Evaluation of a meta-analysis of ambient air quality as a risk factor for asthma exacerbation

Supplemental Information (SI) files

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Supplemental Information, SI 1

Estimating the Theoretical Post-Study Probability of Risk Factor−Chronic Disease Research Findings in Epidemiological Observational Studies

a) Prevalence rates for various chronic diseases

Crude estimates of prevalence (*P*) in United States are provided below for selected chronic diseases of interest.

Respiratory Diseases

Asthma among total population – $P = 0.079$ (2017)[1]

Chronic Obstructive Pulmonary Disease (COPD) among adults ≥18 years old – $P = 0.059$ (during 2014−2015)[2]

Heart Disease (includes coronary heart disease, angina or heart attack)

Heart disease among adults ≥18 years old – $P = 0.056$ (2018)[3]

Diabetes

Diabetes among total population – $P = 0.094$ (2015)[4]

Cancers

Breast cancer among females ≥35 years old – $P = 0.037$ (2016)[5]

Prostate cancer among males ≥55 years old – $P = 0.072$ (2016)[6]

Colorectal cancer among total population – $P = 0.0040$ (2016)[7]

Lung & Bronchus among total population – $P = 0.0017$ (2017)[8]

*b) **Sources:***

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2 COPD Foundation, Denver, CO – National and State Estimates of COPD Morbidity and Mortality — United States, 2014-201, https://journal.copdfoundation.org/jcopdf/id/1209/National-and-State-Estimates-of-COPD-Morbidity-and-Mortality-United-States-2014-2015 (accessed 10 August 2019).

3 Centers for Disease Control and Prevention, U.S. Department of Health & Human Services, Atlanta, GA – Trends in Cancer and Heart Disease Death Rates Among Adults Aged 45–64: United States, 1999–2017, National Vital Statistics Reports, Vol. 68, No. 5, May 22, 2019, https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_05-508.pdf (accessed 10 August 2019).

4 Centers for Disease Control and Prevention, U.S. Department of Health & Human Services, Atlanta, GA – National Diabetes Statistics Report, 2017, Estimates of Diabetes and Its Burden in the United States, https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (accessed 10 August 2019).

5 Estimate of number of females living with breast cancer in 2016: National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, Bethesda, MD – Cancer Stat Facts: Female Breast Cancer, https://seer.cancer.gov/statfacts/html/breast.html (accessed 16 October 2019) (Note, of females living with breast cancer it was assumed that 4% were <35 yr old and 96% ≥35 yr old) & Estimate of number of females living in 2016: United States of America 2016 population, https://www.populationpyramid.net/united-states-of-america/2016/ (accessed 16 October 2019).

6 Estimate of number of males living with prostate cancer in 2016: National Cancer Institute, SEER Program, Bethesda, MD – Cancer Stat Facts: Prostate Cancer, https://seer.cancer.gov/statfacts/html/prost.html (accessed 16 October 2019) (Note, of males living with prostate cancer it was assumed that 2% were <55 yr old and 98% ≥55 yr old) & Estimate of number of males living in 2016: United States of America 2016 population, https://www.populationpyramid.net/united-states-of-america/2016/ (accessed 16 October 2019).

7 Estimate of number of people living with colorectal cancer in 2016: National Cancer Institute, SEER Program, Bethesda, MD – Cancer Stat Facts: Colorectal Cancer, https://seer.cancer.gov/statfacts/html/colorect.html (accessed 16 October 2019) & Estimate of number of people living in 2016: United States of America 2016 population, https://www.populationpyramid.net/united-states-of-america/2016/ (accessed 16 October 2019).

8 Estimate of number of people living with lung and bronchus cancer in 2016: National Cancer Institute, SEER Program, Bethesda, MD – Cancer Stat Facts: Lung and Bronchus Cancer, https://seer.cancer.gov/statfacts/html/lungb.html (accessed 16 October 2019) & Estimate of number of people living in 2016: United States of America 2016 population, https://www.populationpyramid.net/united-states-of-america/2016/ (accessed 16 October 2019).

2. Theoretical post-study probabilities of a research finding being true

Our interest is in estimating the theoretical post-study probability of an outcome being true for a single observational study of risk factor−chronic disease relationships. An outcome may either be one that is a positive association (+ve), i.e., one that is statistically significant with p-value ≤.05; or a negative or null association (-ve), i.e., one that is not statistically significant with p-value >.05. Using a Bayesian argument, the former outcome may either be a true or false positive association and the latter outcome may either be a false or true negative (null) association.

a) Disease prevalence (P)

We first provide a formal definition of prevalence (P):

P = The number of persons with a disease divided by the total population at risk at a particular point in time (Wassertheil-Smoller 1995).[1]

We break this down further as:

d^+ = Those in the population under study with the disease.

d^- = Those in the population under study without the disease.

$d^+ + d^-$ = Total population at risk under study.

$$\therefore P = d^+/(d^+ + d^-) \quad (1)$$

Odds of a particular outcome, in this case odds in favor of d^+ given d^+ and d^-, is:[1]

$$\text{Odds}(d^+) = d^+/d^- \quad (2)$$

Probability (P) of outcome d^+ is related to odds:[1]

$$\text{P}(d^+) = \text{Odds}(d^+)/[\text{Odds}(d^+) + 1] \quad (3)$$

Equation (2) is the same as the Ioannidis (2005)[2] definition of R being the "number of *true relationships* to *no relationships* among those tested in the field" (i.e., $\text{Odds}(d^+) \equiv R$). Also, equation (3) is the same as the Ioannidis (2005)[2] definition of "pre-study probability of a relationship being true" (i.e., $\text{P}(d^+) = \text{Odds}(d^+)/[\text{Odds}(d^+) + 1] \equiv R/(R + 1)$).

If we substitute equation (2) into equation (3) and rearrange, we get $\text{P}(d^+) = d^+/(d^+ + d^-)$, which is the same as the prevalence rate of a disease (P). Thus the "pre-study probability of a relationship being true" can be represented by the prevalence rate of a disease (P) for our purposes. As our interest is in estimating the theoretical post-study probability of an outcome being true as a function of *P*, we conservatively assume that all those in the population with the disease (i.e., d^+) being studied are due to the specific risk factor we are examining.

b) <u>2 x 2 Table of true relationships and study findings in absence of bias</u>

Let us consider a 2 x 2 table of measures of association between 'true relationships' and 'study findings' in the absence of bias for a single observational study of risk factor–chronic disease relationships (refer to *Illustration* 1). Hrudey and Leiss (2003)[3] and Baduashvili et al. (2020)[4] are used to derive our 2 x 2 table.

		True Relationship of a Risk Factor		
		Causes disease	Does not causes disease	**Total**
Study Finding	Causes disease	**True Positive association (TP)** with rate = Se (Sensitivity) = 1 – β	**False Positive association (FP)** with rate = α	**= TP + FP**
	Does not cause disease	**False Negative association (FN)** with rate = β	**True Negative (null) association (TN)** with rate = Sp (Specificity) = 1 – α	**= FN + TN**
	Total	**= TP + FN**	**= FP + TN**	**= *c***

***Illustration* 1. 2 x 2 table of true relationships and study findings given *c* relationships probed/tested** (after Hrudey and Leiss 2003[3] and Baduashvili et al. 2020[4]).

(note: TP = # of true positive relationships, TN = # of true negative (null) relationships, FP = # of false positive relationships, FN = # of false negative (null) relationships; α = Type I error rate, β = Type II error rate)

For *c* risk factor–disease relationships probed/tested in a single study, we can derive the following from *Illustration* 1:

Number of true +ve associations, N(TP) = c x Se (sensitivity) x $P = c(1 - \beta)P$ (4)

Number of false −ve associations, N(FN) = $c\beta P$ (5)

Number of true −ve associations, N(TN) =c x Sp (specificity) x $(1 - P) = c(1 - \alpha)(1 - P)$ (6)

Number of false +ve (FP) associations, N(FP) = $c\alpha(1 - P)$ (7)

where α and β are the Type I and Type II error rates, respectively.

The total number of positive associations, N[(TP) + (FN)] =
$c(1 - \beta)P + c\beta P = cP$

The total number of negative associations, N[(FP) + (TN)] =
$c\alpha(1 - P) + c(1 - \alpha)(1 - P) = c(1 - P)$

As a check of the bottom row in *Illustration* 1, the total number of positive and negative associations =
N[(TP) + (FN)] + N[(FP) + (TN)] = $cP + c(1 - P) = c$

Now we do a check of the far-right column in *Illustration* 1:
N[(TP) + (FP)] = $c(1 - \beta)P + c\alpha(1 - P)$
N[(FN) + (TN)] = $c\beta P + c(1 - \alpha)(1 - P)$
∴ N[(TP) + (FP)] + N[(FN) + (TN)] = $c(1 - \beta)P + c\alpha(1 - P) + c\beta P + c(1 - \alpha)(1 - P)$;
rearranging… = $\{c(1 - \beta)P + c\beta P\} + \{c\alpha(1 - P) + c(1 - \alpha)(1 - P)\} = cP + c(1 - P) = c$

c) 2 x 2 Table of true relationships and study findings in presence of bias

Now we consider the role of bias (u) in an observational study of risk factor−chronic disease relationships. Here we use the definition of u after Ioannidis (2005)[2] – *the proportion of probed analyses* [relationships] *that would not have been "research findings," but nevertheless end up presented and reported as such, because of bias*. *"Research findings"* imply nominally significant outcomes (i.e., associations with p-value ≤.05). Bias will transfer a portion of non-significant or null outcomes (associations with p-value >.05) to nominally significant outcomes (associations with p-value ≤.05).

First, we deal with positive associations – FNs & TPs. Because of bias, some outcomes initially showing up as non-significant FN associations (i.e., with p-value >.05) will now end up being reported as significant TP associations (i.e., with p-value ≤.05) proportional to u:

∴ N(FN) in the presence of bias now becomes $= c\beta P(1 - u)$ (8)

∴ N(TP) in the presence of bias now becomes $= c(1 - \beta)P + uc\beta P$ (9)

The total number of positive associations, N[(TP) + (FN)] =
$c(1 - \beta)P + uc\beta P + c\beta P(1 - u) = cP$

Now we deal with negative associations – TNs & FPs. Because of bias, some outcomes initially showing up as non-significant TN associations (i.e., with p-value >.05) will now end up being reported as significant FP associations (i.e., with p-value ≤.05) proportional to u:

∴ N(TN) in the presence of bias now becomes $= c(1 - \alpha)(1 - P)(1 - u)$ (10)

∴ N(FP) in the presence of bias now becomes $= c\alpha(1 - P) + uc(1 - \alpha)(1 - P)$ (11)

The total number of negative associations, N[(FP) + (TN)] =
$c\alpha(1 - P) + uc(1 - \alpha)(1 - P) + c(1 - \alpha)(1 - P)(1 - u)$; rearranging =
$\{c\alpha(1 - P) + c(1 - \alpha)(1 - P)\} + \{[uc(1 - \alpha)(1 - P)] - [uc(1 - \alpha)(1 - P)]\} = c(1 - P)$

As a check of the bottom row in *Illustration* 1, the total number of positive and negative associations =
N[(TP) + (FN)] + N[(FP) + (TN)] $= cP + c(1 - P) = c$

Now we do a check of the far-right column in *Illustration* 1:
N[(TP) + (FP)] $= c(1 - \beta)P + uc\beta P + c\alpha(1 - P) + uc(1 - \alpha)(1 - P)$
N[(FN) + (TN)] $= c\beta P(1 - u) + c(1 - \alpha)(1 - P)(1 - u)$

