Nitrogen dioxide: evidence from epidemiological studies

Workshop on current issues regarding nitrogen dioxide
Department of Health
2-3 March 2011

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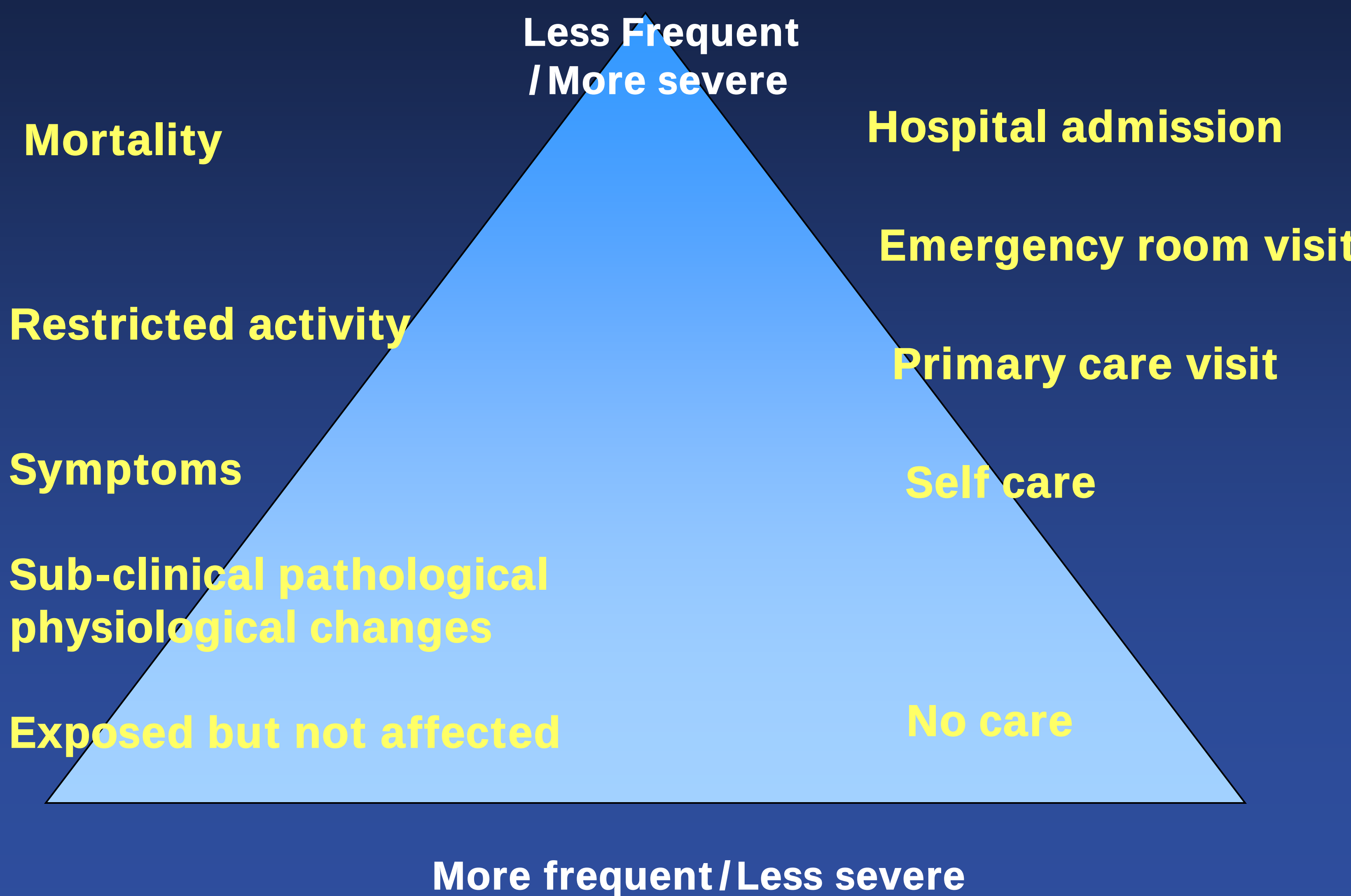
Outline

- Some general concepts
  - Interpretation of epidemiological evidence
  - Paradigm of multifactorial aetiology
- Short-term exposure studies
- Long-term exposure studies
- Traffic studies
- Comment on rationale of WHO GL

DISEASE AND ILLNESS (acute or chronic)

UTILIZATION OF HEALTH SERVICES



Epidemiological study designs

- Temporal:- episode, time series, panel,
- Spatial: - cohort, cross-sectional,
- Exposure context:
  - Between- or within- community contrasts
  - Indoor (domestic, occupational) or outdoor
- Intervention

EVIDENCE FROM POPULATIONS

ASSOCIATIONS:
Air pollution and health

EXCLUDE:
Chance, Bias Confounding

OTHER EVIDENCE (TOXICOLOGY)

APPLY:
Scientific reasoning

Hill's "viewpoints"

JUDGEMENT:
Causality

"Precautionary principle" → **POLICY**

Weighing the evidence of observational studies

"Is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" *Bradford Hill (1965)*

Temporality
Dose response
Consistency
Coherence
Plausibility
Analogy

Size of effect
Specificity

Legal weight of evidence:

Balance of probabilities → public health action

Beyond all reasonable doubt → scientific acceptance

Multifactorial causation of disease

"The cause of a disease event is an antecedent event, condition or characteristic that was necessary (given that all other conditions are fixed) for the occurrence of the disease at the moment it occurred".

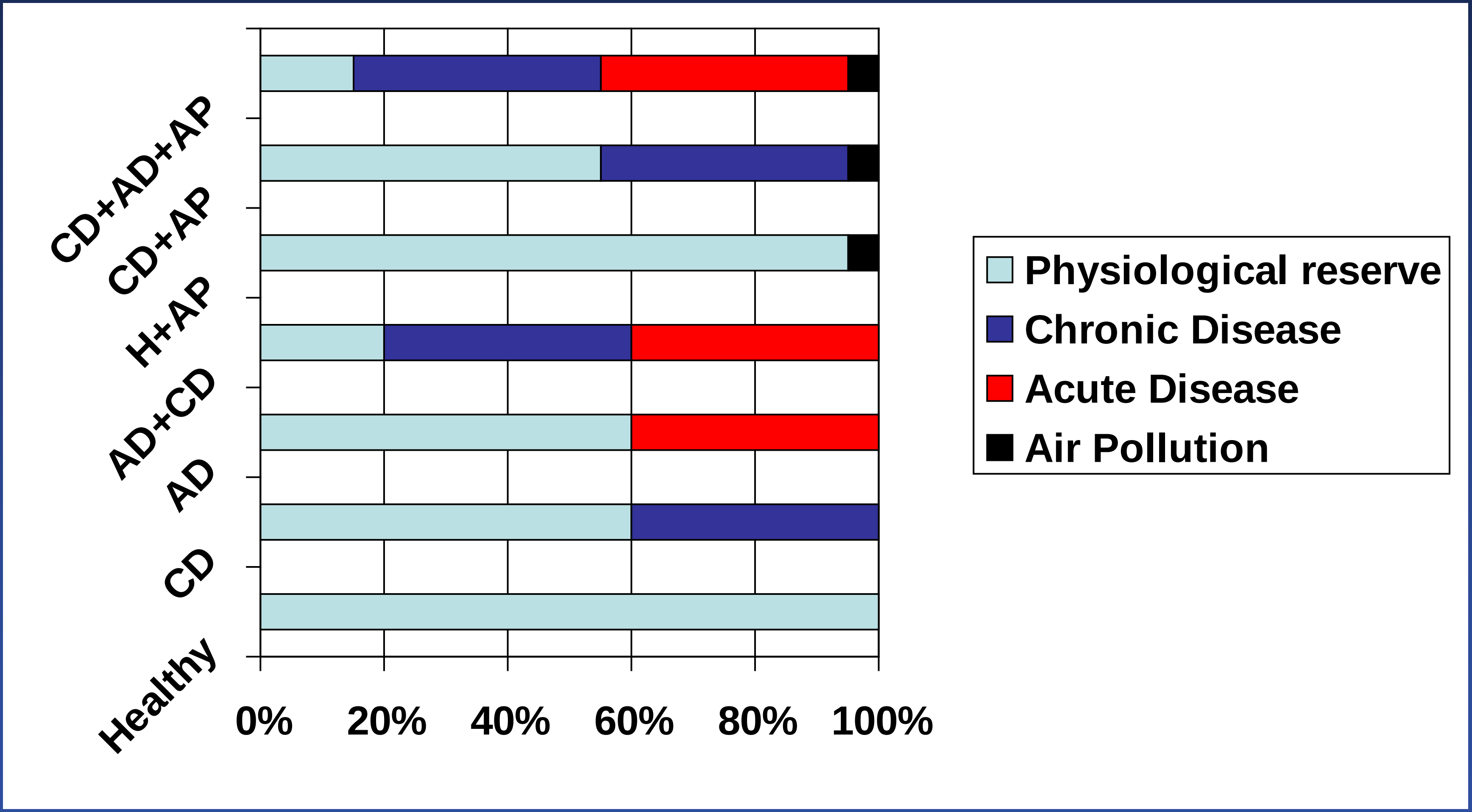
(Rothman and Greenland 2002)

