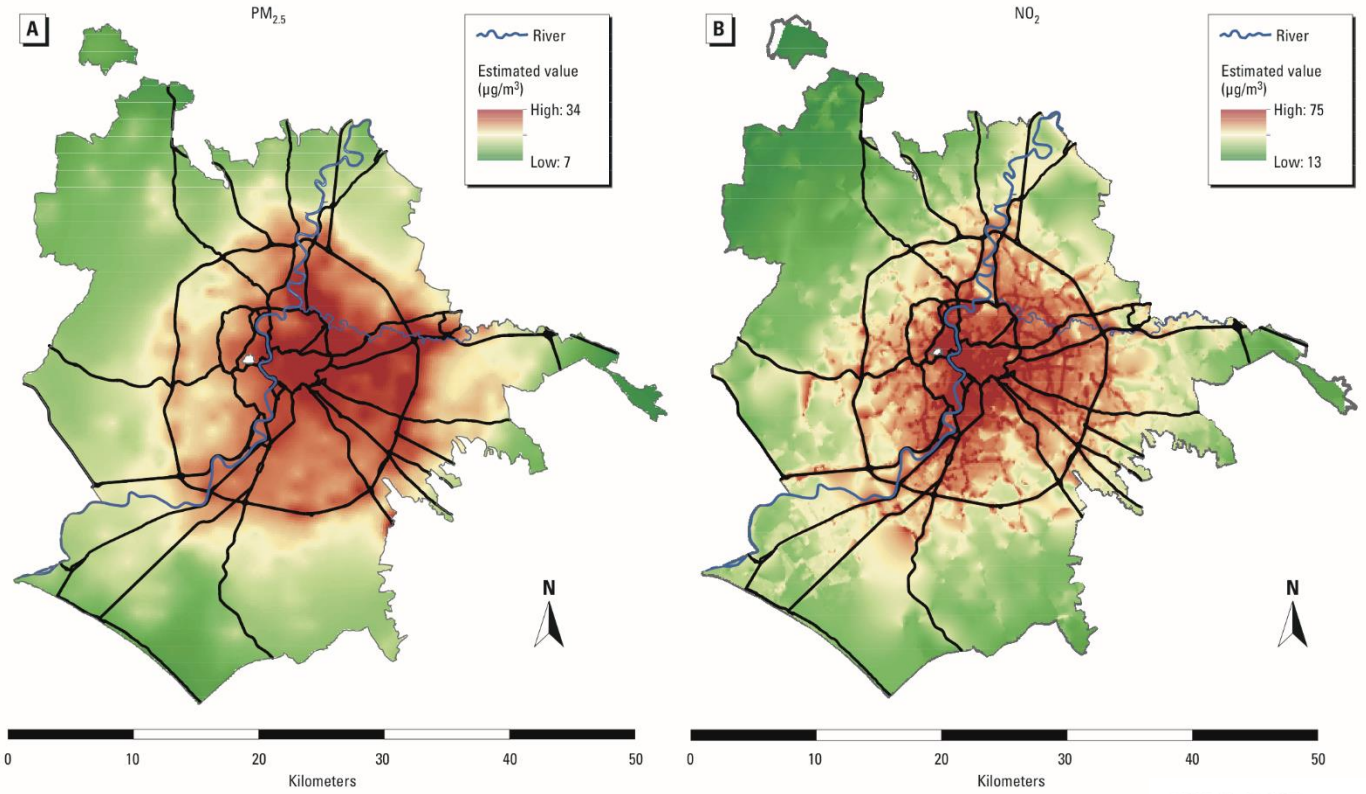
# Six Cities Study (PM)

Lippmann 1998 (Figure 5, page 87)).

P= Portage, Wisconsin; T= Topeka, Kansas; W= Watertown, Massachusetts; L= St Louis, Missouri; H= Harriman, Tennessee; and S= Steubenville, Ohio



# Within city contrasts ($PM_{2.5}$, $NO_2$) (Cesaroni et al (2013) Rome)

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# Hoek et al 2013 ($NO_2$)

| Study name | Central estimate % change per 10 µg/m³ | Lower 95% CI | Upper 95% CI | Reference |
|---|---|---|---|---|
| *Oslo cohort (men) (NOx)* | *8* | *6* | *11* | *Nafstad et al (2004)* |
| Netherlands cohort study | 8 | 0 | 16 | Beelen et al (2008) |
| German cohort (Ruhr) (women) | 11 | 4 | 18 | Heinrich et al (2013) |
| PAARC (France) | 14 | 3 | 25 | Filleul et al (2005) |
| Danish cohort | 8 | 2 | 13 | Rasschou Nielsen et al (2012) |
| US truckers (men) | 5 | 3 | 7 | Hart et al (2011) |
| Rome longitudinal study | 3 | 2 | 3 | Cesaroni et al (2013) |
| California Teachers Study (women) | -3 | -9 | 4 | Lipsett et al (2011) |
| Shizuoka elderly cohort | 2 | -4 | 8 | Yorifuji et al (2010) |
| **Pooled** | **5.5** | **3.1** | **8** | |

Excludes between city studies and district mean studies and ?NOx study.

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# Faustini et al 2014 ($NO_2$)