∴ N[(TP) + (FP)] + N[(FN) + (TN)] $= c(1 - \beta)P + uc\beta P + c\alpha(1 - P) + uc(1 - \alpha)(1 - P) +$
$c\beta P(1 - u) + c(1 - \alpha)(1 - P)(1 - u)$; rearranging =
$\{c\alpha(1 - P) + c(1 - \alpha)(1 - P)\} + cP + \{[uc(1 - \alpha)(1 - P)] - [uc(1 - \alpha)(1 - P)]\} + \{uc\beta P - uc\beta P\} +$
$\{c\beta P - c\beta P\} = c(1 - P) + cP = c$

d) Theoretical post-study probability of an outcome being true

The positive predictive value (PPV)[c] is used to represent the theoretical post-study probability of a positive outcome being true in the presence of bias:

$$\text{PPV} = \text{N(TP)/N[(TP) + (FP)]} \quad (12)$$

$$\therefore \text{PPV} = [(1 - \beta)P + u\beta P] / [(1 - \beta)P + u\beta P + \alpha(1 - P) + u(1 - \alpha)(1 - P)] \quad (13)$$

The negative predictive value (NPV)[c] is used to represent the theoretical post-study probability of a negative (i.e., null) outcome being true in the presence of bias:

$$\text{NPV} = \text{N(TN)/N[(FN) + (TN)]} \quad (12)$$

$$\therefore \text{NPV} = [(1 - \alpha)(1 - P)(1 - u)] / [\beta P(1 - u) + (1 - \alpha)(1 - P)(1 - u)] \quad (13)$$

e) ***Sources***

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4 Baduashvili A, Evans AT, Cutler T. 2020. How to understand and teach P values: a diagnostic test framework. J Clin Epidemiol 122:49−55. https://doi.org/10.1016/j.jclinepi.2020.03.003.

Supplemental Information, SI 2

List of 87 Base Studies used in the Zheng et al. 2015 Meta-analysis

(Note: 'number' preceding reference is the citation number used by Zheng et al.)

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81. Fung KY, et al. Air pollution and daily hospitalization rates for cardiovascular and respiratory diseases in London, Ontario. Int J Environ Stud. 2005; 62: 677–685.

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83. Hua J, et al. Acute effects of black carbon and $PM_{2.5}$ on children asthma admissions: A time-series study in a Chinese city. Sci Tot Envir 2014; 481: 433–438.

84. Cadelis G, et al. Short-term effects of the particulate pollutants contained in Saharan dust on the visits of children to the emergency department due to asthmatic conditions in Guadeloupe (French Archipelago of the Caribbean). PLoS One 2014; 9: e91136 (11 pp).

85. Cheng MH, et al. Fine particulate air pollution and hospital admission for asthma: A case-crossover study in Taipei. J Toxicol Environ Health, Part A, 2014; 77: 1071–1083.

86. Cai J, et al. Acute effects of air pollution on asthma hospitalization in Shanghai, China. Environ Pollut 2014; 191: 139–144.

87. Gleason JA, et al. Associations between ozone, $PM_{2.5}$, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey: A case-crossover study. Environ Res 2014; 132: 421–429.

88. Sacks JD, et al. Influence of urbanicity and county characteristics on the association between ozone and asthma emergency department visits in North Carolina. Environ Health Perspect 2014; 122: 506–512.

89. Raun LH, et al. Using community level strategies to reduce asthma attacks triggered by outdoor air pollution: a case crossover analysis. Environ Health 2014; 13: 58 (14 pp).

17 Base Studies Randomly Selected for Evaluation of Analysis Search Space

(Note: ‘number’ preceding reference is the citation number used by Zheng et al.)

Initial 10 base studies selected:

3. Thompson AJ, Shields MD. Acute asthma exacerbations and air pollutants in children living in Belfast, Northern Ireland. Arch Eviron Heal 2001; 56: 234–241.

18. Tsai SS, et al. Air pollution and hospital admissions for asthma in a tropical city: Kaohsiung, Taiwan. Inh Toxicol 2006; 18: 549–554.

23. Laurent O, et al. Air pollution, asthma attacks, and socioeconomic deprivation: a small-area case-crossover study. Am J Epidemiol 2008; 168: 58–65.

44. Lin M, et al. The Influence of ambient coarse particulate matter on asthma hospitalization in children: case-crossover and time-series analyses. Environ Health Persp 2002; 110: 575–581.

47. Chakraborty P, et al. Effect of airborne Alternariaconidia, ozone exposure, PM_{10} and weather on emergency visits for asthma in school-age children in Kolkata city, India. Aerobiologia 2014; 30: 137–148.

48. Abe T, et al. The relationship of short-term air pollution and weather to ED visits for asthma in Japan. Am J Emerg Med 2007; 27: 153–159.

69. Evans KA, et al. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. Environ Res 2014, 129: 11–19.

70. Sheppard L, et al. Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987–1994. Epidemiology 1999; 10: 23–30.

80. Gouveia N, Fletcher T. Respiratory diseases in children and outdoor air pollution in San Paulo, Brazil: a time series analysis. Occup Environ Med 2000; 57: 477–483.

83. Hua J, et al. Acute effects of black carbon and $PM_{2.5}$ on children asthma admissions: A time-series study in a Chinese city. Sci Tot Envir 2014; 481: 433–438.

Additional 7 base studies selected:

8. Andersen ZJ, et al. Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. Occup Environ Med 2008; 65: 458–466.

15. Chardon B, et al. Air pollution and doctors’ house calls for respiratory diseases in the Greater Paris area (2000–3). Occup Environ Med 2007; 64: 320–324.

31. Tenias JM, et al. Association between hospital emergency visits for asthma and air pollution in Valencia, Spain. Occup Environ Med 1998; 55: 541–547.

35. Magas OK, et al. Ambient air pollution and daily pediatric hospitalizations for asthma. Env Sci Pollut Res 2007; 14: 19–23.

57. Lavigne E, et al. Air pollution and emergency department visits for asthma in Windsor, Canada. Can J Public Heal 2012; 103: 4–8.

64. Mar T, et al. Associations between asthma emergency visits and particulate matter sources, including diesel emissions from stationary generators in Tacoma, Washington. Inhal Toxicol 2010; 22: 445–448.

74. Santus P, et al. How air pollution influences clinical management of respiratory diseases. A case-crossover study in Milan. Respir Res 2012; 13: 95.

Details of the 87 base studies included in the Zheng et al. 2015 meta-analysis

Notes: Data presented in the tables below obtained from Zheng et al. (2015).
Study: '#', 'Name', 'year': Zheng et al. 2015 citation number, first author, year published.
Quality score: 0 (low) to 5 (high quality); ICD: International Classification of Diseases; ICPC2: International Classification of Primary Care 2; GP: GP's house calls; NAEPP: National Asthma Education and Prevention Program; PC: primary care visits; TS: time-series; CC: case crossover.
Default concentration for CO in mg/m^3 and for NO_2, SO_2, PM_{10} and $PM_{2.5}$ all in $\mu g/m^3$ is 24-h averaged concentration; and for O_3 in $\mu g/m^3$ is 8-hr max concentration.

Study	Location, Period	Quality score	Sample size	Population	Type of study	Pollutants & concentration						Measurement quality score (0 or 1 point)	Lag pattern (single day/ mean days)	Adjustments (long-term trend, seasonality, temperature, humidity, pressure, day for the week, holiday and influenza epidemics)
						CO	PM_{10}	$PM_{2.5}$	SO_2	NO_2	O_3			
Base studies with emergency room visit indices:														
3, Thompson AJ, 2001	Belfast, Northern Ireland, 3 yr	5	-	Children	TS	0.65	28.4	-	47.1	43.6	38.4	1	Both	long-term trend, seasonality, temperature, humidity, day of week, public holiday
14, Sunyer J, 1997	Barcelona, Helsinki, Paris, London, 6 yr	5	75190	Children + adults	TS				27.8	49.8	43.8	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemics
15, Chardon B, 2007	Paris, 3 yr	5/4[b]	8027	General	TS		23.0	14.7		44.4		1/0[b]	Cumulative	long-term trends, seasonality, temperature, humidity, day-of-week, influenza epidemic, pollen
16, Halonen JI, 2008	Helsinki, Finland, 6 yr	5	4807	General	TS	0.5[a]		9.5		28.2		1	Single	long-term trends, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemics
30, Hajat S, 1999	London,UK, 3 yr	5	38653	General	TS	1.0	28.5		21.2	69.0	37.5	1	Both	long term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
41, Galan I, 2003	Madrid, Spain, 3 yr	5	4827	General	TS		32.1		23.6	67.1	45.8	1	Single	long-term trend, seasonality, temperature, humidity, pressure, day-of-week, public holiday, influenza epidemics

51, Atkinson RW, 2001	Barcelona, Birmingham, London, Milan, the Netherlands, Paris, Rome, and Stockholm, 4 yr	5	-	General	TS		29.3					1	Single	long-term trend, seasonality, temperature, humidity, day for the week, holiday and influenza epidemics
55, Medina S, 1997	Paris, France, 4 yr	5	-	General	TS				19.0	56.0	34.0	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemics
58, Stieb DM, 2009	Canada (Montreal, Ottawa, Edmonton, Saint John, Halifax, Toronto, Vancouver), 10 yr	5/4 [b]	83563	General	TS	0.8	8.3	20.6	14.6	37.6	40.0	0/1 [a]	Single	long-term trend, seasonality, temperature, humidity, day-of-week, holiday
60, Wilson AM, 2005	Portland, Maine, Manchester, New Hampshire, 2 yr	5	7300	General	TS				39.4 [b]		41.0	1/0(ozone)	Single	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
75, Sunyer J, 2003	Birmingham, London, Milan, the Netherlands, Par is, Rome, Stockholm, 2-8 yr	5	-	Children + adults	TS				17.6			1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, influenza epidemic
27, Szyszkowicz M, 2008	Edmonton, Canada, 10 yr	4	62563	General	TS	0.9	22.6	8.5		45.0	39.9	1	Single	long term trend, temperature, seasonality humidity, day-of-week
29, Norris G, 1999	Seattle, US, 27 mon	4	1458	Children	TS		21.7		17.1	41.5		1	Single	long term trend, seasonality temperature, humidity, day-of-week
31, Tenias JM, 1998	Valencia, Spain, 3 yr	4	734	Adults + elderly	TS				26.6	57.7	62.8	1	Single	long-term trend, seasonality, temp., humidity, day-of-week, public holiday, influenza epidemics
32, Stieb DM, 1996	Saint John, New Brunswick, Canada, 8 yr	3	1163	General	TS						89.1	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
43, Mohr LB, 2008	St. Louis, US, 2 yr	3	12836	Children	TS			-		-	-	1	Single	long-term trend, seasonality, temperature