Multifactorial causation explains some important epidemiological observations

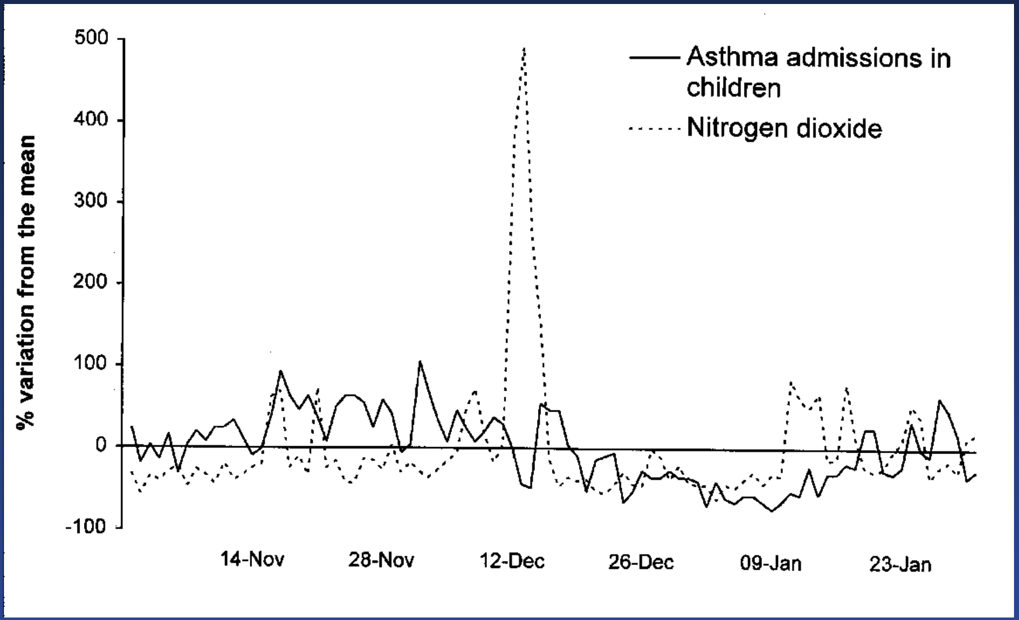
- Why small exposures can have clinically important effects, including death
- Why there is a lack of threshold in exposure response relationships
- Why effects vary between individuals and between populations

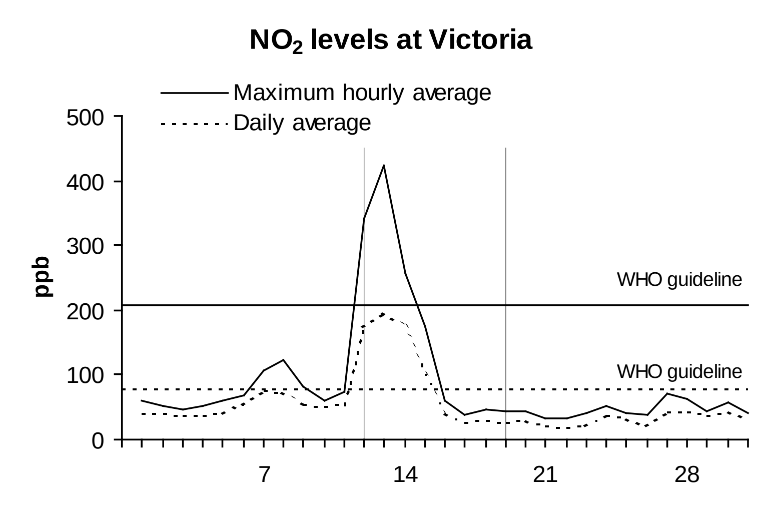
The last straw theory of air pollution health effects.

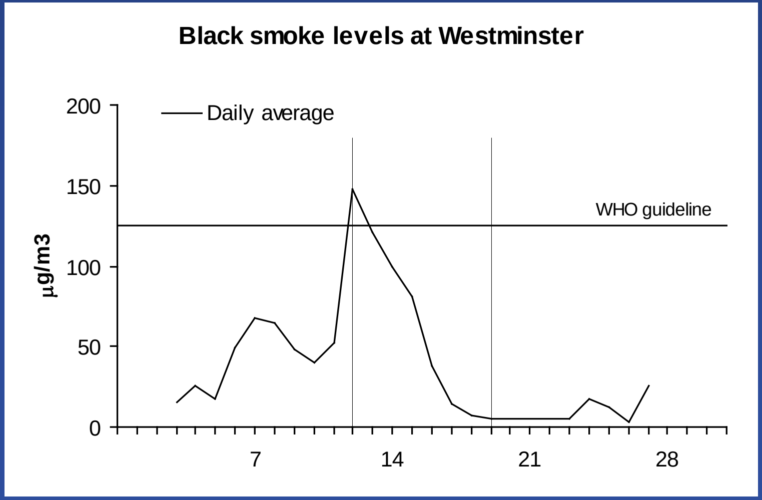
Added contribution of air pollution to loss of reserve due to acute/chronic disease



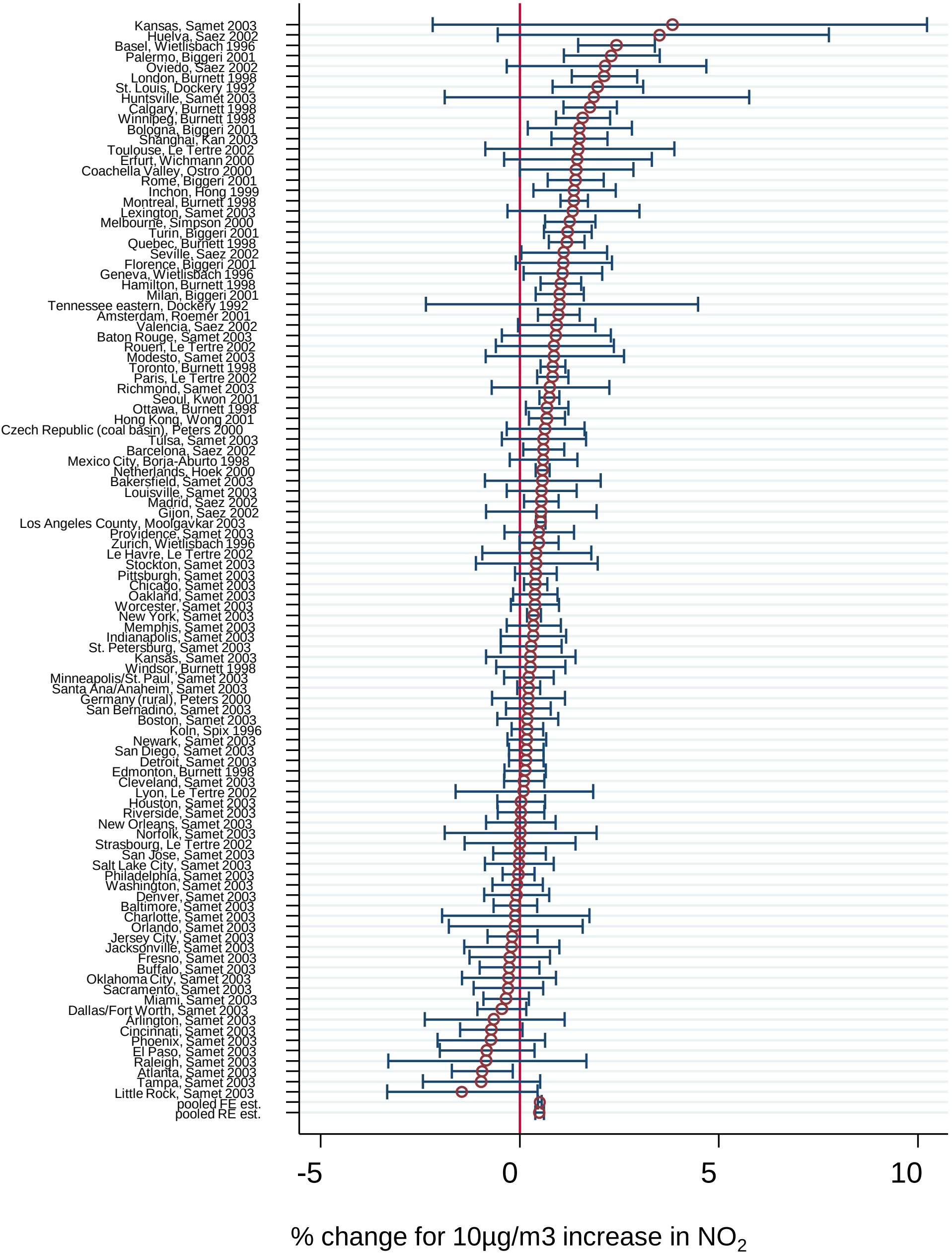
Air pollution episode: London 1991







% variation from mean of daily asthma admissions 0-14 age group: 1991 London smog episode