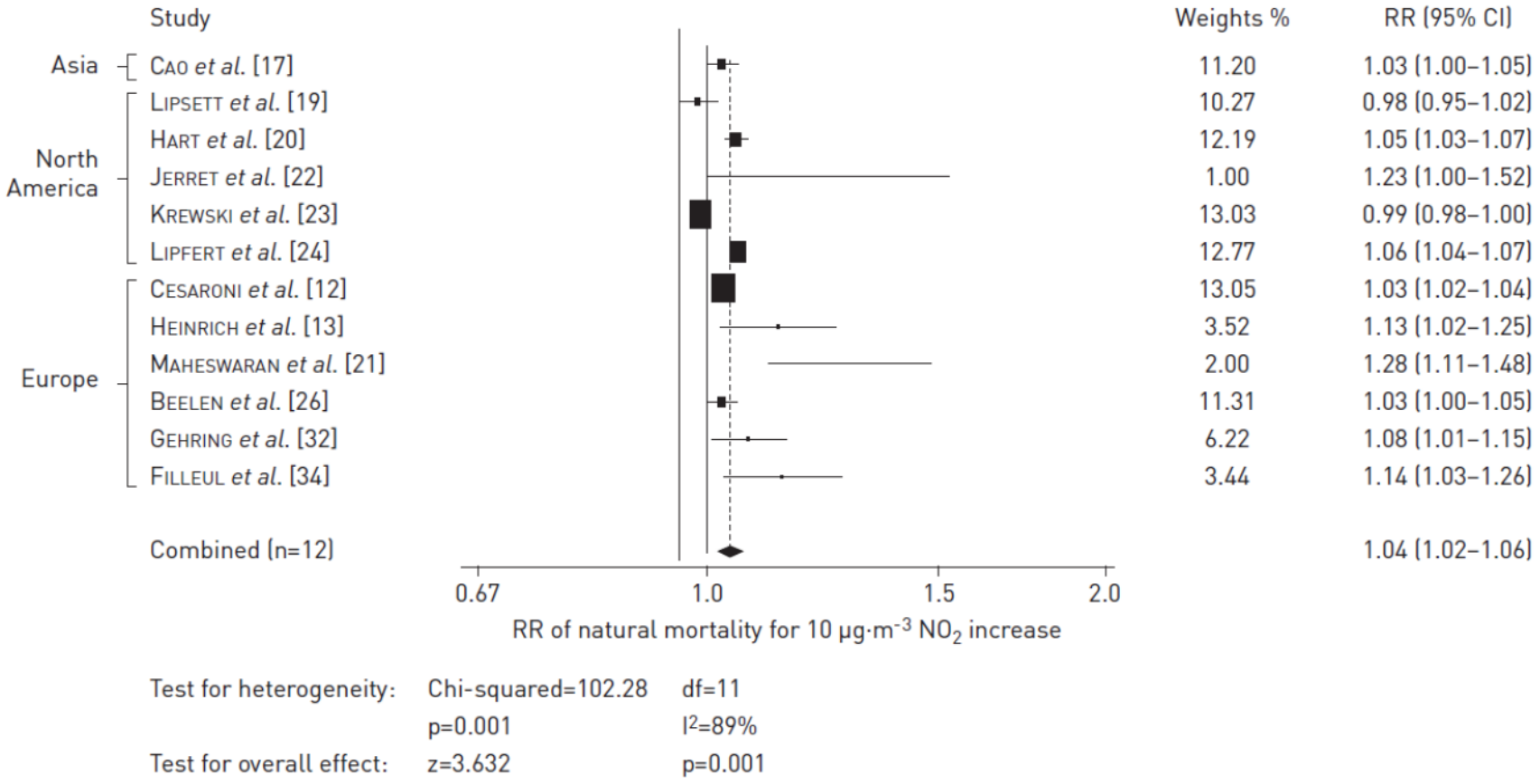


FIGURE 1 Relative risks (RR) of natural mortality with increasing chronic exposure to nitrogen dioxide ($NO_2$). df: degrees of freedom; $I^2$: inconsistency.

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# $NO_2$ cohort studies controlling for PM

Table 4. ESs for $NO_2$ from single- and multipollutant models on all-cause (natural) mortalit

| Reference pollutant | Parameter | All-cause (natural) mortality | | | % reduction on adjustment | Comments |
|---|---|---|---|---|---|---|
| | | Estimate | 95% CI | | | |
| **Gehring et al. (2006a)** | | | | | | |
| $NO_2$ single (per 16 µg/m$^3$) | Rate ratio | 1.19 | 1.02 | 1.39 | n/a | Women only |
| With traffic indicator | | No change with traffic indicator (data not shown) | | | | |
| **Jerrett et al. (2009b)** | | | | | | |
| $NO_2$ single (per 4 pbb) | Rate ratio | 1.17 | 1.00 | 1.36 | | Not in Hoek et al. (2013); cohort is from a respiratory clinic |
| with traffic indicator | | 1.13 | 0.97 | 1.32 | 24% | |
| **Hart et al. (2011)** | | | | | | |
| $NO_2$ single (per 8 pbb) | Percentage increase | 8.20 | 4.50 | 12.10 | | Truck drivers |
| with $PM_{10}$ and sulphur dioxide | | 7.40 | 2.40 | 12.50 | 9.8% | CIs widen |
| **Cao et al. (2011)** | | | | | | |
| NOx single (per 10 µg/m$^3$) | Percentage increase | 1.50 | 0.40 | 2.50 | | General population |
| with total suspended particles | | 1.40 | 0.30 | 2.50 | 6.7% | CIs widen slightly |
| **Cesaroni et al. (2013)** | | | | | | |
| $NO_2$ single (per 10 µg/m$^3$) | Rate ratio | 1.03 | 1.02 | 1.04 | | General population |
| with $PM_{2.5}$ | | 1.02 | 1.01 | 1.03 | 33% | |
| with traffic indicator | | No change (data not shown) | | | | |
| **Jerrett et al. (2013)** | | | | | | |
| $NO_2$ (per 4.1167 ppb) | Rate ratio | 1.031 | 1.008 | 1.056 | | General population |
| With $PM_{2.5}$ | | 1.025 | 0.997 | 1.054 | 19% | |

# $NO_2$ cohort studies controlling for PM (ii)

- REVIHAAP:

'Adjustment of $NO_2$ associations for PM10 or $PM_{2.5}$ may not be sufficient, as there is often a closer correlation between $NO_2$ and traffic pollutants, such as primary PM and its constituents.'

So also need to consider causality from other types of evidence.

# $NO_2$ causality (short term)

- Criticism: Chamber study responses are variable and well above ambient concentrations
- The time series study effects are all due to particles anyway
- REVIHAAP responded to these points

# $NO_2$ causality (Chamber studies)

| | Effect level starting concentrations | | Micro-environments |
|---|---|---|---|
| | **Healthy** | **Asthmatics** | Peaks outdoors polluted cities Kerbside 0.2-0.3ppm 1 hr ave on occasion In car can be similar. Other sites 0.1ppm 1 hr ave often exceeded across Europe |
| **Inflammation** | Yes > 1 ppm<br>? 0.2-0.6 ppm | | |
| **Allergen-induced inflammation** | | Ambiguous, yes 0.26 ppm, no 0.3-0.4 ppm | |
| **Non-specific airway responsiveness** | 1.5 – 2 ppm | 0.2 – 0.6 ppm | |
| | No clear dose response 0.1-0.5 ppm but responders at all doses | | |