46, Castellsague J, 1995	Barcelona, Spain, 5 yr	3	6019	Adults+ elderly	TS				45.5	58.0	70.5	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
47, Chakraborty P, 2013	Kolkata city, India, 2 yr	4	2703	Children	TS		3.8				1.3[c]	1	-	long term trend, seasonality, temperature, humidity
56 Jaffe DH, 2003	Cincinnati, Cleveland, and Columbus, 5 yr	4	4416	Children+ adults	TS		49.5		28.8	10.1	35.8	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
64, Mar TF, 2010	Tacoma, Washington, 3.5 yr	3	10091	General	TS	1.2		12.3				1	Single	long-term trend, seasonality, temperature, humidity
66, Cirera L, 2012	Cartagena, Spain, 4 yr	4	1617	General	TS				32	51	81	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemic
67, Cassino C, 1999	New York, US, 3.5 yr	4	285	Adults	TS	1.2			29.4	92.4	37.5[c]	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
76, Babin S, 2008	Washington DC, US, 11 yr	4	61218	General	TS		-	-			-	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
78, Mar TF, 2009	Seattle, Washington, US, 4 yr	3	3217	Children + adults	TS						84.0	0	Single	long-term trend, seasonality, temperature, humidity, day-of-week
79, Hernandez-Cadena L, 2000	Ciudad Juárez, Chihuahua, Mexico, 1 yr	4	2459	General	TS		34.46				110.6	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
82, Ito K, 2007	New York, US, 4 yr	3		General	TS	1.6[a]	15.7		22.3	31.1	65.1	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
84, Cadelis G, 2014	Guadeloupe, France, 1 yr	3	836	Children	TS		19.2					1	Both	long-term trend, seasonality, temperature
42, Jazbec A, 1999	Zagreb, Croatia, 1.5 yr	0	1372	Children +adults	TS					45.1		0	Cumulative	long-term trend, seasonality,
48, Abe T, 2007	Tokyo, Japan, 1 yr	2	6447	General	TS	1.4			15.1			1	Single	seasonality, temperature, humidity
61, Chimonas MAR, 2007	Anchorage, Alaska, 3.5 yr	2	11037	Children	TS		27.6	6.1				0	Single	long-term trend, seasonality, temperature
4, Strickland MJ, 2010	Atlanta, US, 11 yr	5	91386	Children	CC	1.1[b]	23.8	16.4	30.9[b]	47.8[b]	97.3	1	Both	long-term trend, seasonality, temperature, humidity, day of week and influenza epidemics

11, Paulu C, 2008	Maine, US, 4 yr	5	8020	General	CC			8.5			83.6	1	Both	long-term trend, seasonality, temperature, humidity, day of week, holiday
54, Jalaludin BB, 2008	Sydney, Australia, 5 yr	5	317724	Children	CC	1.0	16.8	9.4	3.1	47.6	67.7	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday
57, Lavigne E, 2010	Windsor, Canada, 7 yr	5	3728	General	CC	0.4		7.3	5.3	17.4	41.5	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
22, Malig BJ, 2013	California, 4 yr	4	74978	General	CC		35.0	12.1				1	Single	long-term trends, seasonality, temperature, humidity, day of week
49, Boutin-Forzano S, 2004	Marseille, France, 1 yr	3	549	Children + adults	CC				22.5	34.9	50.1	1	Single	long-term trend, seasonality, temperature, humidity
72, Yamazaki S, 2013	Himeji, Japan, 2 yr	3	956	Children	CC		34.3	21.2		22.9	55.3	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
74, Santus P, 2012	Milan, Italy, 2 yr	3	3569	General	CC	1.5	47.1	32.8	4.13	102.6	74.3	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
77, Yamazaki S, 2009	Tokyo, Japan, 1 yr	4	403	Children+ adults	CC			19.1		45.3	60.2	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week, holiday
6, Mehta AJ, 2012	Switzerland, 2 yr	1	147	adults	CC					33.9		1	Single	long-term trend, influenza epidemics
23, Laurent O, 2008	France, 5 yr	2	4677	General	CC		22.6		8.9	36.0	57.7	1	Both	temperature, pressure, humidity, influenza epidemic and pollen count
50, Pereira G, 2010	Perth, Australia, 5 yr	2	603	Children	CC	0.3				12.9		1	Single	not declared
69, Evans KA, 2013	New York, US, 3 yr	0	71	Children	CC	0.5		8.6	15.4		55.9	0	Both	temperature, humidity
87, Gleason JA, 2014	New Jersey, US, 4 yr	5	21,854	Children	CC			-			-	1	Both	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, viral upper respiratory infections
88, Sacks JD, 2014	North Carolina, US, 3 yr	5	121,621	General	CC						93.4	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, viral upper respiratory infections

89, Raun LH, 2014	Houston, Texas, US, 7 yr	3	11,754	General	CC	0.3		10.7	4.3	21.6	76.7	0	Both	long-term trend, seasonality, temperature, humidity, day-of-week, holiday, viral upper respiratory infections

Study	Location, Period	Quality score	Sample size	Population	Type of study	Pollutants and concentration (CO in units of mg/m^3; all other pollutants in units of μg/m^3)						Measurement quality score (0-1 point)	Lag pattern (single day/ mean days)	Adjustments (long-term trend, seasonality, temperature, humidity, pressure, day for the week, holiday and influenza epidemics)
						CO	**PM_{10}**	**$PM_{2.5}$**	**SO_2**	**NO_2**	**O_3**			
Base studies with hospital admission indices:														
7, Samoli E, 2010	metropolitan area of Athens, 3 yr	5	3601	Children	TS		43.9		16.8	84.8	70.9	1	Single	long-term trends, seasonality, temperature, humidity, day of week, public holidays and influenza epidemics
19, Wong TW, 1999	Hong Kong, 1 yr	5	-	General	TS		45.0		17.1	51.4	24.2	1	Both	long-term trends, seasonality, temperature, humidity, days-of-week, public holiday
20, Fusco D, 2001	Rome, Italy, 2 yr	5	4635	General	TS	3.6			9.1	86.7	27.0	1	Single	long-term trends, seasonality, temperature, humidity, day- of-week, public holiday, influenza
21, Morgan G, 1998	Sydney, Australia, 5 yr	5	-	General	TS		19.2			30.8	53.6	1	Single	long-term trends, seasonality, temperature, humidity, day-of-week, holiday
24, Anderson HR, 1998	London, UK, 5 yr	5	63039	General	TS				32	76.4	33.2	1	Both	Long-term trends, temperature, humidity, seasonality, days of the week, public holidays and influenza epidemics
28, Lee SL, 2006	Hong Kong, 5 yr	5	26663	Children	TS		56.1	45.3	17.7	64.7	28.6	1	Single	Long-term trend, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemic

34, Petroeschevsky A, 2001	Brisbane, Australia, 8 yr	5	13246	Children + adults	TS				11.7	28.5	40.7	1	Both	long term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
Ko FWS38 2007	Hong Kong, China, 6yr	5	69176	General	TS		52.5	36.4	18.8	53.2	43.4	1	Both	long term trend, seasonality, temperature, humidity, day-of-week, public holiday
39, Krmpotic D, 2011	Zagreb, Croatia, 3 yr	5	808	Adults	TS	0.8	39.0			30.3		1	Single	long term trend, seasonality, temperature, humidity, day-of-week, influenza epidemic
59, Romero-Placeres M, 2004	Habana, Cuba, 2 yr	5	44 029	General	TS		59.2		21.1			1	Single	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday
71, Morgan G, 2010	Sydney, Australia, 8.5 yr	5	65448	Children + adults	TS		62.0					1	Single	long-term trend, seasonality, temperature, humidity, day of week, influenza epidemic
80, Fletcher T, 2000	San Paulo, Brazil, 2 yr	4/5	-	Children	TS	5.8	64.9		18.3	174.3	63.4[c]	1	Single	long-term trend, seasonality, temperature, humidity, day of week, holiday
5, Son JY, 2013	Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, Ulsan, Korea, 6 yr	4	-	General	TS	1.0[a]	52.4		15.7	48.0	71.7	1	Both	long-term trend, seasonality, temperature, humidity, pressure, day-of-week
8, Andersen ZJ, 2008	Copenhagen, Denmark, 3yr	4	-	Children	TS	0.36	24.0	10.0		22.6	51.4	0	Cumulative	long-term trends, seasonality, temperature, humidity, day-of-week, public holidays, influenza epidemics
10, Kim SY, 2012	Denver, US, 4 yr	4	10,590	General	TS			8.0				1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
12, Lee JT, 2002	Seoul, Korea, 2 yr	4	6436	General	TS	2.3	64.0		22	64.7	77.1	1	Cumulative	long-term trend, seasonality, temperature, and humidity, day-of-week
13, Delfino RJ, 1994	Montreal, Canada, 4 yr	3	10385	General	TS		29.5					0	Single	long-term trend, seasonality, temperature, humidity, day-of-week

25, Ye F, 2001	Tokyo, Japan, 15 yr	3	2200	Elderly	TS		46.0					1	Single	long-term trends, seasonality, temperature
36, Lee JT, 2006	Seoul, Korea, 1 yr	4	2952	Children	TS	8.0[a]	135.2		25.0	156.2	63.9	1	Single	Long-term trend, seasonality, temperature, humidity, day-of-week,
40, Lin M, 2004	Vancouver, BC, Canada, 12 yr	4	3754	Children	TS	1.2			13.6	38.4	60.0[c]	1	Both	long term trend, seasonality, temperature, humidity, day-of-week
45, Schouten JP, 1996	Amsterdam, The Netherlands, 12 yr	4	-	General	TS				28.0	50.0	69.0	0	Both	long-term trend, seasonality, temperature, humidity, day-of-week, public holiday, influenza epidemics
52, Silverman RA, 2010	New York, US, 7 yr	4	75383	General	TS			13. 0			87.9	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of- week
65, Amancio CT, 2012	San Paulo, Brazil, 2 yr	4	841	Children	TS		25.2		4.6		74.3	1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
70, Sheppard L, 1999	Seattle, Washington, 8 yr	3/4[b]	7837	Children + adults	TS	2.3	31.5	16.7	22.9		65.1	1/0[a]	Single	long-term trend, seasonality, temperature, humidity, day-of-week
75, Neidell M, 2010	Southern California, 8 yr	4	-	General	TS						175.7	1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week
81, Fung KY, 2005	London, Ontario, Canada, 5 yr	4	?	Children + adults	TS		38.0					1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
83, Hua J, 2014	Shanghai, China, 7 yr	4		Children	TS			34.0				1	cumulative	long-term trend, seasonality, temperature, humidity
9, Walters S, 1994	Birmingham, UK, 2 yr	2	-	General	TS				39.1			1	Cumulative	not declared
35, Magas OK, 2007	Oklahoma city metropolitan area, US, 3 yr	1	1270	Children	TS					-		0	Single	temperature, day-of-week, humidity, holiday
53, Barnett AG, 2005	Australia - Brisbane, Canberra, Melbourne, Perth, Sydney, New Zealand - Auckland, Christchurch, 3 yr	5	-	Children	CC	1.1	17.6	9.4	7.0	17.6	49.6	1	Cumulative	long-term trend, seasonality, temperature, humidity, day for the week, holiday and influenza epidemics

17, Yang CY, 2007	Taipei, 8 yr	4	25602	General	CC	1. 7	49.0		12.3	63.0	44.0	1	Cumulative	long-term trend, seasonality, temperature, humidity
18, Tsai SS, 2006	Kaohsiung, 8 yr	4	17682	General	CC	1.00	76.7		27.1	55.9	56.3	1	Cumulative	long-term trends, seasonality, temperature, humidity
37, Lin M, 2003	Toronto, Ontario, Canada. 13 yr	4	7319	Children	CC	1.5			15.3	51.8	65.1[c]	1	Both	long term trend, seasonality, temperature, humidity, day-of-week,
44, Lin M, 2002	Toronto, Canada, 14 yr	4	7319	Children	CC		30.2	18.0				1	Both	long-term trend, seasonality, temperature, humidity, day-of-week
68, Iskandar A, 2012	Copenhagen, Denmark, 8 yr	4	8226	Children	CC		26.2	10.3		23.3		1	Cumulative	long-term trend, seasonality, temperature, humidity, day-of-week
85, Cheng MH, 2014	Taipei, China, 5 yr	3	10,440	General	CC			30.0				1	Cumulative	long-term trend, seasonality, temperature, humidity
86, Cai J, 2014	Shanghai, China, 7y r	4	15,678	General	TS		88.0		45.0	60.0		1	Both	long-term trend, seasonality, temperature, humidity, day-of-week