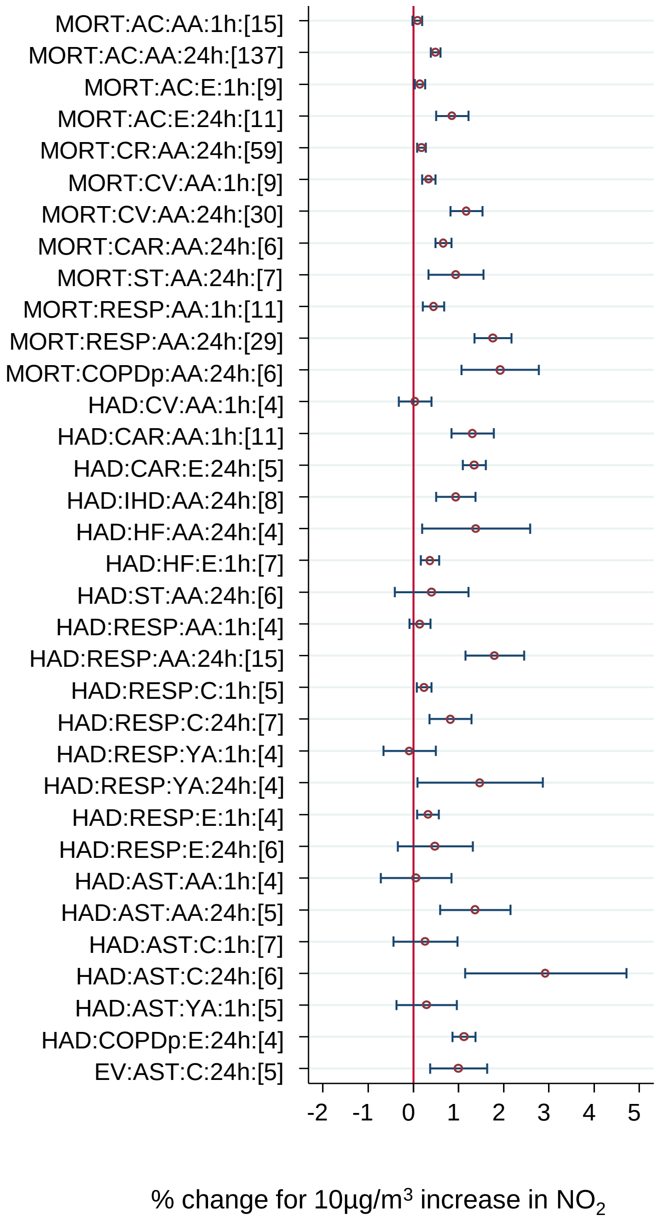


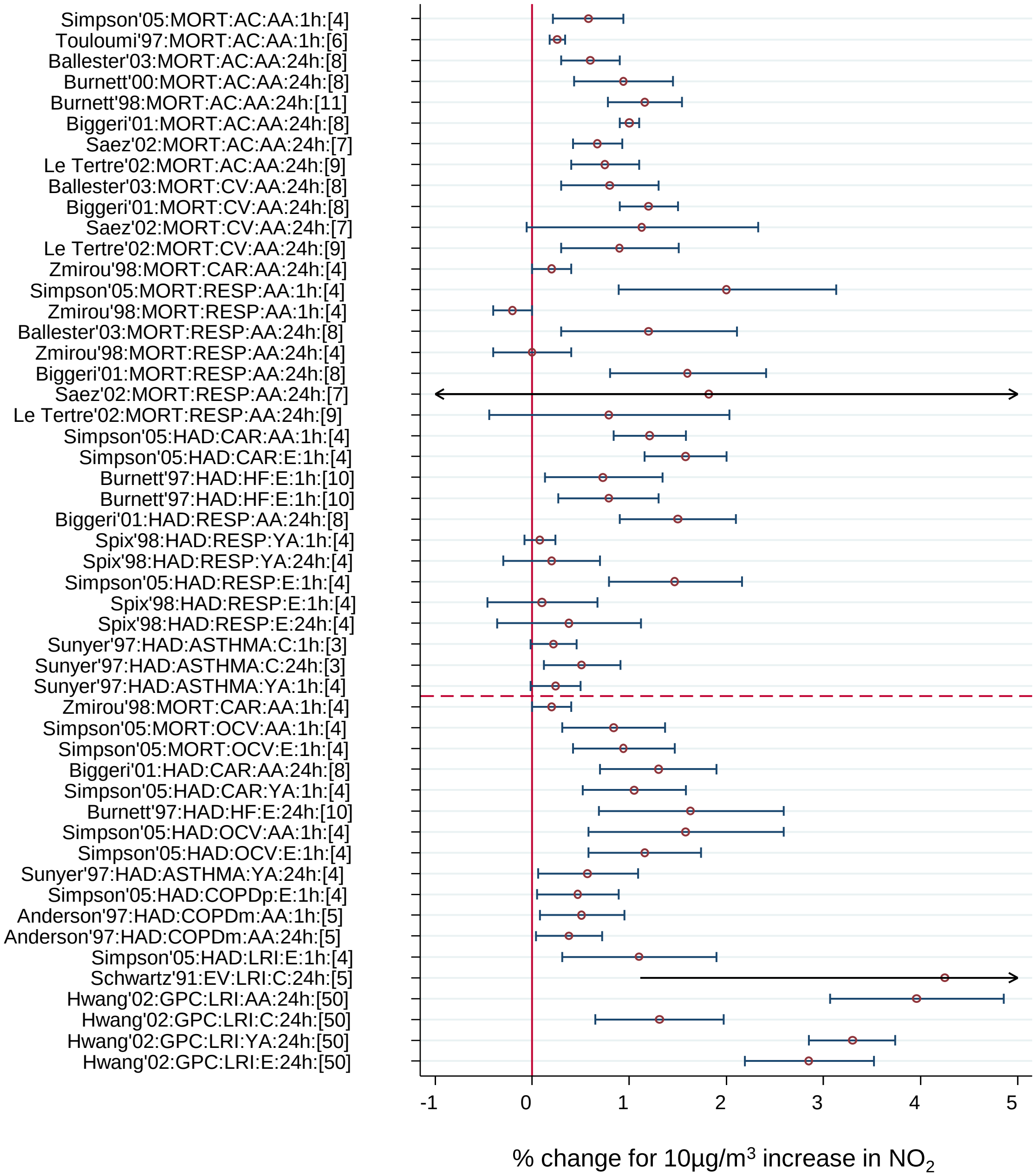
Single city time-series estimates for NO2(24h) and all cause mortality: all age and all year.

Anderson HR, Atkinson RW, Bremner SA, Carrington J, Peacock J (2007) Quantitative systematic review of short term associations between ambient air pollution (particulate matter, ozone, nitrogen dioxide, sulphur dioxide and carbon monoxide), and mortality and morbidity.

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_121200

Summary random effects estimates of NO_2 from meta-analyses of single city time-series estimates. Anderson et al 2007





Summary estimates of NO_2 for single pollutant analyses from multicity studies of mortality and morbidity

Anderson et al 2007

Investigating the dose-response relation between air pollution and total mortality in the APHEA-2 multicity project

E Samoli, G Touloumi, A Zanobetti, A Le Tertre, Chr Schindler, R Atkinson, J Vonk, G Rossi, M Saez, D Rabczenko, J Schwartz, K Katsouyanni