# Variation in response (Jenkins et al 1999)

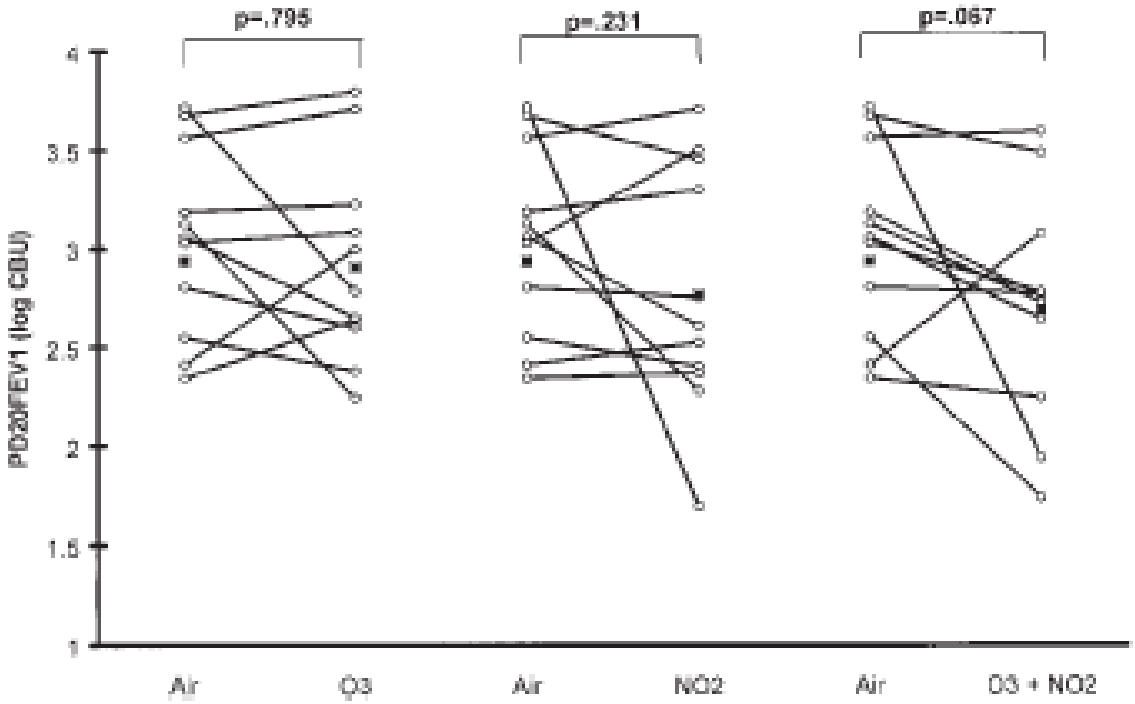
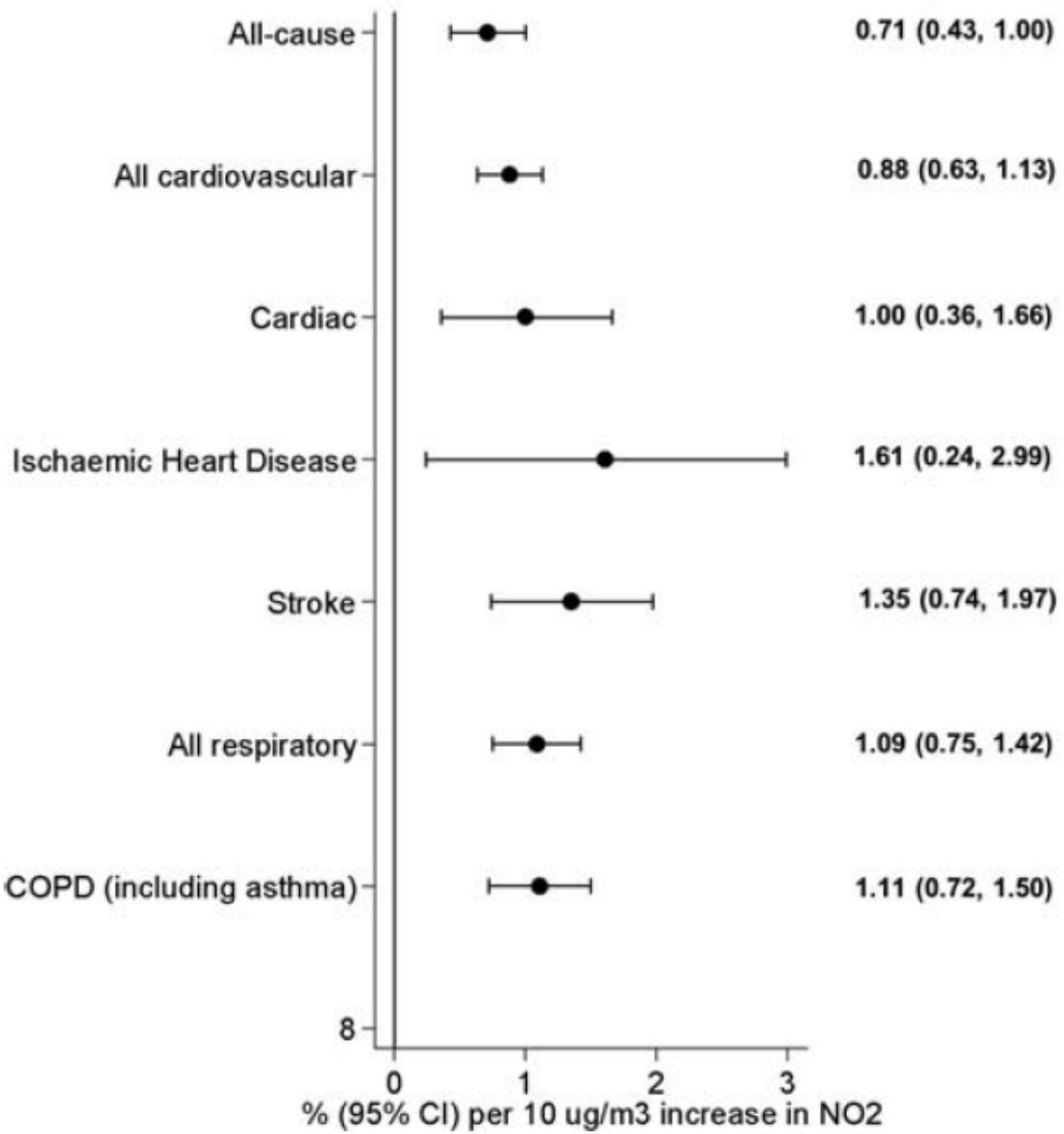



***Figure 1.*** The effect of 6 h exposure to 100 ppb $O_3$, 200 ppb $NO_2$, and 100 ppb $O_3$ + 200 ppb $NO_2$, compared with air, on allergen $PD_{20}FEV_1$ in mild asthmatics. *Squares* represent geometric means.