Study	Location/Period	Quality score	Sample size	Population	Type of study	Pollutants and concentration						Measurement quality score (0-1 point)	Lag pattern (single day/ mean days)	Adjustments (long-term trend, seasonality, temperature, humidity, pressure, day for the week, holiday and influenza epidemics)
						CO	PM_{10}	$PM_{2.5}$	SO_2	NO_2	O_3			
Studies with both emergency room visit and hospital admission indices														
33, Chew FT, 1999	Singapore, 5 yr	4	6000(HA), 23000(ER)	Children	TS				38.1	18.9		1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
62, Sluaghter JC, 2005	Spokane, Washington DC, US, 7 yr	4	2191/2373	General	TS	1.6 - 3.8	7.9 - 41.9	4.2 - 20.2				1	Single	long-term trend, seasonality, temperature, humidity, day-of-week
26, Smargiassi A, 2009	0.5–7.5 km of the refinery stacks, Montreal Canada, 8 yr	4	1579/263	Children	CC				12.3			1	Both	long-term trends, seasonality, temperature, humidity, day-of-week
63, Li S, 2001	Detroit, Michigan, 2 yr	4	7063	Children	CC	0.5		15.0	10.8	34.4[c]		1	Both	long-term trend, seasonality, temperature, humidity, day-of-week

Supplemental Information, SI 3

Summary Statistics of Other Air Quality Components and Calculated p-values

(Note: Publ year=publication year; RR=relative risk; LCL=lower confidence limit; UCL=upper confidence limit; p-value calculated after Altman and Bland (2011)[1]; bold, italicized p-value <.05)

CO2

Study 1st author	Publ year	RR	LCL	UCL		***p-value***
Thompson AJ	2001	1.025	1.000	1.055		0.0702351
Fusco D	2001	1.005	0.975	1.038		0.7676324
Szyszkowicz M	2008	1.076	1.032	1.120		***0.000482***
Norris G	1999	1.133	1.027	1.253		***0.013787***
Hajat S	1999	1.020	0.985	1.058		0.2811338
Lee JT	2006	1.186	0.894	1.532		0.2162465
Lin M	2003	1.080	1.000	1.176		0.0623584
Lin M	2003	1.000	0.888	1.096		1
Krmpotic D	2011	1.218	1.026	1.436		***0.021316***
Lin M (ML)	2004	1.096	0.984	1.226		0.1020115
Lin M (MH)	2004	1.096	0.968	1.226		0.128406
Lin M (FL)	2004	1.160	0.872	1.176		0.0513557
Lin M (FH)	2004	1.080	0.904	1.256		0.3649995
Abe T (A)	2007	1.163	0.960	1.409		0.122931
Abe T (C)	2007	1.019	0.953	1.089		0.5922572
Pereira G (M)	2010	2.215	1.243	3.465		***0.002413***
Pereira G (F)	2010	1.382	0.451	2.424		0.4596406
Jalaludin BB	2008	1.017	1.010	1.025		***0.0001***
Lavigne E	2012	1.000	0.720	1.280		1
Stieb DM	2009	0.997	0.974	1.021		0.8145069
Sluaghter JC (E)	2005	1.000	0.960	1.048		1
Sluaghter JC (H)	2005	1.016	0.936	1.104		0.7193821
Li S	2011	1.005	0.959	1.052		0.8436515
Mar TF	2010	1.000	0.966	1.034		1
Sheppard L	1999	1.052	1.026	1.078		***0.0001***
Santus P	2012	1.030	0.938	1.132		0.5488283
Fletcher T	2000	1.009	0.977	1.022		0.4438295
Strickland MJ (W)	2010	1.120	1.072	1.169		***0.0001***
Strickland MJ (C)	2010	1.004	0.975	1.033		0.7987727
Son JY	2013	1.003	0.957	1.048		0.905164
Halonen JI	2008	0.927	0.820	1.035		0.2034389
Halonen JI	2008	1.090	0.947	1.240		0.2118576
Evans KA	2013	1.420	0.037	3.395		0.7736967

CO2 (continued)

Study 1st author	Publ year	RR	LCL	UCL		*p-value*
Ito K	2007	1.078	1.066	1.090		***0.0001***
Yang CY	2007	1.417	1.270	1.578		***0.0001***
Yang CY	2007	1.115	1.029	1.205		***0.006901***
Tsai SS	2006	1.612	1.380	1.860		***0.0001***
Tsai SS	2006	2.140	1.826	2.479		***0.0001***
Barnett AG	2005	1.020	0.990	1.050		0.188257
Andersen ZJ	2008	1.000	0.993	1.008		1
Lee JT	2002	1.128	1.080	1.176		***0.0001***
Raun LH	2014	1.155	1.000	1.258		***0.013784***

NO2

Study 1st author	Publ year	RR	LCL	UCL		*p-value*
Thompson AJ	2001	1.039	1.015	1.063		***0.001219***
Samoli E	2010	1.011	0.990	1.029		0.2702846
Fusco D	2001	1.021	0.998	1.043		0.0643187
Morgan G (C)	1998	1.009	0.995	1.024		0.2235095
Morgan G (A)	1998	1.007	0.991	1.022		0.3812297
Laurent O	2008	1.025	0.990	1.062		0.1687421
Anderson HR	1998	1.006	1.002	1.010		***0.003242***
Szyszkowicz M	2008	1.020	1.008	1.032		***0.001015***
Lee SL	2006	1.016	1.009	1.023		***0.0001***
Norris G	1999	1.020	0.996	1.049		0.134508
Hajat S	1999	1.004	0.999	1.010		0.1534962
Tenias JM	1998	1.076	1.020	1.134		***0.006746***
Chew FT	1999	1.006	0.945	1.011		0.7413803
Magas OK	2007	1.133	1.047	1.227		***0.002086***
Lee JT	2006	1.018	1.006	1.033		***0.008283***
Lin M (M)	2003	1.018	0.996	1.044		0.1375644
Lin M (F)	2003	0.996	0.965	1.027		0.8126995
Ko FWS	2007	1.009	1.005	1.014		***0.0001***
Krmpotic D	2011	1.058	1.006	1.110		***0.02447***
Lin M (ML)	2004	1.097	1.030	1.172		***0.004995***
Lin M (MH)	2004	1.030	0.963	1.105		0.4068878
Lin M (FL)	2004	1.052	0.970	1.142		0.2255329
Lin M (FH)	2004	1.007	0.925	1.097		0.8819162
Galan I	2003	1.013	0.991	1.035		0.2464135
Schouten JP	1996	1.006	0.989	1.027		0.5450544
Boutin-Forzano S	2004	1.007	0.996	1.018		0.2124552
Pereira G (M)	2010	1.779	1.049	2.558		***0.011266***
Pereira G (F)	2010	1.195	0.562	1.925		0.582443
Jalaludin BB	2008	1.012	1.007	1.016		***0.0001***
Jaffe DH	2003	1.015	0.995	1.034		0.1291189
Lavigne E	2012	0.989	0.923	1.054		0.7568099
Stieb DM	2009	0.999	0.988	1.010		0.8685931
Li S	2011	1.019	1.003	1.036		***0.022479***
Cirera L	2012	1.026	1.004	1.049		***0.021576***
Yamazaki S (W)	2013	1.054	0.784	1.591		0.7833535
Yamazaki S (C)	2013	0.939	0.809	1.126		0.4645442
Santus P	2012	0.968	0.954	0.981		***0.0001***
Fletcher T	2000	1.003	0.998	1.009		0.287819
Son JY	2013	1.009	1.001	1.016		***0.018085***
Halonen JI (A)	2008	1.015	0.983	1.048		0.3681822
Halonen JI (O)	2008	1.026	0.983	1.073		0.2535308

NO2 (continued)

Study 1st author	**Publ year**	**RR**	**LCL**	**UCL**		***p-value***
Sunyer J (A)	1997	1.006	1.001	1.011		***0.018198***
Sunyer J (C)	1997	1.005	1.001	1.010		***0.028699***
Mehta AJ	2012	1.019	0.849	1.223		0.8504996
Ito K	2007	1.024	1.015	1.032		***0.0001***
Cassino C	1999	0.990	0.951	1.029		0.6298615
Chardon B	2007	0.997	0.967	1.027		0.8553863
Yang CY (W)	2007	1.086	1.055	1.120		***0.0001***
Yang CY (C)	2007	1.062	1.037	1.088		***0.0001***
Tsai SS (W)	2006	1.074	1.032	1.122		***0.000859***
Tsai SS (C)	2006	1.321	1.251	1.399		***0.0001***
Wong TW	1999	1.026	1.010	1.042		***0.001305***
Petroeschevsky A	2001	0.998	0.997	0.999		***0.000102***
Jazbec A (C)	1999	1.137	1.005	1.287		***0.041512***
Jazbec A (A)	1999	1.098	1.002	1.203		***0.044647***
Castellsague J (W)	1995	1.018	1.004	1.032		***0.010979***
Castellsague J (C)	1995	1.022	1.004	1.042		***0.021497***
Barnett AG	2005	1.023	0.992	1.054		0.1417651
Barnett AG	2005	1.055	1.016	1.096		***0.005655***
Medina S	1997	1.041	1.026	1.053		***0.0001***
Iskandar A	2012	1.075	1.030	1.119		***0.000662***
Strickland MJ	2010	1.014	1.007	1.021		***0.0001***
Andersen ZJ	2008	1.032	0.935	1.146		0.5553011
Lee JT	2002	1.050	1.033	1.067		***0.0001***
Cai J	2014	1.011	1.005	1.016		***0.0001***
Raun LH	2014	1.073	1.042	1.104		***0.0001***