Occup Environ Med 2003;**000**:1–7

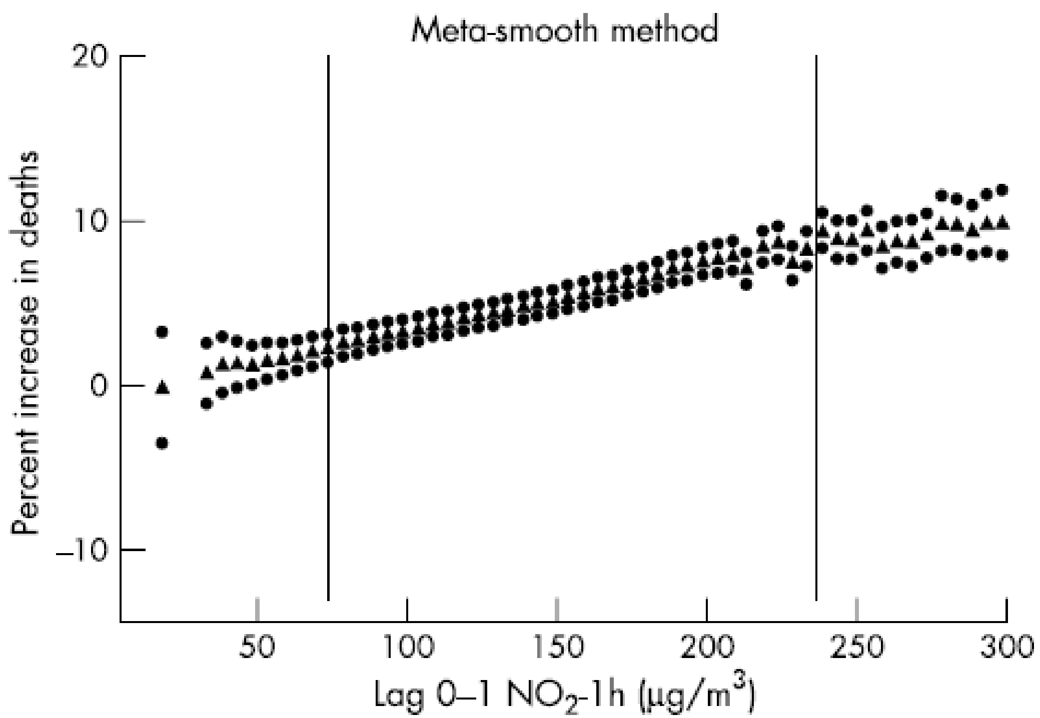


Figure 2 Average dose-response curves across nine cities and their 95% CIs provided by the cubic spline method (top) and the meta-smooth method (bottom). The vertical lines in both plots mark the common range of NO_2 values in all analysed cities.

NO2: Multipollutant models in multicity studies of mortality and morbidity. Summary estimates (% increase and 95% CI). Anderson et al 2007

Set no.	Ref Man Id	Access Id	1st Author	Year	Cities	Outcome[1]	Diagnostic group[2]	Age group[3]	Lag	Selected	Averaging time	Co-Pollutant	Random effects estimate and 95% CL: Est	Lcl	Ucl
1	133	13847	Simpson	2005	4 Australian Cities	MORT	AC	AA	lag 0-1	Selected	1 hour	Single pollutant	0.58	0.21	0.94
1	133	13884	Simpson	2005	4 Australian Cities	MORT	AC	AA	lag 0-1	Other	1 hour	other	1.00	0.52	0.05
1	133	13885	Simpson	2005	4 Australian Cities	MORT	AC	AA	lag 0-1	Other	1 hour	O_3	1.05	0.63	0.21
1	240	1211	Touloumi	1997	6 European Cities	MORT	AC	AA	single	Selected	1 hour	Single pollutant	0.26	0.18	0.34
1	240	1215	Touloumi	1997	6 European Cities	MORT	AC	AA	single	Other	1 hour	O_3	0.42	0.30	0.18
1	240	1216	Touloumi	1997	6 European Cities	MORT	AC	AA	single	Other	1 hour	BS	0.24	0.12	0.00
2	66	13729	Zeka	2004	90 US Cities	MORT	AC	AA	lag 0-1	Selected	24 hours	PM_{10}	0.07	0.02	-0.03
2	66	13730	Zeka	2004	90 US Cities	MORT	AC	AA	lag 0-1	Selected	24 hours	SO_2	0.07	0.00	-0.07
2	66	13731	Zeka	2004	90 US Cities	MORT	AC	AA	lag 0-1	Selected	24 hours	CO	0.01	0.00	-0.02
2	66	13732	Zeka	2004	90 US Cities	MORT	AC	AA	lag 0-1	Selected	24 hours	O_3	0.03	-0.01	-0.05
2	135	5771	Burnett	2000	8 Canadian Cities	MORT	AC	AA	lag 1	Selected	24 hours	Single pollutant	0.94	0.43	1.45
2	135	5798	Burnett	2000	8 Canadian Cities	MORT	AC	AA	lag 1	Other	24 hours	$PM_{2.5}$	1.33	0.73	0.13
2	135	5799	Burnett	2000	8 Canadian Cities	MORT	AC	AA	lag 1	Other	24 hours	$PM_{2.5-10}$	1.46	0.91	0.37
2	135	5800	Burnett	2000	8 Canadian Cities	MORT	AC	AA	lag 1	Other	24 hours	PM_{10}	1.39	0.77	0.17
2	1416	8362	Saez	2002	7 Spanish Cities	MORT	AC	AA	single	Selected	24 hours	Single pollutant	0.67	0.42	0.93
2	1416	8374	Saez	2002	7 Spanish Cities	MORT	AC	AA	single	Other	24 hours	$CO+SO_2+O_3$+other	0.86	0.43	0.00
7	1416	8386	Saez	2002	7 Spanish Cities	MORT	CV	AA	single	Selected	24 hours	Single pollutant	1.13	-0.06	2.33
7	1416	8398	Saez	2002	7 Spanish Cities	MORT	CV	AA	single	Other	24 hours	$CO+SO_2+O_3$+other	1.85	1.04	0.24
11	1416	8410	Saez	2002	7 Spanish Cities	MORT	RESP	AA	single	Selected	24 hours	Single pollutant	1.82	-8.74	13.61
11	1416	8422	Saez	2002	7 Spanish Cities	MORT	RESP	AA	single	Other	24 hours	$CO+SO_2+O_3$+other	2.64	1.07	-0.48
14	134	13893	Simpson	2005	4 Australian Cities	HAD	CAR	AA	lag 0-1	Selected	1 hour	Single pollutant	1.21	0.84	1.58
14	134	13939	Simpson	2005	4 Australian Cities	HAD	CAR	AA	lag 0-1	Other	1 hour	other	1.16	0.73	0.31
14	134	13940	Simpson	2005	4 Australian Cities	HAD	CAR	AA	lag 0-1	Other	1 hour	O_3	2.11	1.68	1.26
26	134	13922	Simpson	2005	4 Australian Cities	HAD	RESP	E	lag 0-1	Selected	1 hour	Single pollutant	1.47	0.79	2.16
26	134	13945	Simpson	2005	4 Australian Cities	HAD	RESP	E	lag 0-1	Other	1 hour	other	1.95	1.21	0.47
26	134	13946	Simpson	2005	4 Australian Cities	HAD	RESP	E	lag 0-1	Other	1 hour	O_3	2.11	1.47	0.84
31	398	1658	Sunyer	1997	3 European Cities	HAD	ASTHMA	C	single	Selected	24 hours	Single pollutant	0.51	0.12	0.91
31	398	1688	Sunyer	1997	3 European Cities	HAD	ASTHMA	C	single	Other	24 hours	BS	2.34	0.71	-0.90
31	398	1691	Sunyer	1997	3 European Cities	HAD	ASTHMA	C	single	Other	24 hours	SO_2	1.59	0.67	-0.24
*	409	1446	Burnett	1997	10 Canadian Cities	HAD	HF	E	lag 0	Selected	24 hours	Single pollutant	1.63	0.69	2.59
*	409	3299	Burnett	1997	10 Canadian Cities	HAD	HF	E	lag 0	Selected	24 hours	Single pollutant	0.93	0.41	1.45
*	409	1458	Burnett	1997	10 Canadian Cities	HAD	HF	E	lag 0	Selected	24 hours	$CO+SO_2+O_3$+other	1.60	0.89	0.19
*	398	2070	Sunyer	1997	4 European Cities	HAD	ASTHMA	YA	cum	Other	24 hours	Single pollutant	0.75	0.16	1.34
*	398	1693	Sunyer	1997	4 European Cities	HAD	ASTHMA	YA	lag 0-1	Other	24 hours	Single pollutant	0.67	0.18	1.16
*	398	2069	Sunyer	1997	4 European Cities	HAD	ASTHMA	YA	single	Selected	24 hours	Single pollutant	0.57	0.06	1.09
*	398	1682	Sunyer	1997	3 European Cities	HAD	ASTHMA	YA	single	Other	24 hours	BS	2.06	1.08	0.10
*	398	1684	Sunyer	1997	3 European Cities	HAD	ASTHMA	YA	cum	Other	24 hours	BS	2.92	1.70	0.50

* published estimates for diagnostic groups for which no single city meta-analytic estimates are available (Table 5.2)

[1] MORT=mortality, HAD=hospital admissions, EV=emergency room visits

[2] AC=all cause, ASTHMA=asthma, COPDp=chronic obstructive pulmonary disease (inc.asthma), COPDm=chronic obstructive pulmonary disease (not inc.asthma), LRI=lower respiratory infection, RESP=respiratory, URD=upper respiratory conditions, CAR=cardiac, CV=cardiovascular, DYS=dysrhythmias, HF=heart failure, IHD=ischaemic heart disease, ST=stroke, OCV=other cardiovascular, O=any other groups of ICD codes eg diabetes