# $NO_2$ time series mortality (Mills et al 2015)

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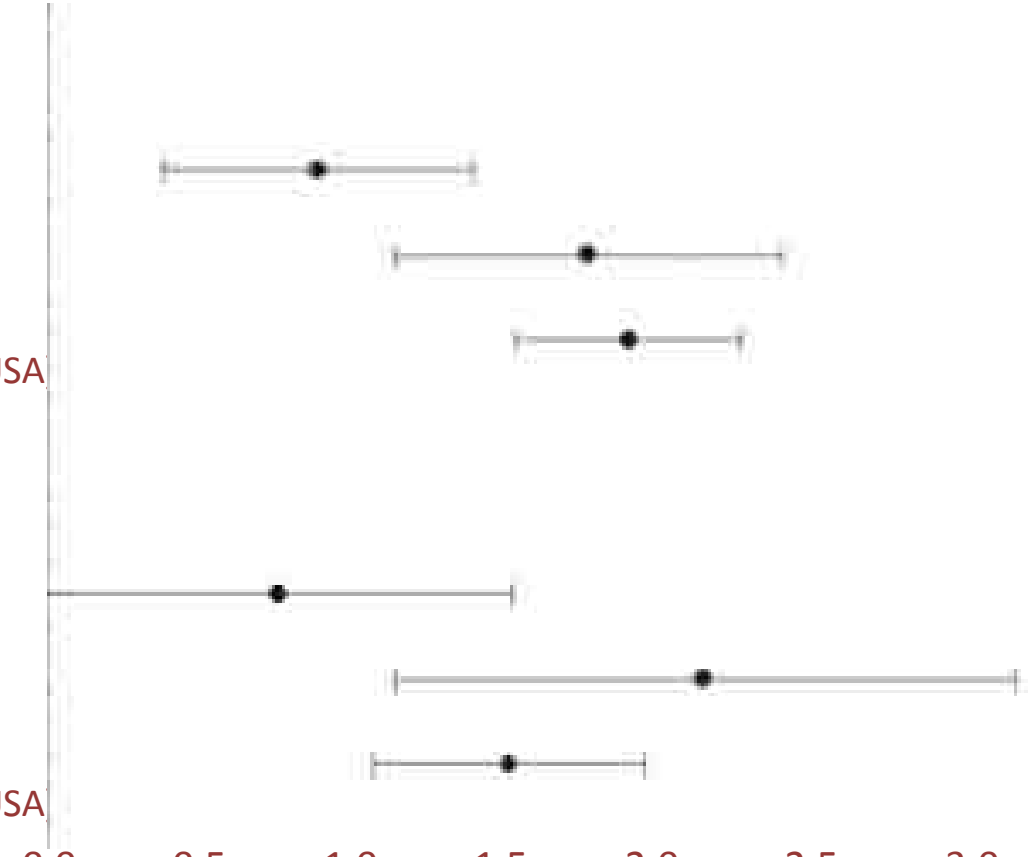
# Forest plot for cardiac admissions $NO_2$ with and without adjustment for $PM_{10}$ COMEAP (2006)

- NO2 SINGLE ESTIMATES
- Wong et al 2002 [London]
- Wong et al 2002 [Hong Kong]
- Moolgavkar 2000 [Cook County, USA]
- NO2 CONTROLLING FOR PM10
- Wong et al 2002 [London]
- Wong et al 2002 [Hong Kong]
- Moolgavkar 2000 [Cook County, USA]

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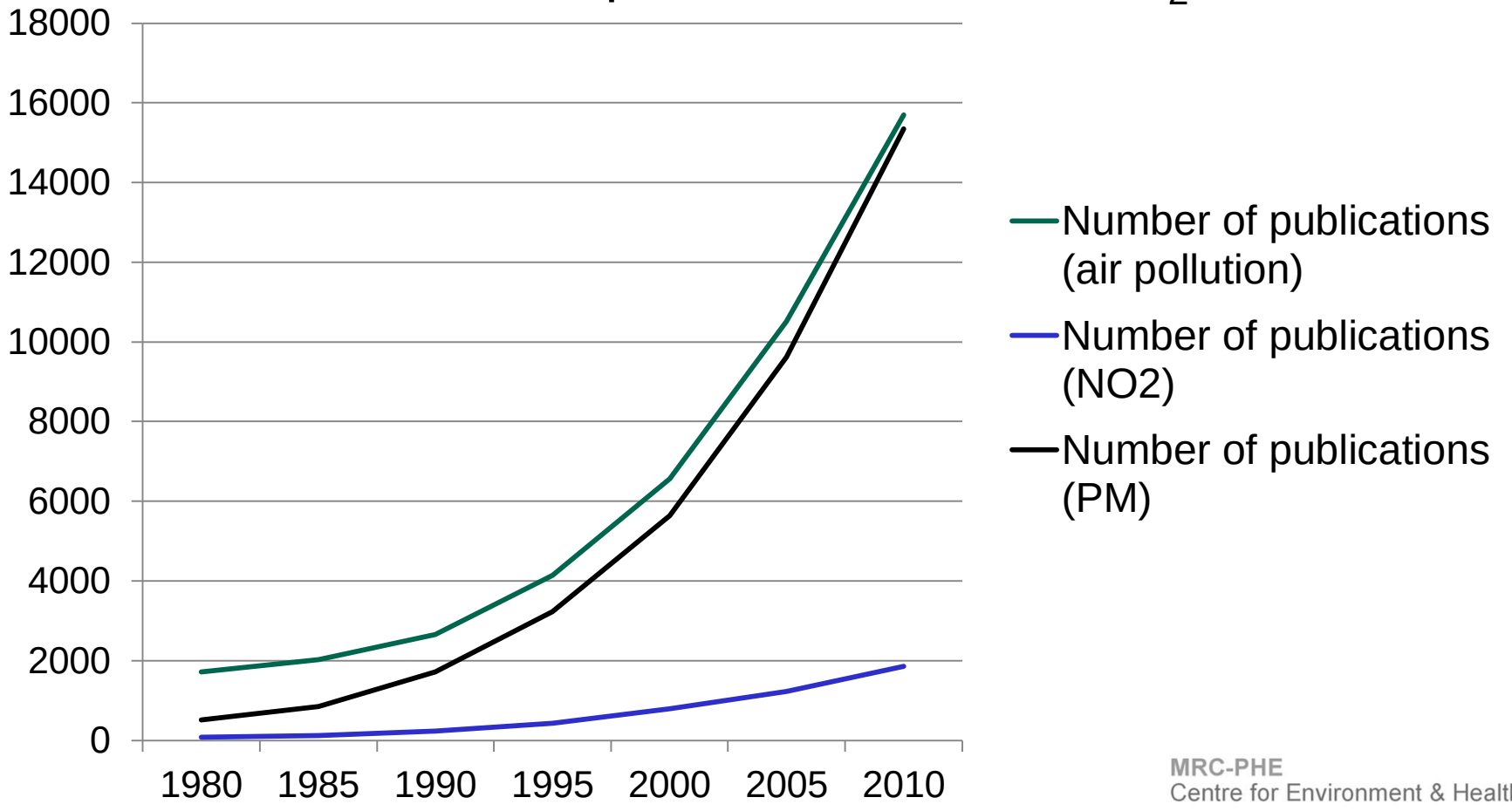
# Cardiovascular endpoints (REVIHAAP)