O3

Study 1st author	Publ year	RR	LCL	UCL		*p-value*
Thompson AJ	2001	0.977	0.953	1.005		0.0856757
Samoli E	2010	0.969	0.934	1.005		0.091725
Fusco D	2001	1.016	0.987	1.046		0.2875781
Anderson HR	1998	1.003	1.000	1.005		***0.018427***
Szyszkowicz M	2008	1.028	1.013	1.043		***0.000229***
Lee SL	2006	1.010	1.002	1.019		***0.020273***
Hajat S	1999	0.997	0.990	1.004		0.4090144
Tenias JM	1998	1.063	1.014	1.114		***0.010857***
Stieb DM	1996	1.036	1.017	1.055		***0.000175***
Lee JT	2006	1.025	1.005	1.027		***0.0001***
Galan I	2003	1.039	1.010	1.068		***0.007249***
Mohr LB (W)	2008	0.981	0.953	1.014		0.2276172
Mohr LB (C)	2008	1.023	0.986	1.065		0.2501553
Boutin-Forzano S	2004	1.006	1.000	1.016		0.1398602
Medina S	1997	1.012	0.995	1.033		0.2139423
Jaffe DH	2003	1.014	1.000	1.028		***0.048062***
Lavigne E	2012	1.042	1.004	1.081		***0.028827***
Stieb DM	2009	1.000	0.990	1.011		1
Wilson AM (P)	2004	1.020	1.000	1.030		***0.008634***
Wilson AM (M)	2004	0.990	0.980	1.010		0.1926288
Amancio CT	2012	1.000	1.000	1.001		1
Cirera L	2012	0.971	0.938	1.006		0.099055
Sheppard L	1999	1.014	1.005	1.026		***0.008407***
Yamazaki S (W)	2013	1.054	0.970	1.154		0.2376168
Yamazaki S (C)	2013	0.956	0.860	1.080		0.4472306
Babin S	2008	1.004	1.001	1.008		***0.024531***
Mar TF	2009	1.047	1.005	1.089		***0.024703***
Hernandez-Cadena L	2000	1.004	0.997	1.012		0.2987379
Fletcher T	2000	1.000	0.991	1.011		1
Morgan G (C)	1998	0.997	0.992	1.002		0.242804
Morgan G (A)	1998	1.003	0.997	1.010		0.3709557
Sunyer J (A)	1997	1.003	0.987	1.040		0.8336614
Sunyer J (C)	1997	0.998	0.988	1.008		0.7085282
Yamazaki S	2009	1.009	1.005	1.110		0.7368412
Chakraborty P	2013	0.998	0.996	0.999		***0.009064***
Evans KA	2013	0.957	0.887	1.154		0.5232048
Ito K	2007	1.011	0.999	1.014		***0.004056***
Yang CY (W)	2007	1.012	0.986	1.039		0.3782693
Yang CY (C)	2007	1.073	1.046	1.104		***0.0001***
Tsai SS (W)	2006	1.067	1.046	1.089		***0.0001***
Tsai SS (C)	2006	1.047	1.017	1.081		***0.003229***

O3 (continued)

Study 1st author	**Publ year**	**RR**	**LCL**	**UCL**		***p-value***
Wong TW	1999	1.031	1.017	1.460		0.753609
Laurent O	2008	0.998	0.965	1.032		0.914377
Petroeschevsky A	2001	1.004	1.002	1.007		***0.00172***
Lin M(M)	2003	0.975	0.925	1.025		0.3389074
Lin M(F)	2003	0.913	0.863	1.025		***0.037762***
Lin M(ML)	2004	0.964	0.943	0.986		***0.001316***
Lin M(MH)	2004	0.983	0.960	1.095		0.6219986
Lin M(FL)	2004	1.026	0.993	1.066		0.1566245
Lin M(FH)	2004	0.979	0.948	1.012		0.2043825
Ko FWS	2007	1.010	1.006	1.014		***0.0001***
Schouten JP	1996	1.009	0.993	1.027		0.3009679
Castellsague J (W)	1995	0.996	0.976	1.018		0.7223679
Castellsague J (C)	1995	1.022	0.999	1.046		0.0631237
Silverman RA	2010	1.019	1.013	1.025		***0.0001***
Barnett AG	2005	0.990	0.953	1.031		0.6291404
Barnett AG	2005	0.980	0.940	1.025		0.3663807
Jalaludin BB	2008	1.003	1.001	1.005		***0.003287***
Cassino C	1999	1.087	1.033	1.146		***0.001684***
Neidell M	2010	1.013	1.010	1.016		***0.0001***
Santus P	2012	1.010	0.991	1.052		0.5243647
Yamazaki S	2009	1.073	1.000	1.151		***0.049155***
Strickland MJ	2010	1.010	1.005	1.015		***0.000093***
Son JY	2013	1.004	0.999	1.009		0.1160943
Paulu C	2008	1.009	1.000	1.023		0.1224737
Andersen ZJ	2008	1.043	0.914	1.226		0.5860823
Evans KA	2013	0.911	0.793	1.121		0.2951183
Lee JT	2002	1.026	1.015	1.034		***0.0001***
Gleason JA	2014	1.032	1.026	1.037		***0.0001***
Raun LH	2014	1.009	1.002	1.016		***0.011329***
Sacks JD	2014	1.004	1.000	1.009		0.0803567

PM10

Study 1st author	Publ year	RR	LCL	UCL		*p-value*
Thompson AJ	2001	1.009	1.000	1.019		0.0616359
Samoli E	2010	1.025	1.001	1.051		***0.046683***
Szyszkowicz M	2008	1.018	1.001	1.036		0.0415255
Lee SL	2006	1.017	1.011	1.023		***0.0001***
Norris G	1999	1.121	1.043	1.198		***0.001279***
Lee JT	2006	1.016	1.008	1.023		***0.0001***
Ko FWS	2007	1.005	1.002	1.009		***0.005019***
Krmpotic D	2011	0.989	0.942	1.044		0.6863417
Galan I	2003	1.006	0.976	1.037		0.7120714
Atkinson RW (C)	2001	1.012	1.002	1.023		***0.023976***
Atkinson RW (A)	2001	1.011	1.003	1.018		***0.003914***
Jalaludin BB	2008	1.014	1.008	1.022		***0.0001***
Jaffe DH	2003	1.010	0.986	1.038		0.4566827
Stieb DM	2009	1.004	0.950	1.015		0.8246528
Romero-Placeres M	2004	0.998	0.943	1.003		0.9066903
Chimonas MAR	2007	1.006	1.001	1.013		***0.048715***
Sluaghter JC (ER)	2005	1.012	0.992	1.028		0.1908417
Sluaghter JC (H)	2005	1.012	0.980	1.048		0.4956615
Amancio CT	2012	1.006	0.999	1.013		0.0916967
Sheppard L	1999	1.025	1.010	1.040		***0.000987***
Morgan G (C)	2010	1.006	0.976	1.038		0.7165524
Morgan G (A)	2010	1.025	0.993	1.058		0.126933
Yamazaki S (W)	2013	0.968	0.818	1.146		0.7185001
Yamazaki S (C)	2013	1.022	0.902	1.158		0.7457867
Santus P	2012	1.005	0.987	1.024		0.6075507
Babin S	2008	0.990	0.960	1.010		0.4462646
Hernandez-Cadena L	2000	1.013	0.993	1.033		0.2012836
Fletcher T	2000	1.005	0.992	1.020		0.4922045
Son JY	2013	1.005	1.001	1.008		***0.005062***
Delfino RJ	1994	1.021	1.006	1.040		***0.014173***
Ye F	2001	1.003	1.001	1.004		***0.0001***
Morgan G (C)	1998	0.997	0.984	1.011		0.6765743
Morgan G (A)	1998	1.005	0.992	1.018		0.4586868
Malig BJ	2013	1.022	1.003	1.031		***0.002***
Chakraborty P	2013	1.000	1.000	1.003		1
Fung KY	2005	1.096	1.011	1.201		***0.036618***
Chardon B	2007	1.025	0.983	1.068		0.2457323
Yang CY (W)	2007	1.017	0.989	1.048		0.2570002
Yang CY (C)	2007	1.018	1.004	1.033		***0.013982***
Tsai SS	2006	1.048	1.025	1.075		***0.000128***
Wong TW	1999	1.015	1.002	1.028		***0.022532***

PM10 (continued)

Study 1st author	Publ year	RR	LCL	UCL		*p-value*
Laurent O	2008	1.035	0.997	1.075		0.073024
Lin M	2002	1.033	0.966	1.115		0.3815059
Barnett AG (0-4y)	2005	1.023	1.007	1.039		***0.004424***
Barnett AG (4-14y)	2005	1.025	1.001	1.051		***0.046683***
Iskandar A	2012	1.052	1.022	1.090		***0.00209***
Andersen ZJ	2008	1.015	0.946	1.092		0.6974281
Strickland MJ	2010	1.014	1.002	1.026		***0.021146***
Lee JT	2002	1.012	1.009	1.027		***0.008187***
Cadelis G	2014	1.010	0.941	1.046		0.7254741
Cai J	2014	1.001	0.998	1.005		0.5870548

SO2

Study 1st author	Publ year	RR	LCL	UCL		*p-value*
Thompson AJ	2001	1.007	1.003	1.011		***0.000614***
Wong TW	1999	1.017	0.998	1.036		0.0766384
Fusco D	2001	0.978	0.904	1.057		0.5890392
Anderson HR	1998	1.016	1.005	1.028		0.0059914
Hajat S	1999	1.018	1.001	1.034		0.0308161
Petroeschevsky A	2001	0.998	0.996	1.000		***0.049846***
Ko FWS	2007	1.004	0.998	1.011		0.2287405
Galan I	2003	1.018	0.984	1.054		0.3133554
Schouten JP	1996	0.980	0.970	0.992		***0.000444***
Medina S	1997	1.026	1.010	1.041		***0.000917***
Lavigne E	2012	1.044	0.933	1.133		0.3916664
Stieb DM	2009	0.992	0.980	1.005		0.2130706
Romero-Placeres M	2004	0.994	0.983	1.004		0.2675815
Wilson AM (P)	2004	1.040	1.000	1.070		***0.022883***
Wilson AM (M)	2004	1.020	0.990	1.060		0.2587899
Cirera L	2012	1.060	1.014	1.110		***0.011528***
Romieu I	1995	1.003	0.999	1.008		0.1916958
Santus P	2012	0.950	0.808	1.104		0.5301991
Son JY	2013	1.002	0.983	1.023		0.8548452
Sunyer J	1997	0.999	0.992	1.007		0.8059108
Samoli E	2010	1.060	1.009	1.113		***0.019747***
Lee SL	2006	0.989	0.974	0.998		0.0744936
Norris G	1999	1.006	0.985	1.026		0.5770494
Tenias JM	1998	1.050	0.973	1.133		0.2107013
Stieb DM	1996	0.997	0.992	1.006		0.4080414
Chew FT	1999	1.015	1.007	1.023		***0.000235***
Lee JT	2006	1.077	1.000	1.161		0.0510455
Lin M (M)	2003	1.000	0.975	1.025		1
Lin M (F)	2003	1.020	0.985	1.055		0.2611838
Lin M (ML)	2004	1.021	0.934	1.106		0.6426132
Lin M (MH)	2004	1.032	0.947	1.127		0.4876276
Lin M (FL)	2004	1.053	0.947	1.170		0.3438004
Lin M (FH)	2004	1.074	0.958	1.201		0.2175988
Mohr LB (W)	2008	0.996	0.975	1.018		0.7289469
Mohr LB (C)	2008	1.011	0.985	1.035		0.3933581
Abe T (A)	2007	1.008	0.930	1.092		0.8562393
Abe T (C)	2007	0.996	0.977	1.024		0.751056
Boutin-Forzano S	2004	1.002	0.995	1.010		0.6130637
Jalaludin BB	2008	1.070	1.031	1.105		***0.000146***
Jaffe DH	2003	1.024	1.002	1.046		***0.03026***
Li S	2011	1.027	1.007	1.048		***0.008869***

SO2 (continued)

Study 1st author	**Publ year**	**RR**	**LCL**	**UCL**		***p-value***
Amancio CT	2012	1.027	1.002	1.053		***0.03511***
Sheppard L	1999	1.014	0.986	1.028		0.1926567
Fletcher T	2000	1.039	0.993	1.091		0.1109411
Sunyer J (C)	2003	1.013	1.004	1.022		***0.004425***
Sunyer J (A)	2003	1.000	0.991	1.010		1
Smargiassi A (H)	2009	1.169	1.000	1.360		***0.046151***
Smargiassi A (E)	2009	1.048	0.976	1.121		0.185688
Evans KA	2013	1.090	0.887	1.350		0.4292189
Ito K	2007	1.033	1.030	1.043		***0.0001***
Cassino C	1999	0.977	0.938	1.019		0.2741459
Yang CY (W)	2007	1.091	1.001	1.187		***0.044792***
Yang CY (C)	2007	0.978	0.920	1.038		0.4793457
Tsai SS (W)	2006	1.011	0.973	1.050		0.5853068
Tsai SS (C)	2006	1.113	1.044	1.190		***0.001395***
Laurent O	2008	1.056	0.979	1.139		0.1588227
Castellsague J (W)	1995	1.021	0.992	1.052		0.1660837
Castellsague J (C)	1995	1.008	0.984	1.034		0.5395251
Barnett AG	2005	1.017	1.004	1.031		***0.012717***
Barnett AG	2005	1.013	0.964	1.084		0.6791539
Strickland MJ	2010	1.004	0.998	1.009		0.1539128
Walters S (W)	1994	1.012	0.987	1.448		0.9105847
Walters S (C)	1994	1.037	1.000	1.076		0.051474
Cai J	2014	1.013	1.005	1.021		***0.001398***
Raun LH	2014	1.150	0.850	1.400		0.275625