[3] AA=all ages, E=elderly, NE=not elderly, YA=young adult, C=children

NO2: panel studies. Random effects summary estimates (% increase 10mcg/m3 and 95% CI). For outcomes with 4 or more individual estimates. Anderson et al 2007

			Estimate numbers			Random effects estimate and 95% CL		
Set no.	**Panel Group[1]**	**Outcome[2]**	**Total**	**In meta-analysis**	**Het.(p)[3]**	**Est**	**Lcl**	**Ucl**
1	symptomatic	iLRS(O)	146	24	.002	-6.56	-10.25	-2.71
2	symptomatic	pLRS(O)	153	26	<.001	-0.35	-1.72	1.03
3	symptomatic	iM	33	16	.07	-5.11	-15.36	6.39
4	symptomatic	pM	50	25	.02	0.31	-1.08	1.72
5	symptomatic	PEFR (l/m)	122	25	.01	0.04	-0.10	0.18
6	symptomatic	iURS	49	23	.71	-3.44	-5.55	-1.27
7	symptomatic	pURS	52	25	.33	-0.24	-0.86	0.38

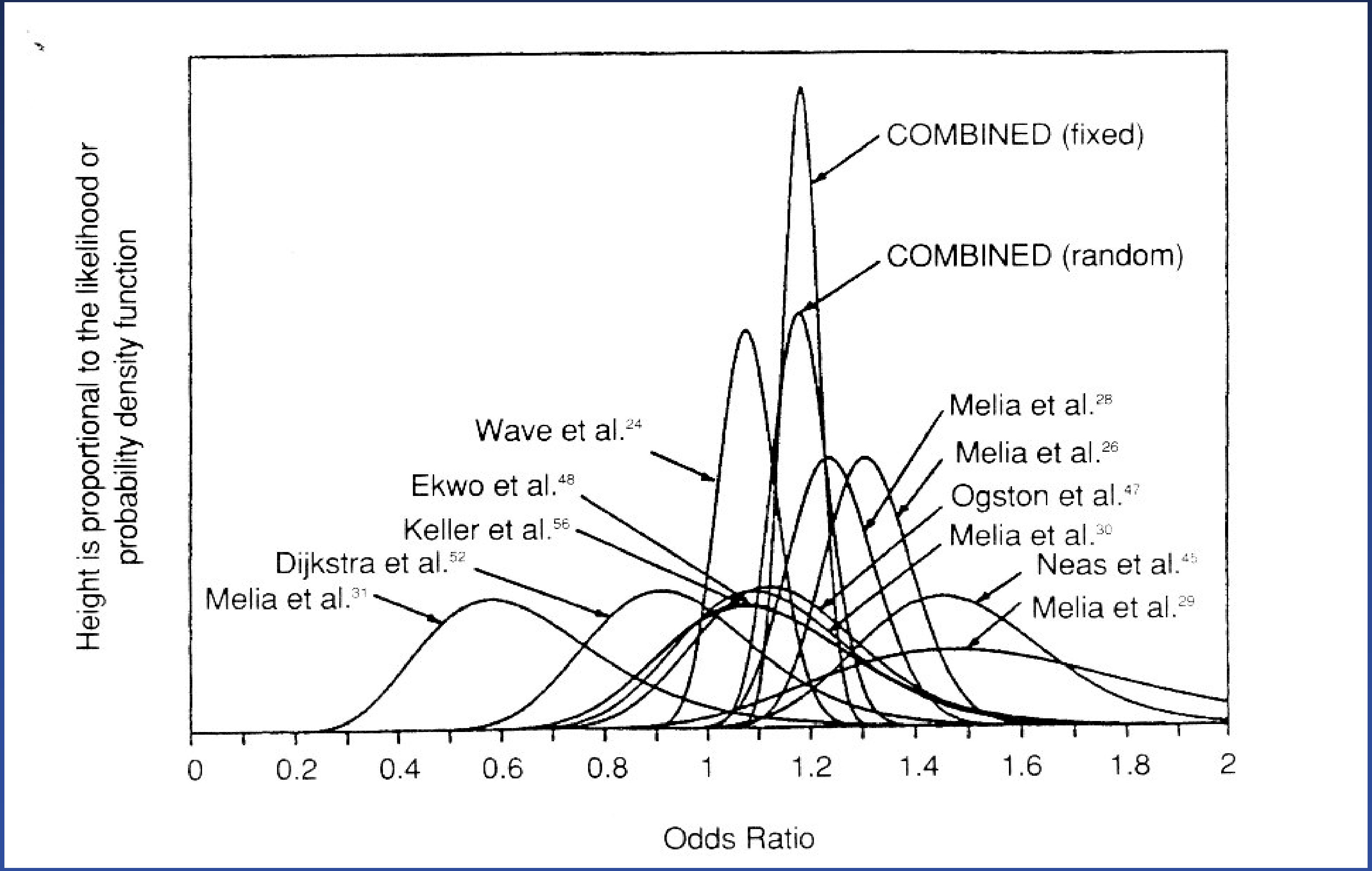
[1] unselected = mixture of healthy/not healthy children

[2] PEFR = peak expiratory flow rate, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, LRS(O) = lower respiratory symptoms (not dyspnoea), URS = upper respiratory symptoms, M = medication use (bronchodilator). The i/p prefix refers to incident or prevalent outcomes.

Summary estimates from meta-analyses of pollution-outcome pairs with 4+ estimates: overview of direction and significance of results. Anderson et al 2007

Pollutant	Design	No. summary estimates (*no. individual estimates*)	No. significantly adverse association (%)
NO2	TS - mortality	12 *(329)*	11 (92%)
	TS - HADs	22 *(130)*	14 (64%)
	Panel	7 *(164)*	0 (0%)
PM	TS - mortality	31 *(685*)	25 (81%)
	TS - HADs	31 *(283*)	23 (74 %)
	Panel	15 *(358)*	0 (0 %)
Ozone	TS - mortality	13 *(299)*	11 (85 %)
	TS - HADs	15 *(80)*	5 (33 %)
	Panel	4 *(32)*	4 (100%)

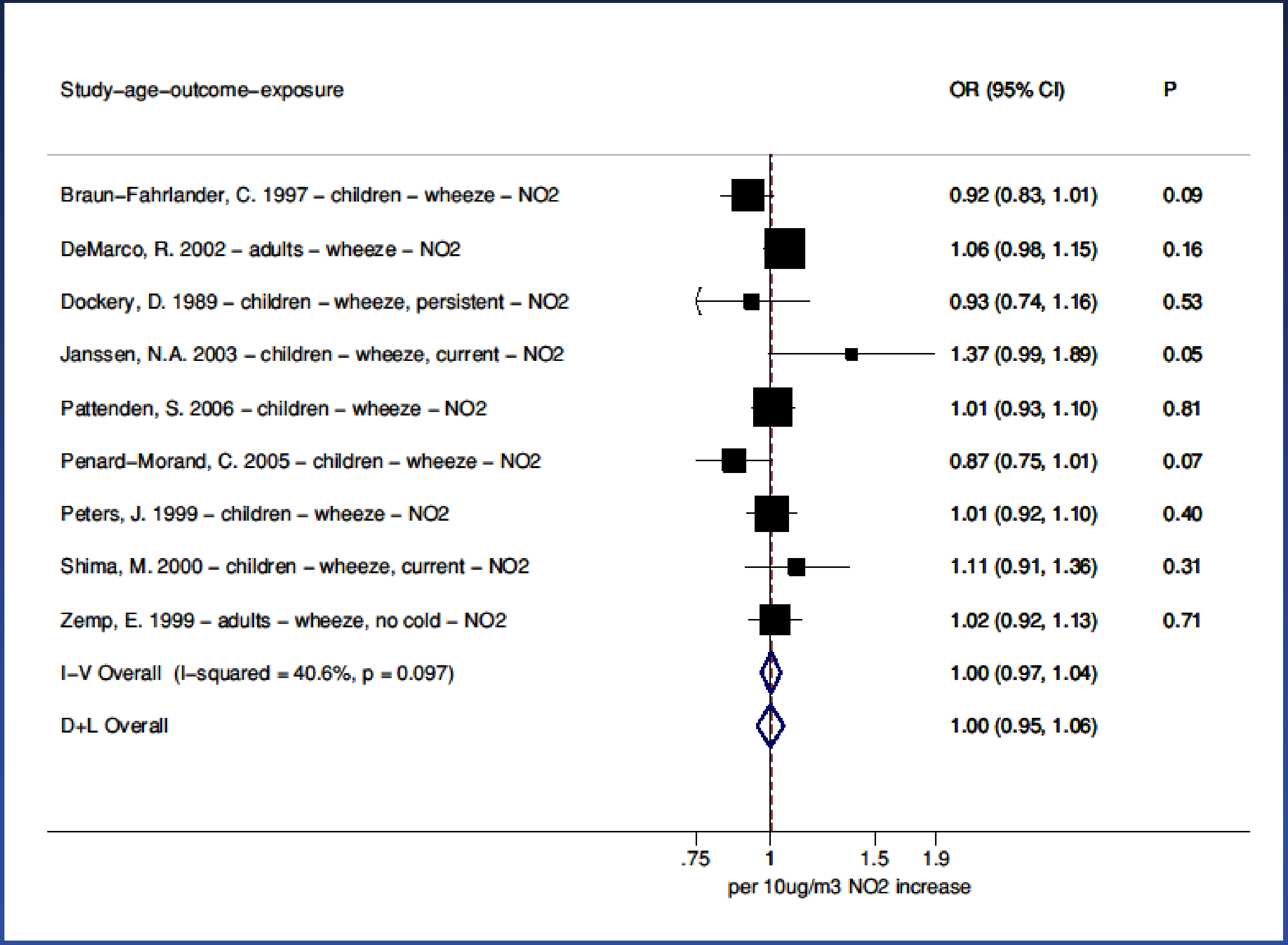
Indoor nitrogen dioxide and respiratory symptoms: Synthesis of evidence. (Hasselblad et al 1992)