- Only two since 2008/9 (EPA etc), neither suggestive of effects
- 8 studies of biomarkers of cardiovascular disease with mixed results
- Chanell et al 2012 plasma from volunteers exposed to 0.5ppm $NO_2$ for 2 hours activated cultured coronary artery endothelial cells
- 2 recent rat studies showing effects on endothelial function and on recovery from stroke at 2-10 ppm
- Too little for conclusion on causality of cv endpoints one way or the other

# Number of publications "air pollution" or "(nitrogen dioxide or NO2)" or "(particulate matter or PM10 or PM2.5 or black smoke or sulphate or nitrate or secondary particles)" and health (PubMed)

2015 25,000 air pollution/PM, 3000 $NO_2$

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# $NO_2$ one hypothesis for mechanism

- $NO_2$ inhalation leads to nitrite in the blood
- *Following points established in the general literature on nitrative stress but not studied in relation to NO2 inhalation specifically*
- Nitrite can be converted to NO in the tissues
- In normal circumstances NO is beneficial (e.g. vasodilation)
- In disease it can combine with superoxide radical to form peroxynitrite
- Peroxynitrite can nitrate proteins forming 3-nitrotyrosine
- In the wrong place and in too many proteins, this is a problem.
- Increased levels of 3-nitrotyrosine in the blood have been associated with heart disease

# REVIHAAP conclusions long-term exposure to $NO_2$ and mortality (edited summary)

- Harder to judge the independent effects of $NO_2$ in long-term studies - correlations between concentrations of $NO_2$ and other pollutants are often high, so that $NO_2$ might represent the mixture of traffic-related air pollutants.
- No chamber studies for long-term effects and toxicological evidence is limited.
- However, some epidemiological studies do suggest associations of long-term $NO_2$ exposures with respiratory and cardiovascular mortality and with children's respiratory symptoms and lung function that were independent of PM mass metrics.
- The mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations are suggestive of a causal relationship.

# HRAPIE recommendations for $NO_2$

Limited set –

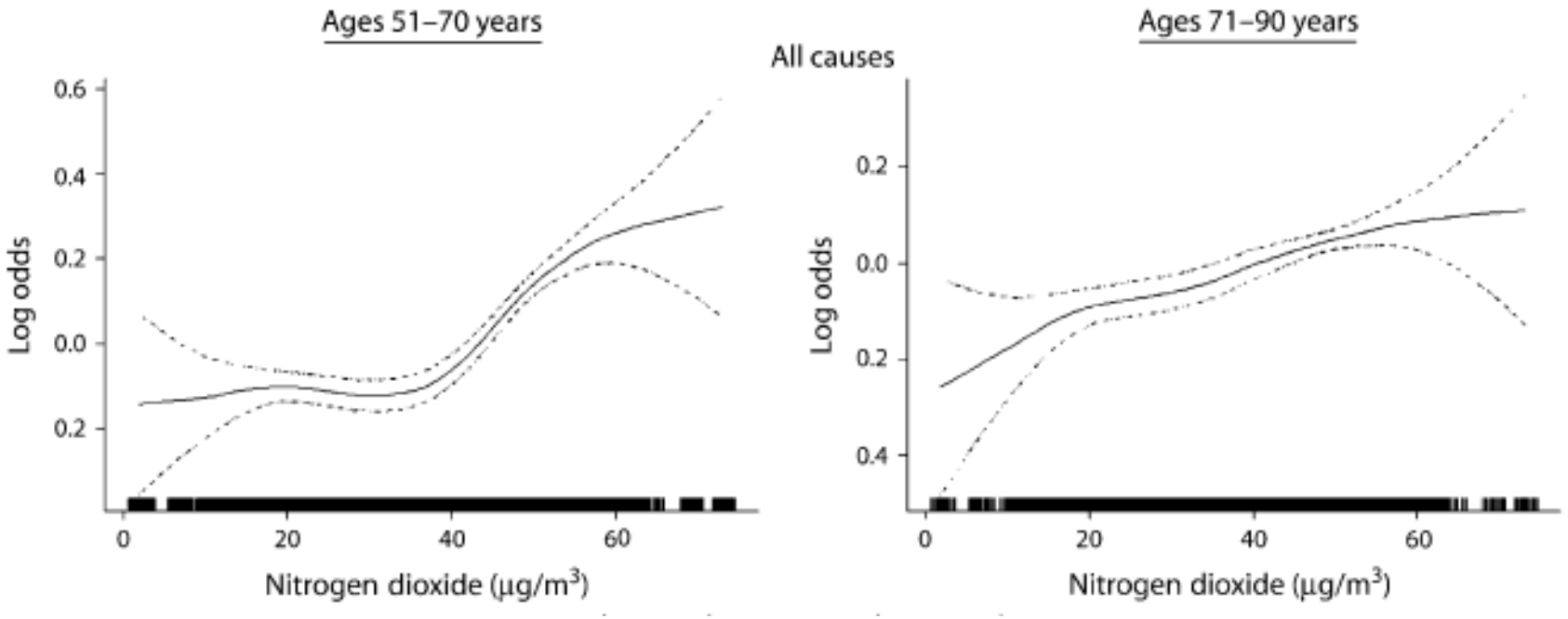
- All cause mortality (short term), adjusted
- Respiratory hospital admissions, single pollutant