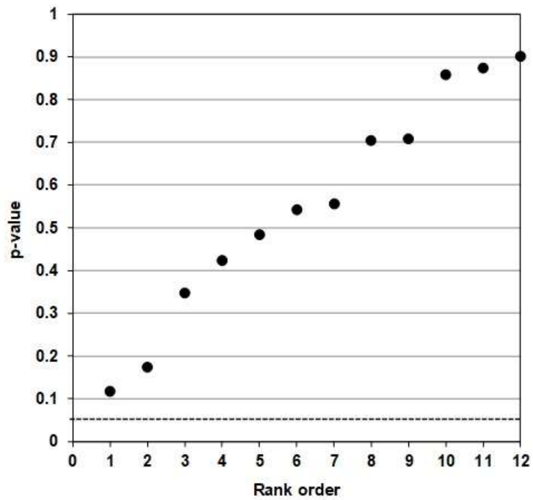
Source:

1 Altman DG, Bland JM. 2011. How to obtain the p-value from a confidence interval. BMJ. 343:d2304. https://doi.org/10.1136/bmj.d2304.

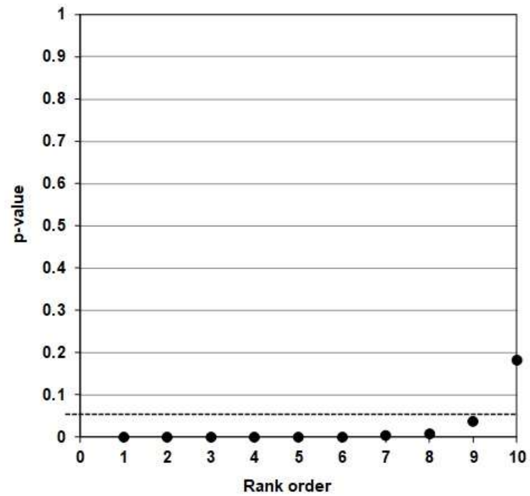
Supplemental Information, SI 4

P-value Plots and Summary Statistics of Datasets from Meta-analysis of Selected Cancers in Petroleum Refinery Workers after Schnatter et al. (2018)

p-Value plots for meta-analysis of observational datasets representing: (i) petroleum refinery worker−chronic myeloid leukemia risk and (ii) petroleum refinery worker−mesothelioma risk after Schnatter et al. (2018):[1]



(i) petroleum refinery worker−chronic myeloid leukemia risk (n=12)



(ii) petroleum refinery worker− mesothelioma risk (n=10)

(Note below: Base study=base study 1st author name in Schnatter et al. (2018)[1]; RR=relative risk; LCL=lower confidence limit; UCL=upper confidence limit; p-value calculated after Altman and Bland (2011)[2]; bold, italicized p-value <.05)

Summary statistics for chronic myeloid leukemia risk for petroleum refinery workers:

Base study	**RR**	**LCL**	**UCL**	**p-value**
Collingwood 1996	0.53	0.07	3.74	0.54263
Divine 1999a	1.05	0.60	1.85	0.87478
Gun 2006b	1.09	0.45	2.61	0.85800
Huebner 2004	1.68	0.88	3.23	0.11778
Lewis 2000a	1.08	0.35	3.35	0.90196
Rushton 1993a	0.89	0.50	1.61	0.70923
Satin 1996	0.85	0.38	1.88	0.70346
Satin 2002	0.45	0.14	1.39	0.17355
Tsai 2007	0.66	0.21	2.05	0.48425
Wong 2001a	1.31	0.55	3.15	0.55549
Wong 2001b	1.96	0.49	7.84	0.34689
Wongsrichanalia 1989	0.44	0.06	3.12	0.42318

Summary statistics for mesothelioma risk for petroleum refinery workers (based on mesothelioma subgroup analysis using Schnatter et al. (2018)[1] 'Best Methods' dataset):

Base study	**RR**	**LCL**	**UCL**	**p-value**
Devine 1999a	2.97	2.21	3.99	***0.0001***
Gamble 2000	2.43	1.35	4.39	***0.00321***
Gun 2006a	3.77	2.14	6.64	***0.0001***
Honda 1995	2.00	1.04	3.84	***0.03720***
Hornstra 1993	5.51	3.38	8.99	***0.0001***
Huebner 2009	2.44	1.83	3.24	***0.0001***
Kaplan 1986	2.41	1.26	4.64	***0.00817***
Lewis 2000a	8.68	5.77	13.06	***0.0001***
Tsai 2003	2.16	0.70	6.69	0.18215
Tsai 2007	2.50	1.63	3.83	***0.0001***

Sources:

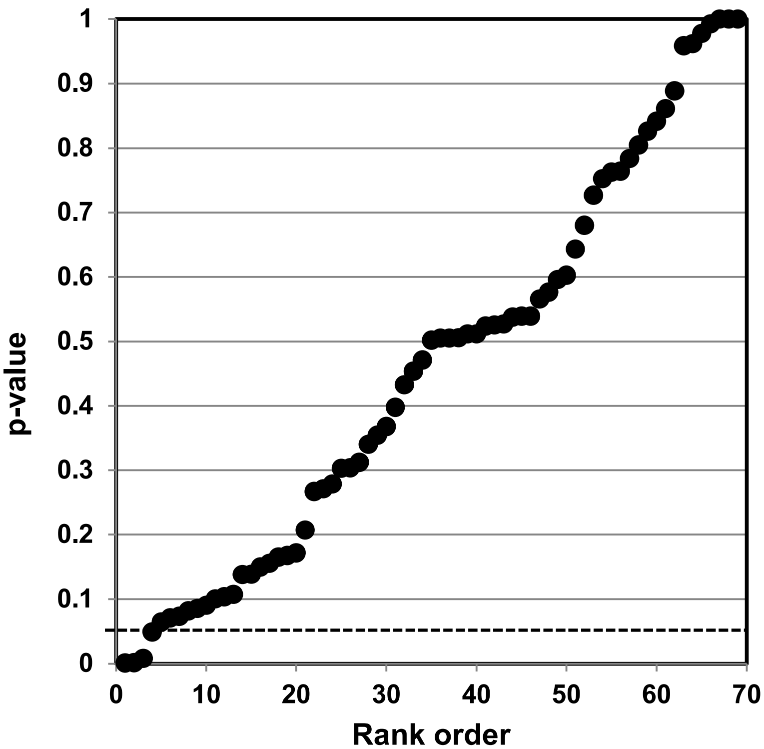
1 Schnatter AR, Chen M, DeVilbiss EA, Lewis RJ, Gallagher EM. 2018. Systematic review and meta-analysis of selected cancers in petroleum refinery workers. J Occup Environ Med. 60(7):e329−e342. https://doi.org/10.1097/JOM.0000000000001336.

2 Altman DG, Bland JM. 2011. How to obtain the p-value from a confidence interval. BMJ. 343:d2304. https://doi.org/10.1136/bmj.d2304.

Supplemental Information, SI 5

P-value Plot and Summary Statistics of Datasets from Meta-analysis of Elderly Long-term Exercise Training−Mortality & Morbidity Risk after de Souto Barreto et al. (2019)

p-Value plot for meta-analysis of observational datasets representing elderly long-term exercise training−mortality & morbidity risk after de Souto Barreto et al. (2019)[1];



(Note below: Base study=base study 1st author name in de Souto Barreto et al. (2019)[1]; RR=relative risk; LCL=lower confidence limit; UCL=upper confidence limit; p-value calculated after Altman and Bland (2011)[2]; bold, italicized p-value <.05)

Summary statistics for observational datasets representing elderly long-term exercise training−mortality & morbidity risk:

Outcome	**No.**	**Base Study ID (n=69)**	**RR**	**LCL**	**UCL**	***p-value***
Mortality	1	Belardinelli et al. 2012	0.38	0.13	1.15	0.08153
	2	Barnett et al. 2003	0.14	0.01	2.63	0.16736
	3	O'Connor et al. 2009	0.96	0.80	1.16	0.67980
	4	Campbell et al. 1997	0.50	0.09	2.70	0.43245
	5	El−Khoury et al. 2015	0.84	0.26	2.72	0.78350
	6	Galvão et al. 2014	3.00	0.13	71.92	0.50544
	7	Gianoudis et al. 2014	1.00	0.06	15.72	1.00000
	8	Hewitt et al. 2018	1.02	0.52	2.03	0.95866
	9	Karinkanta et al. 2007	0.33	0.01	7.93	0.52568
	10	Kemmler et al. 2010	0.33	0.01	8.10	0.52704
	11	King et al. 2002	0.32	0.01	7.68	0.51168
	12	Kovács et al. 2013	0.40	0.14	1.17	0.09039
	13	Lam et al. 2012	0.64	0.06	7.05	0.72673
	14	Lam et al. 2015	0.30	0.03	2.82	0.30309
	15	Lord et al. 2003	4.84	0.55	42.33	0.15519
	16	Merom et al. 2015	1.36	0.22	8.23	0.75225
	17	Pahor et al. 2006	0.99	0.14	6.97	0.99276
	18	Pahor et al. 2014/Gill et al. 2016	1.14	0.76	1.71	0.53739
	19	Patil et al. 2015	0.11	0.01	2.04	0.10355
	20	Pitkälä et al. 2013	0.25	0.06	1.14	0.06455
	21	Prescott et al. 2008	0.42	0.08	2.12	0.30363
	22	Rejeski et al. 2017	0.34	0.01	8.16	0.53914
	23	Rolland et al. 2007	0.88	0.34	2.28	0.80441
	24	Sherrington et al. 2014	1.10	0.46	2.63	0.84135
	25	Underwood et al. 2013	1.06	0.84	1.35	0.64301
	26	Van Uffelen et al. 2008	0.36	0.01	8.72	0.56573
	27	von Stengel et al. 2011	0.34	0.01	8.15	0.53907
	28	Voukelatos et al. 2015	9.09	0.49	167.75	0.13843
	29	Wolf et al. 2003	0.97	0.14	6.86	0.97786

(continued)