Effect estimates from European cohort studies on air pollution and mortality, expressed per 10 μg/m3 NO2 or NOx (Assembled by Bert Brunekreef for GBD Expert Group)

Source	All cause mortality	Cardiopulmonary deaths
(Hoek et al., 2002) (NO_2)	1.12 (0.98 – 1.33)	1.27 (1.00 – 1.78)
(Nafstad et al., 2004) (NO_x)	1.08 (1.06 – 1.11)	1.08 (IHD) (1.03 – 1.12)
(Filleul et al., 2005) (NO_2)	1.14 (1.05 – 1.17)	1.27 (1.04 – 1.56)
(Gehring et al., 2006) (NO_2)	1.11 (1.01 – 1.21)	1.36 (1.14 – 1.63)
(Naess et al., 2006) (NO_2)		1.05 (51-70 yr olds)

NO2 and period prevalence of wheeze/asthma: meta-analysis of between-community studies



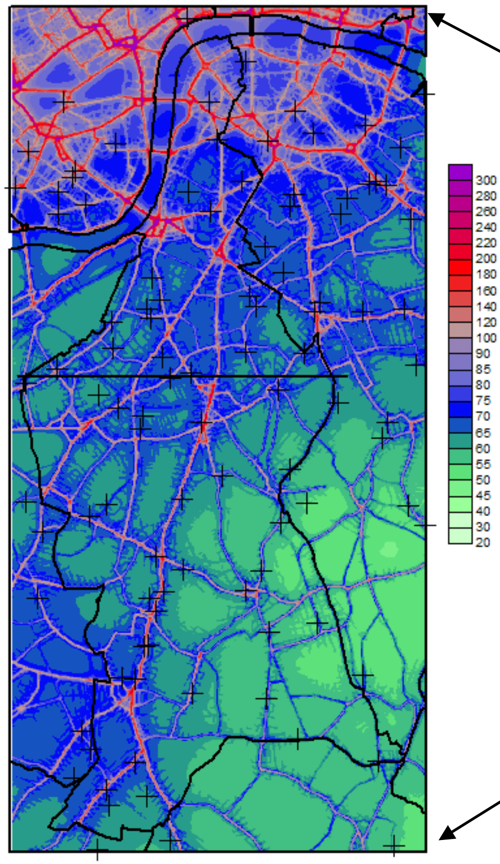
Anderson et al. unpublished data

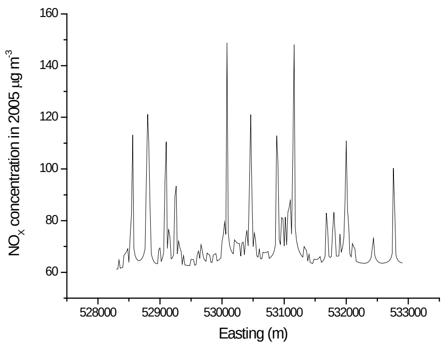
Traffic related air pollution and health outcomes: current opinion as to causality. (HEI 2009)

• Mortality – all cause and CV	Suggestive, not sufficient
• Cardiovascular morbidity	Suggestive, not sufficient
• Child asthma incidence/prevalence	Sufficient/suggestive, not suff.
• Child asthma exacerbation	Sufficient
• Child resp. symp. (non asthmatics)	Inadequate, insufficient
• Adult onset asthma	Inadequate, insufficient
• Adult respiratory symptoms	Suggestive, not sufficient
• Pulmonary function (adults & child)	Suggestive, not sufficient
• COPD	Inadequate, not sufficient
• Allergy	Inadequate, insufficient
• Birth outcomes	Inadequate, insufficient
• *Cancer*	Inadequate. insufficient

Inadequate and insufficient: evidence of effects but not sufficient to draw firm conclusions about causality