Extended set –

- All cause mortality (long-term), single pollutant, above 20 µg/$m^3$;
- Bronchitic symptoms in asthmatics, adjusted

# Næss *et al* (2007) Oslo

Am. J. Epidemiol. 2007;165:435-443

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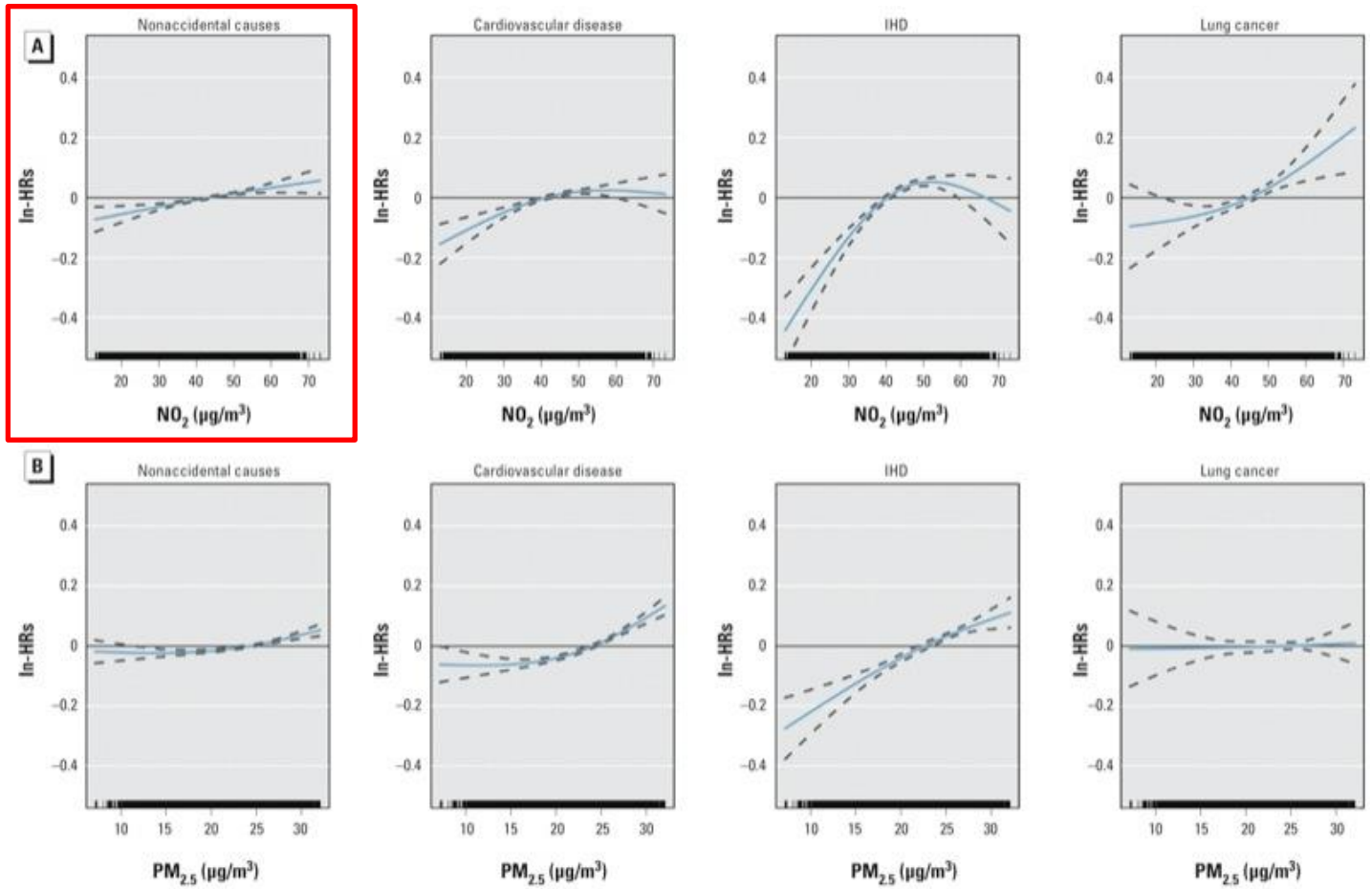
# Cesaroni et al (2013) Rome






Update on evidence for quantification of $NO_2$ impacts: *Mortality associated with long-term average concentrations*

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# Quantifying the health impacts of ambient air pollutants: recommendations of a WHO/Europe project

International Journal of Public Health 2015:690
**DOI:** 10.1007/s00038-015-0690-y

MarieEve Héroux, H. Ross Anderson, Richard Atkinson, Bert Brunekreef, Aaron Cohen,Francesco Forastiere, Fintan Hurley, Klea Katsouyanni, Daniel Krewski, Michal Krzyzanowski,Nino Künzli, Inga Mills, Xavier Querol, Bart Ostro and Heather Walton

