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Epidemiological time series studies of $PM_{2.5}$ and daily mortality and hospital admissions: a systematic review and meta-analysis

R W Atkinson,[1] S Kang,[1] H R Anderson,[1,2] I C Mills,[3] H A Walton[2,4]

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[1]Population Health Research Institute and MRC-PHE Centre for Environment and Health, St George's, University of London, London, UK
[2]MRC-PHE Centre for Environment and Health, King's College London, London, UK
[3]Public Health England, Centre for Radiation, Chemical and Environmental Hazards, Chilton, Oxfordshire, UK
[4]NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK

Correspondence to
Dr R W Atkinson, Population Health Research Institute and MRC-PHE Centre for Environment and Health, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK; atkinson@sgul.ac.uk

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ABSTRACT

Background Short-term exposure to outdoor fine particulate matter (particles with a median aerodynamic diameter <2.5 μm ($PM_{2.5}$)) air pollution has been associated with adverse health effects. Existing literature reviews have been limited in size and scope.

Methods We conducted a comprehensive, systematic review and meta-analysis of 110 peer-reviewed time series studies indexed in medical databases to May 2011 to assess the evidence for associations between $PM_{2.5}$ and daily mortality and hospital admissions for a range of diseases and ages. We stratified our analyses by geographical region to determine the consistency of the evidence worldwide and investigated small study bias.

Results Based upon 23 estimates for all-cause mortality, a 10 μg/m^3 increment in $PM_{2.5}$ was associated with a 1.04% (95% CI 0.52% to 1.56%) increase in the risk of death. Worldwide, there was substantial regional variation (0.25% to 2.08%). Associations for respiratory causes of death were larger than for cardiovascular causes, 1.51% (1.01% to 2.01%) vs 0.84% (0.41% to 1.28%). Positive associations with mortality for most other causes of death and for cardiovascular and respiratory hospital admissions were also observed. We found evidence for small study bias in single-city mortality studies and in multicity studies of cardiovascular disease.

Conclusions The consistency of the evidence for adverse health effects of short-term exposure to $PM_{2.5}$ across a range of important health outcomes and diseases supports policy measures to control $PM_{2.5}$ concentrations. However, reasons for heterogeneity in effect estimates in different regions of the world require further investigation. Small study bias should also be considered in assessing and quantifying health risks from $PM_{2.5}$.

Key messages

What is the key question?

- Is there convincing and consistent evidence worldwide that short-term exposure to outdoor fine particulate matter (particles with a median aerodynamic diameter <2.5 μm ($PM_{2.5}$)) air pollution is associated with increased risk of death and emergency admission to hospital?

What is the bottom line?

- We found evidence for adverse health effects of short-term exposure to $PM_{2.5}$ across a range of important health outcomes, diseases and age groups with substantial variation between different regions of the world that needs explanation.

Why read on?

- Our study provides a systematic, quantitative summary of the time series literature and reports new findings that suggest larger associations for respiratory causes of death than for cardiovascular causes and that the presence of publication bias in the literature could have important implications for public health policy.

INTRODUCTION

The adverse health effects of exposure to outdoor particulate matter air pollution are of concern to governments and health organisations worldwide.[1 2] The evidence for these health effects has come from studies of the clinical, mechanistic and epidemiological evidence of short-term and long-term exposures. While the epidemiological evidence relating short-term exposure to PM_{10} (particles with a median aerodynamic diameter <10 μm) and related metrics (black smoke, total suspended particles) with health effects is substantial, there are relatively few studies of fine particles measured as $PM_{2.5}$ (particles with a median aerodynamic diameter <2.5 μm). Reviews of the evidence linking exposure to $PM_{2.5}$ to adverse health effects have relied upon a small number of published studies, restricted in health outcomes and geographical coverage, or focused on differential $PM_{2.5}$ toxicity.[3–11]

To summarise the existing evidence we conducted a comprehensive and systematic meta-analysis of time series studies of daily $PM_{2.5}$ and daily mortality and hospital admissions published worldwide in the peer reviewed literature to May 2011. This included all disease outcomes for which there were sufficient studies for meta-analysis and combined results from single-city and multicity studies. We focused our analysis on single-pollutant rather than multipollutant models and upon all-year results in order to maximise the number of estimates available for inclusion in the review. We present estimates for WHO regions and assess between-region heterogeneity. We also investigate whether there is evidence of publication (small study) bias between single-city study estimates and between multicity summary estimates.