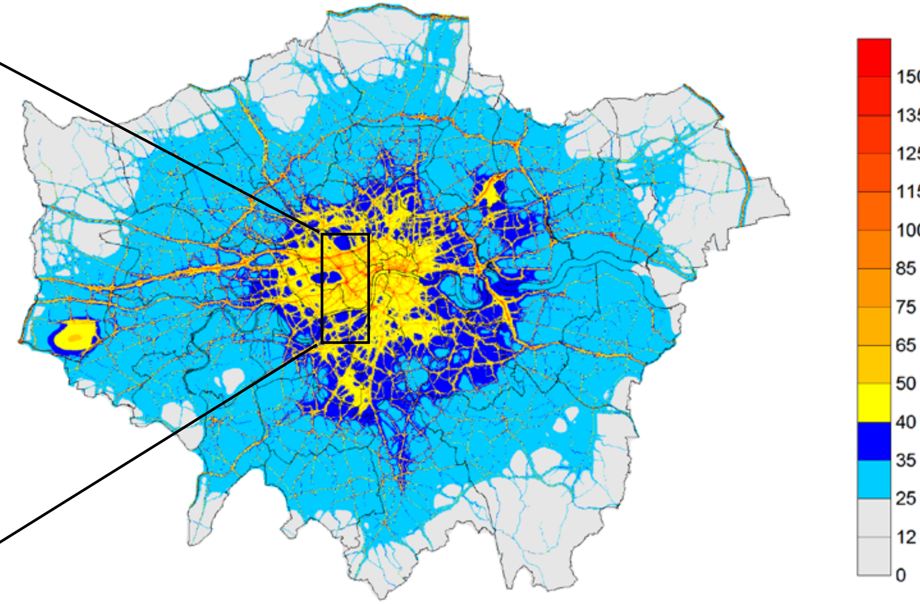
NOx, Borough of Lambeth 2005

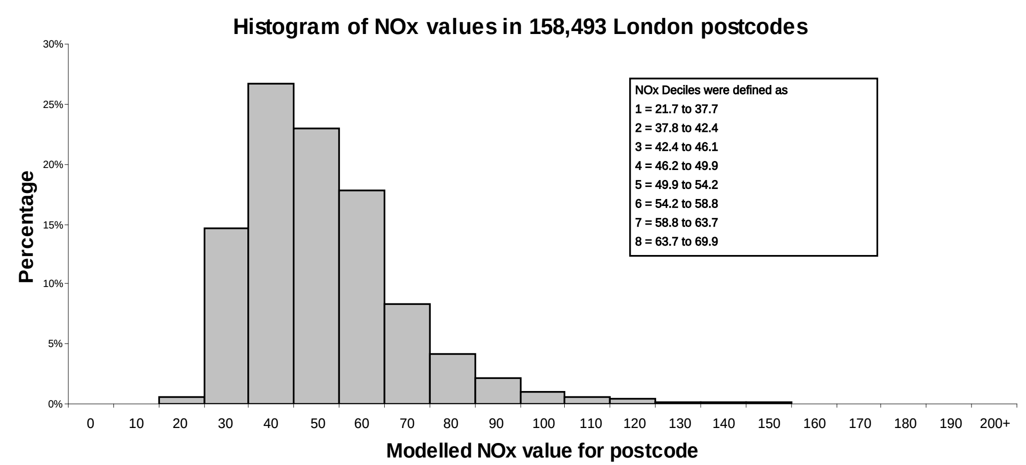




Transect. NOx 2005

London annual mean NOx (20x20m) 2004

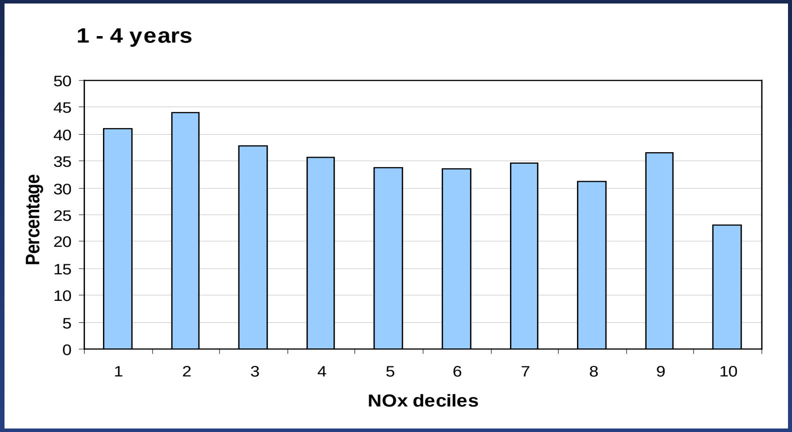




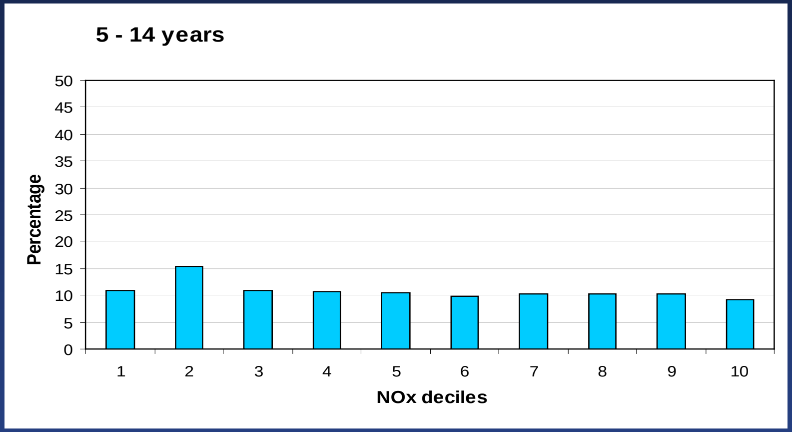
% distribution of NOx for population of London

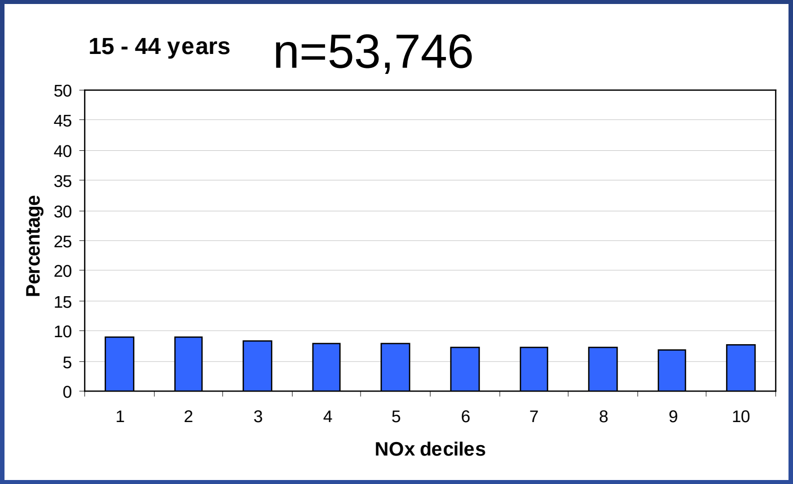
DIN practices: incidence of respiratory tract infections in 2005 (spells)

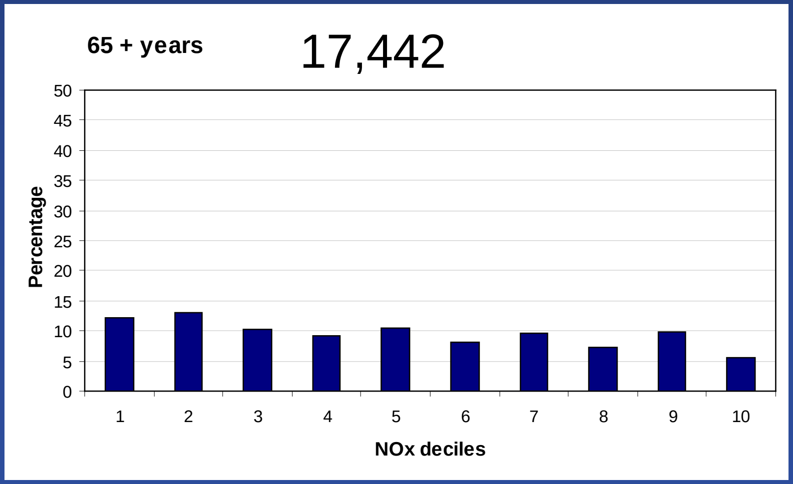
n=6,115



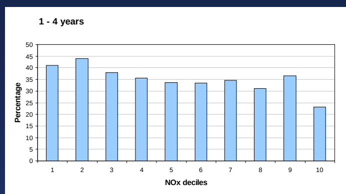
n=14,264

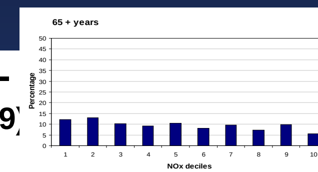






OR's for respiratory infections adjusted for age (within age group), sex, IMD, practice and smoking





	AGES 1 - 4 (n=5,991)			AGES 65 - (n=16,219)		
NOx decile	**OR**	**95% CI**		**OR**	**95% CI**	
1	**1.56**	1.00	2.43	**0.82**	0.57	1.18
2	**1.12**	0.75	1.68	**0.89**	0.71	1.14
3	**1.03**	0.70	1.53	**0.91**	0.77	1.07
4	**0.99**	0.81	1.21	**0.92**	0.79	1.07
5	**0.98**	0.88	1.09	**1.12**	0.93	1.34
6	**1**			**1**		
7	**0.97**	0.89	1.05	**1.14**	0.99	1.32
8	**0.94**	0.81	1.08	**0.94**	0.83	1.06
9	**1.13**	1.04	1.23	**1.19**	0.88	1.61
10	**0.58**	0.41	0.84	**0.66**	0.49	0.90
Test for trend	p=0.01 (neg)			p=0.26		

Note that practice is fitted as random effect in all above models

NOx Deciles are: 1= 21.7 to 37.7, 2= 37.8 to 42.4, 3= 42.4 to 46.1, 4= 46.2 to 49.9, 5= 49.9 to 54.2,
6= 54.2 to 58.8, 7= 58.8 to 63.7, 8= 63.7 to 69.9, 9= 69.9 to 82.1, 10= 82.1 to 386.3.

p-value for test for NOx trend indicates positive trend unless stated

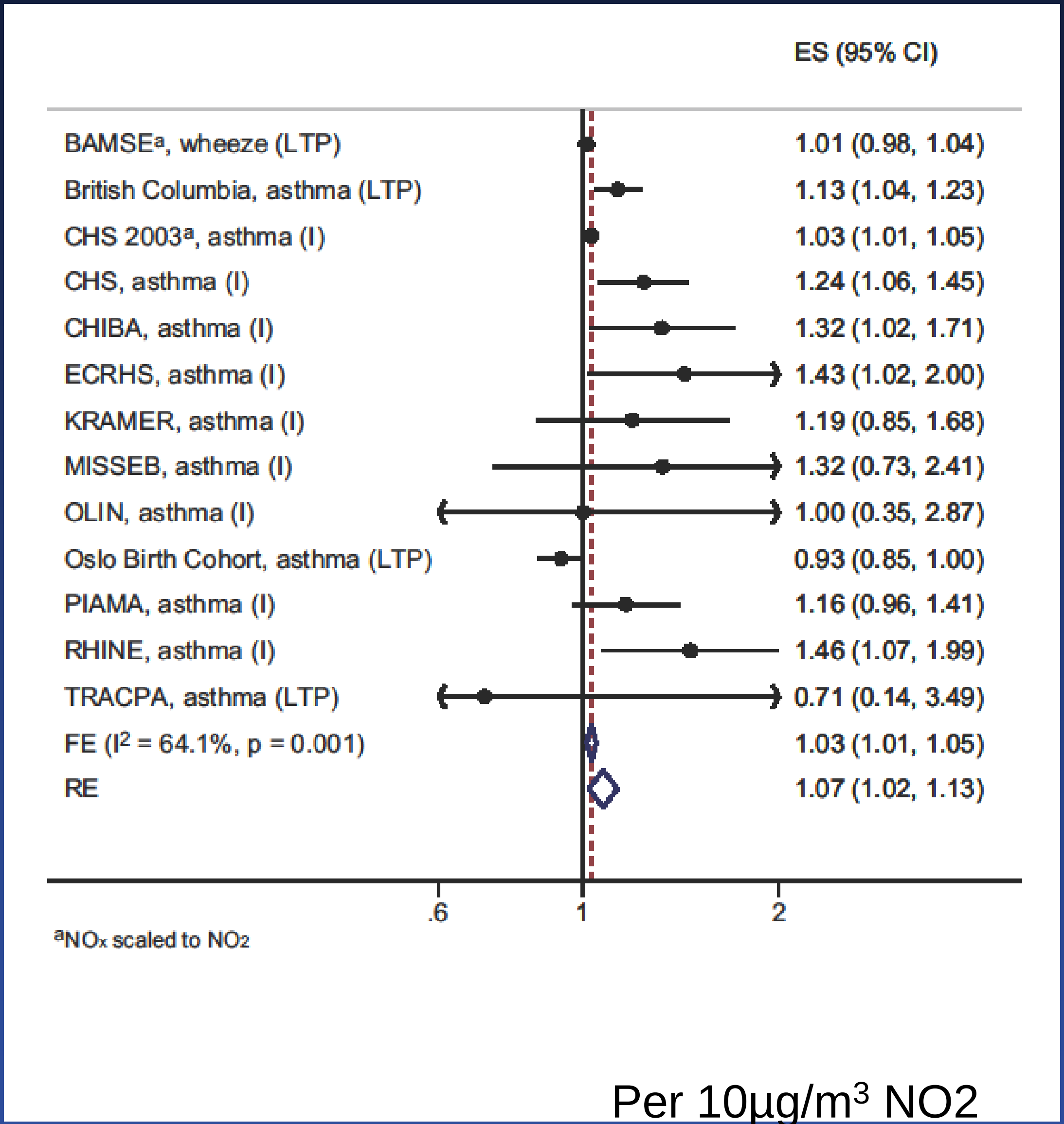
US Health Effects Institute 2010: Special Report