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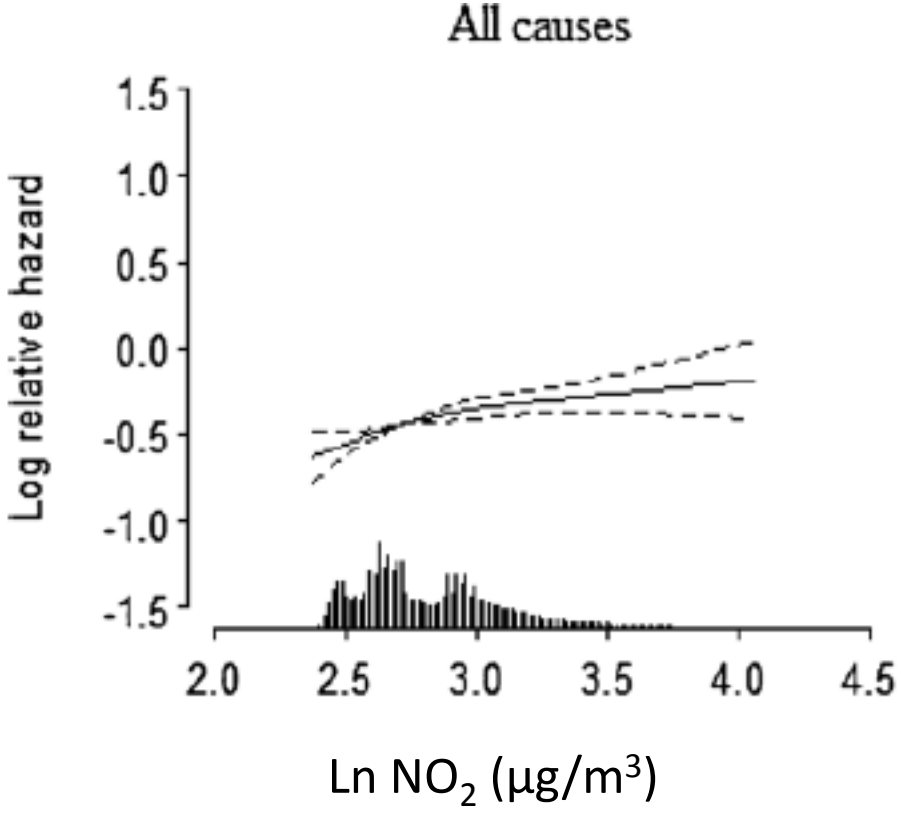
# Evolution of lower limit for quantification in journal article (i)

- We also note that a recent cohort study ….(Raaschou-Nielsen et al. *2012*) has shown a significant, almost linear concentration–response relationship between long-term $NO_2$ concentration …and mortality… throughout the observed range of $NO_2$ concentrations, which in the large majority of subjects was below 20 $\mu g/m^3$ (minimum 10.5 $\mu g/m^3$, median 15.1 $\mu g/m^3$, maximum 59.6 $\mu g/m^3$).

- This study was included in the Hoek et al. (*2013*) meta-analysis, but we did not explicitly consider it when discussing lower limits of quantification in the HRAPIE project.

# Raaschou-Nielsen et al (2012)



# Evolution of lower limit for quantification in journal article (ii)

- All-cause mortality increased by 8 % per 10 μg/m$^3$ $NO_2$long-term exposure at the residence address in the study by Raaschou-Nielsen et al. (*2012*), so slightly more than estimated in the Hoek et al. meta-analysis.

- Therefore, the HRAPIE recommendation to calculate the impacts of long-term $NO_2$ exposure on mortality for levels over 20 μg/m$^3$, ignoring potential impacts at lower concentrations, may be too conservative.

# Workshop 26th February 2015

- Involved many people from HRAPIE
- HRAPIE recommendations were not in the context of burden discussions (where counter factuals more crucial)
- Workshop discussed both (i) general concepts regarding thresholds and cut-offs and (ii) specific discussion of counter factuals for $NO_2$
- (ii) described here
- Separate analysis Rome study above and below 20 $\mu g/m^3$ - steeper below 20 $\mu g/m^3$ but wide Cis (Cesaroni/Forastiere personal communication)

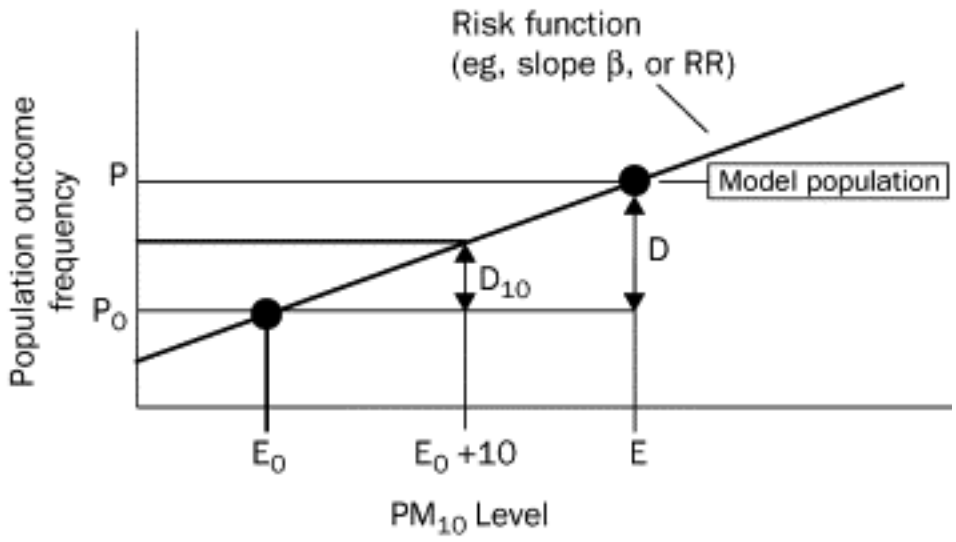



Figure 1 Model to derive number of cases attributable to air pollution Based on exposure-response function (slope or relative risks, RR, from epidemiological studies), population frequency of the outcome, P (ie, prevalence, incidence, or number of days), ...

N Künzli , R Kaiser , S Medina , M Studnicka , O Chanel , P Filliger , M Herry , F Horak Jr , V Puybonnieux-Tex...

**Public-health impact of outdoor and traffic-related air pollution: a European assessment**

The Lancet, Volume 356, Issue 9232, 2000, 795 - 801

http://dx.doi.org/10.1016/S0140-6736(00)02653-2

# Possible criteria for choosing counterfactuals

- Threshold for effect
- Studied range in epidemiological studies (5$^{th}$ percentile)
- Range over which there is most confidence in the shape of the curve / concentration response function
- Policy-relevant range
- Lowest concentration in the environment (5$^{th}$ percentile)
- Zero

- GBD for $PM_{2.5}$ suggested using the 5$^{th}$ percentile of the exposure distribution of the key epidemiological study or studies as the counter-factual, with the minimum concentration as the lower bound

  (Lim et al., 2012; Burnett et al., 2014).