Outcome	No.	Base Study ID (n=69)	RR	LCL	UCL	*p-value*
Hospitalization	30	Belardinelli et al. 2012	0.30	0.15	0.62	***0.00092***
	31	O'Connor et al. 2009	0.97	0.91	1.03	0.34039
	32	Hambrecht et al. 2004	0.16	0.02	1.31	0.08551
	33	Hewitt et al. 2018	0.64	0.27	1.50	0.31209
	34	Kovács et al. 2013	2.00	0.19	21.21	0.57619
	35	Messier et al. 2013	8.54	0.46	157.06	0.14992
	36	Mustata et al. 2011	0.33	0.02	7.32	0.47075
	37	Pahor et al. 2006	0.99	0.68	1.44	0.96195
	38	Pahor et al. 2014/Gill et al. 2016	1.10	0.99	1.22	0.07332
	39	Pitkala et al. 2013	0.78	0.55	1.12	0.17166
	40	Rejeski et al. 2017	3.04	0.13	73.46	0.50161
	41	Rolland et al. 2007	1.82	0.95	3.49	0.07083
Injurious falls	42	Barnett et al. 2003	0.77	0.48	1.21	0.27108
	43	Campbell et al. 1997	0.67	0.45	1.00	***0.04892***
	44	El−Khoury et al. 2015	0.90	0.78	1.05	0.16541
	45	Hewitt et al. 2018	0.58	0.42	0.81	***0.00120***
	46	MacRae et al. 1994	0.16	0.01	2.92	0.20731
	47	Pahor et al. 2014/Gill et al. 2016	0.89	0.66	1.20	0.45350
	48	Patil et al. 2015	0.51	0.31	0.84	***0.00810***
	49	Pitkälä et al. 2013	0.65	0.39	1.09	0.10016
	50	Reinsch et al. 1992	1.46	0.37	5.81	0.60232
Fractures	51	Belardinelli et al. 2012	0.19	0.01	3.89	0.27847
	52	O'Connor et al. 2009	0.60	0.32	1.11	0.10725
	53	El−Khoury et al. 2015	0.88	0.60	1.25	0.50488
	54	Gianoudis et al. 2014	3.00	0.12	72.57	0.51161
	55	Hewitt et al. 2018	0.80	0.20	3.11	0.76275
	56	Karinkanta et al. 2007	1.00	0.15	6.73	1.00000
	57	Kemmler et al. 2010	0.49	0.19	1.25	0.13795
	58	Kovács et al. 2013	3.00	0.13	71.56	0.50509
	59	Lam et al. 2012	1.27	0.06	28.95	0.88844
	60	Pahor et al. 2014/Gil et al. 2016	0.87	0.63	1.19	0.39774
	61	Patil et al. 2015	0.66	0.28	1.59	0.35403
	62	Pitkälä et al. 2013	1.00	0.26	3.84	1.00000
	63	Reinsch et al. 1992	0.45	0.04	4.78	0.52344
	64	Rolland et al. 2007	2.50	0.50	12.44	0.26692
	65	Sherrington et al. 2014	0.92	0.46	1.85	0.82585
	66	Underwood et al. 2013	1.05	0.63	1.74	0.86094
	67	Villareal et al. 2011	0.52	0.05	5.39	0.59601
	68	von Stengel et al. 2011	0.58	0.18	1.87	0.36778
	69	Wolf et al. 2003	0.78	0.17	3.67	0.76405

Sources:

1 de Souto Barreto P, Rolland Y, Vellas B, Maltais M. 2019. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults: a systematic review and meta-analysis. JAMA Intern Med. 179(3):394–405. https://doi.org/10.1001/jamainternmed.2018.5406.

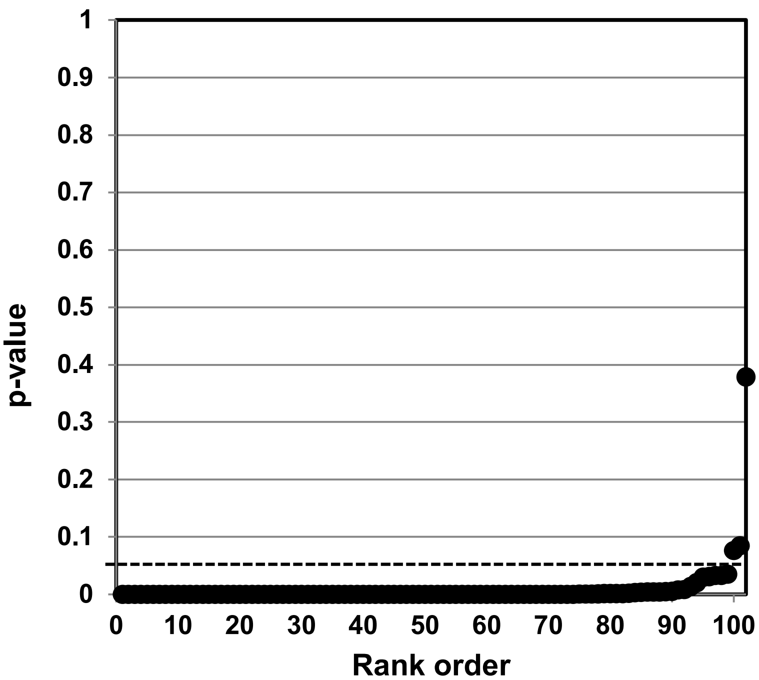
2 Altman DG, Bland JM. 2011. How to obtain the p-value from a confidence interval. BMJ. 343:d2304. https://doi.org/10.1136/bmj.d2304.

Supplemental Information, SI 6

P-value Plot and Summary Statistics of Datasets from Meta-analysis

of Smoking−Squamous Cell Carcinoma Risk after Lee et al. (2012)

p-Value plot for meta-analysis of observational datasets representing (ii) smoking−lung squamous cell carcinoma risk after Lee et al. (2012):[1]



(Note below: Base study=base study 1st author name in Lee et al. (2012)[1]; RR=relative risk; LCL=lower confidence limit; UCL=upper confidence limit; p-value calculated after Altman and Bland (2011)[2]; bold, italicized p-value <.05)

Summary statistics for observational datasets representing smoking−lung squamous cell carcinoma risk:

Place	No.	Base Study ID (n=102)	RR	LCL	UCL	*p-value*
USA	1	1948 WYNDE4 m	12.79	6.19	26.14	***0.0001***
	2	1948 WYNDE4 f	2.82	2.55	13.31	***0.01380***
	3	1949 BRESLO c	3.69	2.06	6.62	***0.0001***
	4	1952 HAMMON m	16.88	6.29	45.29	***0.0001***
	5	1955 HAENSZ f	3.00	1.90	4.73	***0.0001***
	6	1957 BYERS1 m	8.29	5.29	13.00	***0.0001***
	7	1960 LOMBA2 f	4.24	2.40	7.50	***0.0001***
	8	1962 WYNDE2 m	19.72	6.21	62.59	***0.0001***
	9	1964 OSANN2 f	35.10	4.80	256.00	***0.00048***
	10	1966 WYNDE3 m	18.29	5.71	58.56	***0.0001***
	11	1966 WYNDE3 f	6.79	2.45	18.82	***0.00025***
	12	1968 HINDS f	16.13	7.66	33.97	***0.0001***
	13	1969 STAYNE m	3.47	2.17	5.56	***0.0001***
	14	1969 WYNDE6 m	18.59	12.74	27.13	***0.0001***
	15	1969 WYNDE6 f	32.37	17.66	59.35	***0.0001***
	16	1975 COMSTO m	8.07	1.91	34.02	***0.00452***
	17	1975 COMSTO f	46.20	2.74	778.83	***0.00784***
	18	1976 BUFFLE m	14.03	4.73	41.61	***0.0001***
	19	1976 BUFFLE f	13.04	3.99	42.66	***0.0001***
	20	1979 CORREA c	28.30	18.60	43.20	***0.0001***
	21	1979 SIEMIA m	22.70	6.90	75.20	***0.0001***
	22	1980 DORGAN m	18.90	7.00	51.30	***0.0001***
	23	1980 DORGAN f	11.10	7.20	17.10	***0.0001***
	24	1981 JAIN m	18.00	5.50	111.00	***0.00018***
	25	1981 JAIN f	25.50	7.93	156.00	***0.0001***
	26	1981 WU f	24.29	3.40	173.76	***0.00153***
	27	1983 BAND m	37.45	17.60	79.58	***0.0001***
	28	1984 BROWN2 m	11.10	9.50	12.90	***0.0001***
	29	1984 BROWN2 f	20.10	16.40	24.80	***0.0001***

(continued)

Place	No.	Base Study ID (n=102)	RR	LCL	UCL	*p-value*
USA	30	1984 OSANN m	36.10	17.80	73.30	***0.0001***
	31	1984 OSANN f	26.40	14.50	48.10	***0.0001***
	32	1984 SCHWAR m1	32.81	4.48	240.23	***0.0001***
	33	1984 SCHWAR m2	1.81	0.50	6.78	0.37881
	34	1984 SCHWAR f1	43.23	2.60	718.15	***0.00862***
	35	1984 SCHWAR f2	62.61	3.64	1076.10	***0.00441***
	36	1985 KHUDER m	7.82	3.87	15.77	***0.0001***
	37	1986 ANDERS f	25.57	10.29	63.56	***0.0001***
	38	1989 HEGMAN c	30.80	12.48	76.03	***0.0001***
Europe	39	1947 ORMOS m	10.14	2.41	42.79	***0.00165***
	40	1948 DOLL m	13.17	4.12	42.10	***0.0001***
	41	1948 DOLL f	2.13	1.06	4.27	***0.03311***
	42	1948 KREYBE m	10.87	3.47	34.04	***0.0001***
	43	1948 KREYBE f	2.29	0.89	5.88	0.08506
	44	1954 STASZE m	57.77	3.58	933.17	***0.00430***
	45	1954 STASZE f	32.45	1.32	800.04	***0.03297***
	46	1959 TIZZAN c	2.70	1.99	3.67	***0.0001***
	47	1964 ENGELA m	6.45	1.97	21.11	***0.00211***
	48	1966 TOKARS c	6.80	1.20	38.70	***0.03026***
	49	1971 NOU m	27.17	6.60	11.85	***0.0001***
	50	1971 NOU f	7.09	1.35	37.19	***0.02043***
	51	1972 DAMBER m	11.80	6.40	23.00	***0.0001***
	52	1975 ABRAHA m	92.66	5.77	1488.21	***0.00143***
	53	1975 ABRAHA f	5.35	2.22	12.90	***0.00021***
	54	1976 LUBIN2 m	16.66	12.69	21.86	***0.0001***
	55	1976 LUBIN2 f	5.78	4.34	7.71	***0.0001***
	56	1977 ALDERS m	14.70	3.40	63.64	***0.00035***
	57	1977 ALDERS f	6.09	2.68	13.82	***0.0001***
	58	1979 BARBON m	14.52	6.35	33.20	***0.0001***
	59	1979 DOSEME m	3.60	2.60	5.00	***0.0001***
	60	1980 JEDRYC m	12.84	5.58	29.55	***0.0001***
	61	1983 SVENSS f	12.62	3.97	40.14	***0.0001***
	62	1985 BECHER f	10.69	2.43	47.00	***0.00177***
	63	1987 KATSOU f	6.11	2.69	13.87	***0.0001***
	64	1988 JAHN m	23.03	7.29	72.81	***0.0001***
Asia	65	1961 ISHIMA c	21.00	3.38	868.40	***0.03122***
	66	1964 JUSSAW m	25.43	13.87	46.63	***0.0001***
	67	1965 MATSUD m	39.01	5.44	279.84	***0.00029***
	68	1976 CHAN m	15.22	3.61	64.12	***0.00023***
	69	1976 CHAN f	6.44	3.44	12.06	***0.0001***
	70	1976 LAMWK2 m	6.89	2.65	17.90	***0.0001***
	71	1976 LAMWK2 f	6.49	3.27	12.88	***0.0001***

(continued)