“Traffic-Related Air Pollution: A Critical
Review of the Literature on
Emissions, Exposure, and Health Effects”

“living close to busy roads is an independent risk factor for the onset of childhood asthma”.

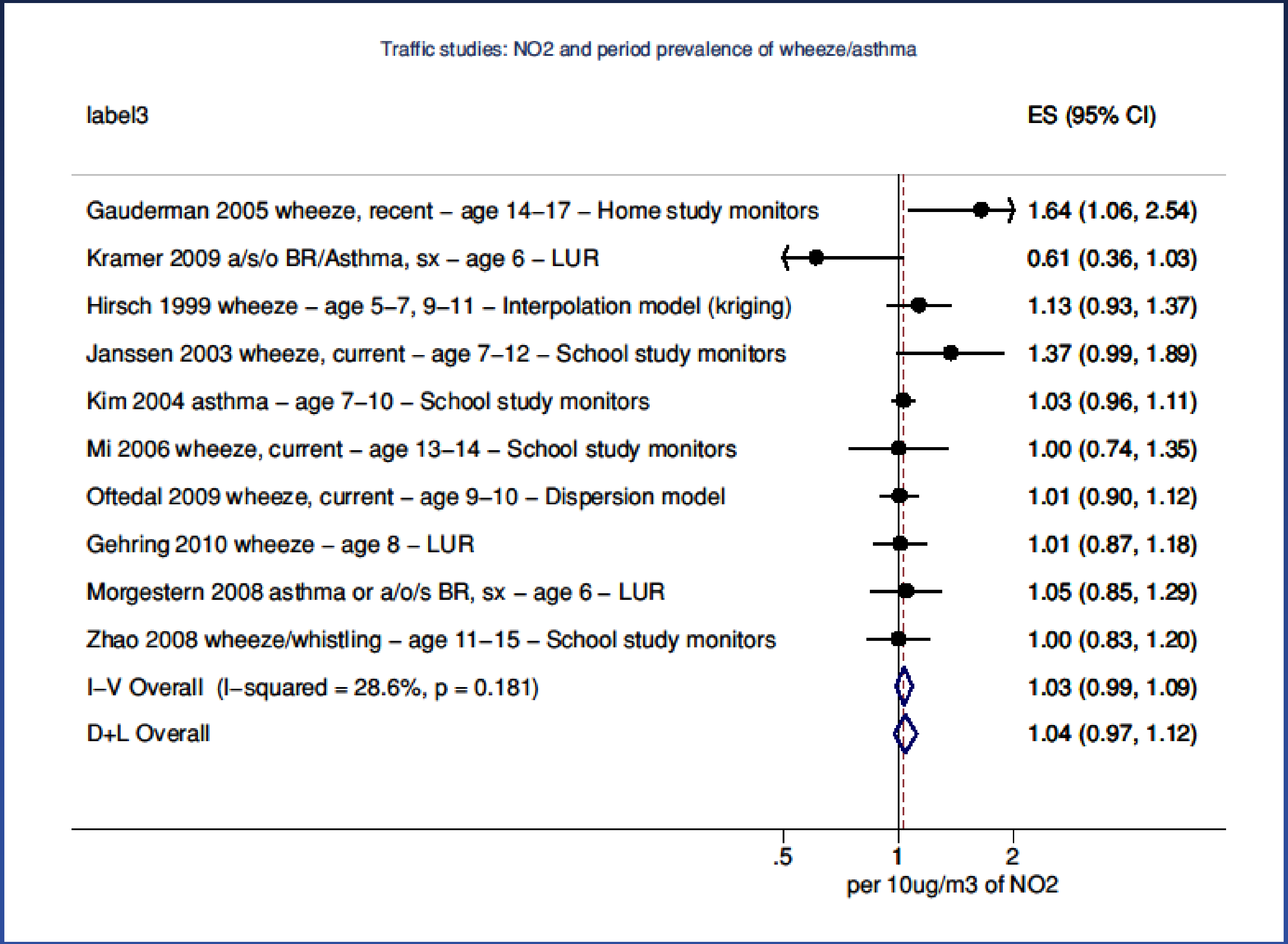
The evidence that this association is causal lies somewhere between
“sufficient” and “suggestive but not sufficient”.

NO_2 and incidence of asthma: meta-analysis of cohort studies



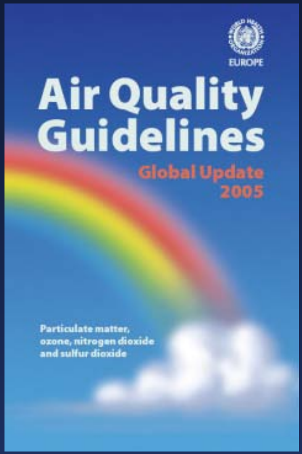
Anderson et al. In press Air Quality Atmosphere and Health

NO2 and period prevalence of wheeze/asthma: meta-analysis of within-community studies



(Anderson et al unpublished data)

WHO AQG:
Global update 2005



Pollutant	Averaging time	AQG value
Particulate matter		
$PM_{2.5}$	1 year 24 hour (99th percentile)	10 µg/m³ 25 µg/m³
PM_{10}	1 year 24 hour (99th percentile)	20 µg/m³ 50 µg/m³
Ozone, O_3	8 hour, daily maximum	100 µg/m³
Nitrogen dioxide, NO_2	1 year 1 hour	40 µg/m³ 200 µg/m³
Sulfur dioxide, SO_2	24 hour 10 minute	20 µg/m³ 500 µg/m³

Contributions of epidemiological and toxicological evidence to WHO GL

	Short term GL	Long term GL
$PM_{2.5}$	EPI (TS PM_{10})	EPI (cohort $PM_{2.5}$)
PM_{10}	EPI (TS PM_{10})	EPI (cohort $PM_{2.5}$)
NO2 (1hr)	Tox	EPI (indoor)
O3 (8hr)	EPI (TS); TOX	No GL
SO2 (10min)	TOX	
SO2 (24hr)	EPI (TS)	No GL

Points

- Epidemiological evidence for short- and long-term associations between NO2 and health effects is relatively strong and robust
- The paradigm of multifactorial aetiology increases the theoretical case for a causal role in ambient concentrations
- Probably not possible to disentangle associations with co-pollutants
- Scientific rationale for WHO guidelines is not consistent across pollutants
- How much of this inconsistency is based on science and how much on predjudice?
- Is the reductionist approach too limited? Should we just concentrate on controlling sources

James Lind
1715-1794
Naval surgeon

“As it is no easy matter to root out prejudices…it became requisite to exhibit a full and impartial view of what had hitherto been published on the scurvy, and that in a chronological order, by which the sources of these mistakes may be detected. Indeed before the subject could be set in a clear and proper light, it was necessary to remove a great deal of rubbish”

A treatise in the scurvy 1753

“If I hadn’t believed it, I wouldn’t have seen it”

Berra Y (1998). The Yogi Book. New York, Workman Press

Cited in Pearce and Douwes, 2009

THANK YOU