# Carey et al (2013) England

| | 2002 ($\mu g/m^3$) |
|---|---|
| | $NO_2$ |
| No. of patients with pollution linkage (%) | 830,429 (99%) |
| Mean pollution (SD) | 22.5 (7.4) |
| Minimum–maximum range | 4.5–60.8 |
| Interquartile range | 10.7 |

% increase in mortality per 10 µg/m$^3$ (95% CI): 2% (0%, 5%)

But $NO_2$/$PM_{2.5}$ correlation 0.9

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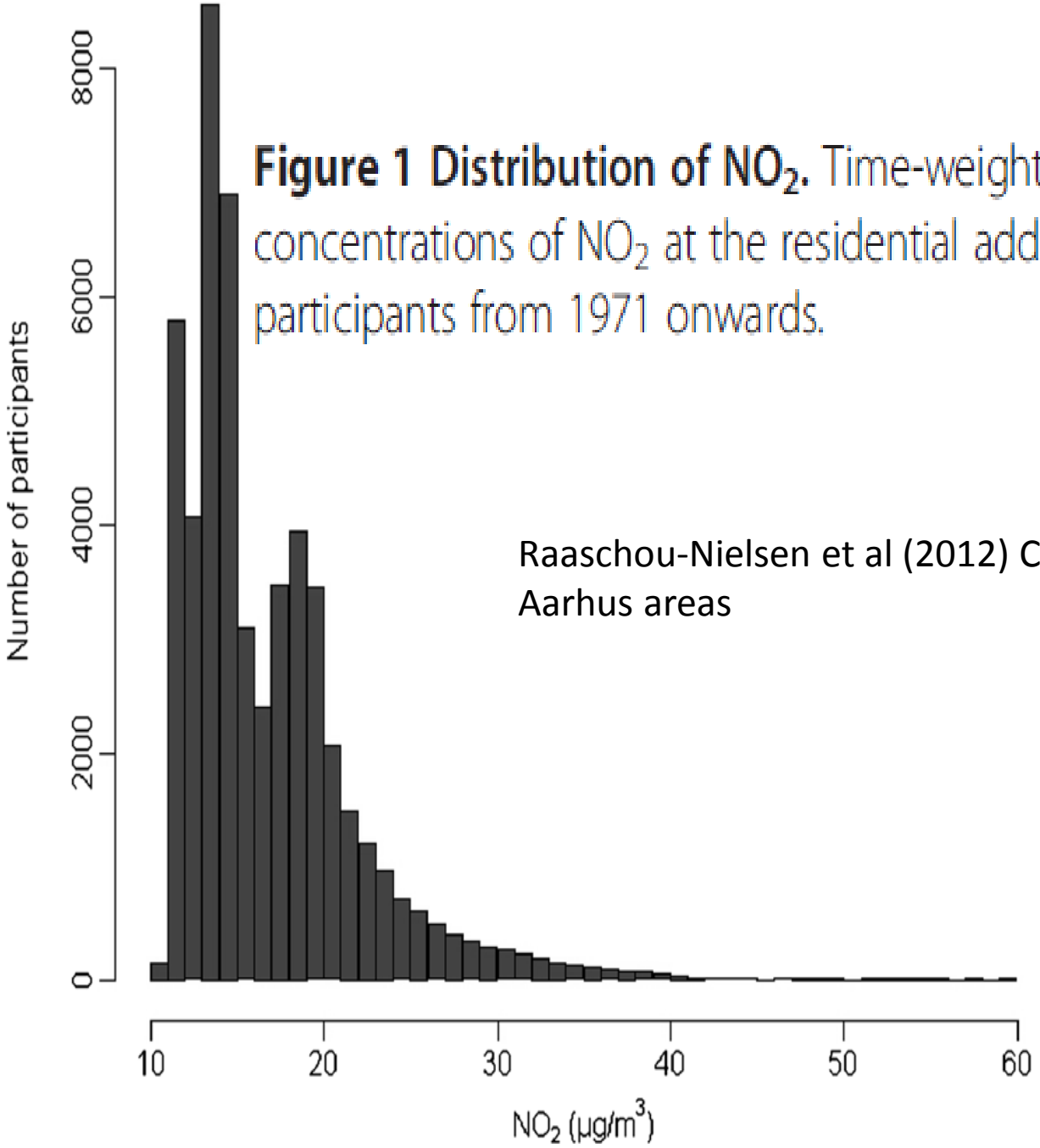


**Figure 1 Distribution of $NO_2$.** Time-weighted average concentrations of $NO_2$ at the residential addresses of 52 061 cohort participants from 1971 onwards.

Raaschou-Nielsen et al (2012) Copenhagen and Aarhus areas

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# Workshop suggestions for $NO_2$ counter factuals

- [20 μg/m$^3$]
- 15 μg/m$^3$ (median Copenhagen study)
- 10 μg/m$^3$ (minimum Copenhagen study)
- 5 μg/m$^3$ (lowest mean ESCAPE cohorts; minimum Carey study)
- [0 μg/m$^3$] (not favoured as outside data range but minimums in ESCAPE get as low as 1.5 μg/m$^3$ (Umeå))

- Could assign probabilities to each of these sensitivities and do a Monte Carlo analysis.

# Choices for quantification

| Relative risk | Central | Lower CI | Upper CI | |
|---|---|---|---|---|
| Relative risk | 1.055 | 1.031 | 1.08 | |
| Adjust for overlap (30%) | 1.039 | 1.022 | 1.056 | |
| **Counterfactual** | | | | |
| Within range 0-20 $\mu g/m^3$ , 5,10,15 $\mu g/m^3$ | | | | |
| **Cessation lag** | | | | |
| As for $PM_{2.5}$ in absence of evidence to the contrary, ?no long lag for lung cancer | | | | |
| **Concentration scale** | | | | |
| Fine within city scale | | | | |
| **Context of health impact assessment (next slide)** | | | | |

# Context of health impact assessment

- Is it $NO_2$ itself being quantified or traffic pollution?
- If traffic pollution, is the proportion of $NO_2$ similar to that in the original studies? If so, can use single pollutant model.
- Are other pollutants e.g. PM being quantified at the same time? If so, need to think about overlap.
- Is it a burden assessment (total effect) or a health impact assessment (effects of a pollution change)?
- WHO cautioned against adding single pollutant model results for $NO_2$ to those for $PM_{2.5}$ (noted overlap up to 33%)
- Currently no recommendations for $PM_{2.5}$ adjusted for $NO_2$
- Best to produce a range of results to account for the possibility that other constituents of traffic account for some of the $NO_2$ effect.

# Conclusions

- Evidence for effects of long-term exposure to NO2 is strengthening
- Still uncertainties that need to be explained
- Need to be clear of the context for quantification
- Many choices to be made about inputs, better to choose a variety of options
- Important to scope the implications of the developing evidence for quantification