Place	No.	Base Study ID (n=102)	RR	LCL	UCL	*p-value*
Asia	72	1976 TSUGAN m	14.55	0.75	283.37	0.07657
	73	1978 ZHOU m	3.14	1.90	5.18	***0.0001***
	74	1978 ZHOU f	3.81	1.50	9.68	***0.00496***
	75	1981 KOO f	4.15	2.46	6.98	***0.0001***
	76	1981 LAMWK f	10.54	4.19	26.52	***0.0001***
	77	1981 XU3 m	5.90	1.69	20.57	***0.00540***
	78	1981 XU3 f	25.67	4.99	131.94	***0.00012***
	79	1982 ZHENG m	16.82	6.05	46.71	***0.0001***
	80	1982 ZHENG f	5.45	3.11	9.54	***0.0001***
	81	1983 LAMTH f	8.10	4.16	15.77	***0.0001***
	82	1984 GAO m	8.40	4.70	15.00	***0.0001***
	83	1984 GAO f	7.20	4.60	11.10	***0.0001***
	84	1984 LUBIN m	6.33	2.29	17.45	***0.00040***
	85	1985 CHOI m	5.45	2.34	12.67	***0.0001***
	86	1985 CHOI f	6.94	2.68	17.96	***0.0001***
	87	1985 WUWILL f	4.20	3.00	5.90	***0.0001***
	88	1986 SOBUE m	17.88	7.82	40.87	***0.0001***
	89	1986 SOBUE f	8.74	5.09	15.02	***0.0001***
	90	1988 WAKAI m	8.61	2.08	35.72	***0.00305***
	91	1988 WAKAI f	25.23	6.87	92.66	***0.0001***
	92	1990 FAN c	11.68	5.04	27.04	***0.0001***
	93	1990 GER c	3.19	1.08	9.42	***0.03547***
	94	1990 LUO c	10.90	2.50	47.90	***0.00157***
	95	1991 KIHARA c	26.97	10.84	67.08	***0.0001***
	96	1997 SEOW f	17.50	6.95	44.09	***0.0001***
Other	97	1978 JOLY m	31.21	7.69	126.68	***0.0001***
	98	1978 JOLY f	18.56	7.74	44.51	***0.0001***
	99	1987 PEZZOT m	62.74	3.86	1019.50	***0.00367***
	100	1991 SUZUK2 c	31.00	4.20	227.00	***0.00078***
	101	1993 DESTE2 m	13.20	4.70	37.10	***0.0001***
	102	1994 MATOS m	8.08	2.58	25.50	***0.00038***

Sources:

1 Lee PN, Forey BA, Coombs KJ. 2012. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. BMC Cancer. 12:385 (90pp.). https://doi.org/10.1186/1471-2407-12-385.

2 Altman DG, Bland JM. 2011. How to obtain the p-value from a confidence interval. BMJ. 343:d2304. https://doi.org/10.1136/bmj.d2304.

Supplemental Information, SI 7

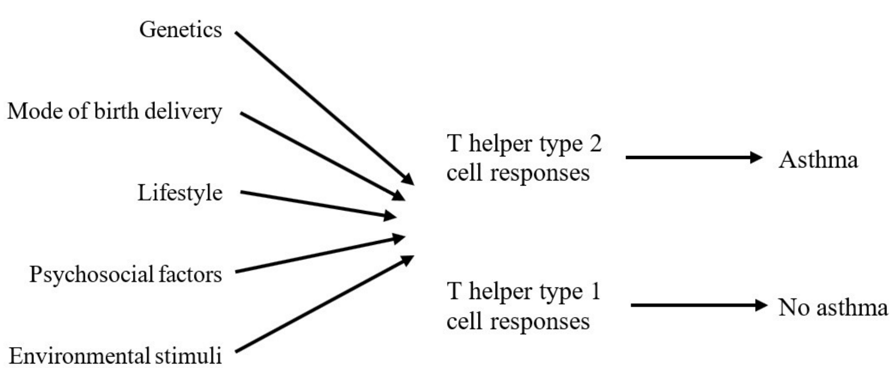
Asthma Characteristics

Table of asthma characteristics:

Possible risk factors for development of asthma in children & adults:		**Possible triggering/precipitating factors for exacerbations in children & adults:**
(1) Induction (sensitization) phase Host factors - genetic predisposition - gender - pre-term delivery (e.g., prematurity causes lung problems) Environmental stimuli - allergens - respiratory infections (viruses)	*(2) Maintenance (progression) phase* Environmental stimuli - allergens - respiratory infections (viruses, bacteria) - tobacco smoke - indoor/outdoor air quality - occupational sensitizer	- emotional factors (stress) - exercise-induced - foods, additives - hormonal factors (premenstrual worsening) - indoor/outdoor allergens - indoor/outdoor air quality - indoor irritants (household sprays, paint fumes) - medications (aspirin, nonsteroidal anti-inflammatory drugs, β-blockers) - occupational agents - substance abuse - tobacco smoke - uncontrolled allergic rhinitis, sinusitis, respiratory viral infections - weather changes (e.g., temperature, humidity)

Notes: (1) after references 1–10 listed at the end; (2) All these factors have support in the scientific literature; some are based on associations, and some may be directly causative.

Proposed childhood asthma causes and risks (Noutsiosa and Floros[2]):



a) Development of asthma

Asthma is associated with three principal characteristics (Pillai and Calhoun,[1] Noutsios and Floros[2]): (1) variable airways obstruction, (2) airway hyperresponsiveness, and spasm with wheezing and coughing and (3) airway inflammation. Clinically asthma is characterized by episodic, reversible obstructive airways obstruction that variably presents as a variety of symptoms from cough to wheezing, shortness of breath, or chest tightness (Busse and Lemanske)[3].

The underlying pathology of asthma, regardless of its severity, is chronic inflammation of the airways and reactivity/spasm of the airways. A combined contribution of genetic predisposition and non-genetic factors account for divergence of the immune system towards T helper (Th) type 2 cell responses that include production of pro-inflammatory cytokines, Immunoglobulin E (IgE) antibodies and eosinophil infiltrates (circulating granulocytes) known to associate with asthma (Noutsiosa and Floros[2]). The release of pro-inflammatory cytokines that cause airway narrowing is responsible for cough, shortness of breath, wheezing and chest tightness characteristic of the asthmatic state (Bernstein[4]). But this fails to account for beta stimulus of bronchiolar muscles that increases airway spasm. Airway inflammation causes secretions and contributes to edema (swelling) but it does not cause hyperresponsiveness.

During exacerbations these airway narrowing processes are accentuated, but it is not completely clear how these events contribute to these underlying changes and the mechanisms underlying an increase in airflow obstruction are not fully understood (Singh and Busse[5]). There is also ongoing debate as to whether asthma is one disease or several different diseases that include airway inflammation; however two thirds (or more) of asthmatic patients have an allergic component to their disease and are felt to have allergic asthma (Scherzer and Grayson[6]). Not enough is currently known to rule out allergic causes for a vast majority of asthma problems. As for development of the disease, asthma frequently first expresses itself early in the first few years of life arising from a combination of host and other factors. Most investigators would agree there is a major hereditary contribution to the underlying causes of asthma and allergic diseases (Lemanske and Busse[7]).

b) Triggering/precipitating factors

Respiratory viruses are present in a majority of asthmatic children during episodes of exacerbation (Johnston[8], Szefler[9], Costa et al.[10]). Airways are made more reactive by infection, so asthmatic children have episodes of asthma that are aggravated or initiated by respiratory infections.

Mechanisms by which air quality components are hypothesized to contribute to asthma exacerbation in subjects with existing airway allergies are thru immune responses, for example:

- Producing Immunoglobulin E antibody responses in the immune system – alteration of T regulatory cell function (which has a role in regulating or suppressing other cells in the immune system) and changes in FEV_1 (forced expiratory volume in 1 second) (Diaz-Sanchez et al.[11], Nadeau et al.[12]). However, changes in FEV_1 are only a measure of airway obstruction and not evidence of a causal factor.

- Modulating or activating inflammasomes (Bauer et al.[13]). Inflammasomes are cytosolic multiprotein oligomers of the innate immune system responsible for activation of inflammatory responses (Latz et al.[14]). They are key signalling platforms that detect pathogenic microorganisms and sterile stressors, and that activate highly pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18.
- Impairing defences of the airway epithelium through reduced barrier function, impaired host defence to pathogens, and inflammatory responses from generation of reactive oxygen species (ROS) and resultant oxidative stress (Huang et al.[15], De Grove et al.[16], Huff et al.[17]).

From an exposure point-of-view, isolating the role/contribution of a particular triggering/precipitating factor in an asthma exacerbation episode is difficult, unless the factor overwhelms. Asthma is a complex interaction between the inhaled environment and the formed elements of the airways. The hypothesis is that exposure to abruptly changing air quality conditions may contribute to symptoms and increase the severity of asthma exacerbations(Holgate[18]); although these effects are not as pronounced as those of viruses and aeroallergens (Trasande and Thurston[19]). By the examination of multiple air quality component‒asthma exacerbation observational studies, our study helps judge if this hypothesis is supported.

Because of multiple triggering/precipitating factors that may be at play, D'Amato et al.[20] indicate it is challenging to evaluate the role of air quality on the timing of asthma exacerbations and on the prevalence of asthma in general. For example, enhanced Immunoglobulin E antibody-mediated response to aeroallergens and resulting enhanced airway inflammation could account for increasing frequency of allergic respiratory allergy and bronchial asthma often attributed to air quality components in observational studies.

c) <u>Seasonality</u>

There is seasonal variation in hospitalization of children due to asthma exacerbations, with fewer hospitalizations in summer and more in fall and winter in North America (e.g., United States – Kimes et al.[21] and Sokol et al.[22]; Canada – Crighton et al.[23] and Johnston[8]). As for adults (≥50 years), Johnston[8] reports that a major asthma exacerbation epidemic occurs annually during the Christmas period, and hovers near average levels for the remainder of the year other than a mild peak in early spring.

International studies reveal the same seasonal variation in asthma exacerbations and peak hospitalizations of children in fall – England (Khot et al.[24], Jackson et al.[25]), Netherlands (Koster et al.[26]), Finland (Harju et al.[27]), Norway (Carlsen et al.[28]), Malta (Grech et al.[29]), New Zealand (Kimbell-Dunn et al.[30]), Israel (Garty et al.[31]), Taiwan (Xirasagar et al.[32]) and Hong Kong (Tseng et al.[33]).

Asthma exacerbations are not so problematic in summer except for those asthmatics that are triggered by seasonal allergens that appear in summer. The onset of cooler weather brings on asthma exacerbations. Wintertime allergenic stimulants is more a problem of inside air—insect offal and dander and household allergens as well as mold in closed in housing or other allergens that are accentuated by inside living. There is also the well-known asthmatic trigger of cooler or cold air.

Possible causes of higher rates of asthma hospitalizations in fall proposed by others include climate factors, increased incidence of viral infections and changes in air quality components (Xirasagar et al.[32], Jackson et al.[25], Koster et al.[26], Sokol et al.[22]). However, house mold and dander as well as insect offal and detritus may also be at play. Crighton et al.[23] stated that ambient levels of air pollutants vary significantly from place to place, and in Ontario Canada these levels typically peak during summer months when asthma hospitalizations are at their lowest. Warmer summer temperatures typically result in an increase in levels of ozone precursors and ozone yet asthma hospitalizations decline. Rather than there being a number of single spiked events such as abrupt changes (increases) in air quality components on a given day, there is more likely to be other triggering/precipitating factors that accumulate and diminish over many days to weeks that more plausibly explain asthma hospitalizations of children in the fall in North America (Kimes et al.[21]).

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