METHODS

Systematic ascertainment of relevant studies

Time series (including case crossover) studies published in peer reviewed journals and indexed in online databases to May 2011 (no start date specified) were identified via search strings using terms relating to study design, pollutant and health outcomes. A sifting process identified (from study titles, abstracts and the full paper) those time series studies suitable for inclusion in the review. Study eligibility depended upon the details of the study design, statistical methods used and presentation of regression estimates and other data in numerical format. Further details are given in the online supplementary material.

Extraction and coding of data

Study details were entered into a Microsoft Access database (Microsoft Office 2010, Microsoft Corporation) and included citation information (title, authors, date of publication, etc) and details of effect estimates including health outcome (mortality or admission), diagnosis (International Classification of Diseases codes), age, and so on, and details of the pollutants (unit of measurement, range of exposure, etc). These data were used to calculate standardised effect estimates expressed as the percentage change (and 95% CI) in the mean number of daily events associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration. The short-term relationships between air pollution and health effects are determined for given time lags (in days) between exposure and health events and investigators vary in which lags they study and report.[12] Hence an a priori lag selection protocol was devised and used to choose lag estimates for inclusion in the review without introducing bias (see online supplementary material for details). Additional data entry included the coding of the WHO region in which the study occurred (see online supplementary material, table S1). Studies were reviewed by a single statistician/epidemiologist before coding. All papers were read by RWA and data range checked prior to meta-analysis.

Meta-analysis

In the time series literature many cities have been studied on more than one occasion, in single-city studies and as part of a larger, coordinated multicity investigation. To ensure results from a city only appeared once in any one meta-analysis we applied an a priori estimate-selection protocol (see online supplementary material for details).

We conducted meta-analyses only if there were 4+ single city estimates or if the set of estimates contained a multicity study summary estimate. Within each WHO region we conducted a two stage meta-analysis using a random-effects model for each stage.[13] In the first stage, single-city estimates were pooled to provide a summary estimate of the evidence from single-city studies. In the second stage, these summary estimates were pooled with the selected multicity study estimates to obtain a WHO region-specific summary estimate of the evidence. To assess heterogeneity between WHO regions we used the I^2 statistic which indicates the proportion of total variability between effect estimates due to heterogeneity.[14] I^2 statistics in the range 0 to 30, 30 to 50 and >50 generally indicate low, moderate and high heterogeneity, respectively. Finally, a global summary estimate was calculated from WHO region-specific single-city summary estimates and multicity study estimates.

Assessment of small study bias

We investigated our selected single-city estimates and our pooled single-city and selected multicity estimates for evidence of small study bias using the methods of Begg and Egger.[15 16] The former uses an adjusted rank correlation method to examine the association between study estimates and their variance whereas the latter uses a regression approach. The impact of adjustment for small study bias was assessed using the 'trim and fill' method.[17] This method removes studies until symmetry in the funnel plot is achieved, recalculating the centre of the funnel before the removed studies are replaced together with their 'missing' mirror-image counterparts. A revised summary estimate is then calculated using all of the original studies, together with the hypothetical 'filled' studies. Our overall assessment of the evidence for small study bias was based upon the combined evidence presented by all three techniques.

All analyses were conducted in STATA (STATA/SE V.10, StataCorp Texas).

RESULTS

One hundred and ten time series studies of daily mortality (68) and hospital admissions (54) indexed in medical databases to May 2011, and providing numerical effect estimates, reported results for $PM_{2.5}$ (see online supplementary material, table S2). Table 1 details the number of studies tabulated by outcome, disease, WHO region, age group and multicity versus single-city study design. The majority of studies of $PM_{2.5}$ and daily mortality and hospital admissions have been conducted in North America and Europe with a small number of studies in other regions of the world. The most frequently reported estimates for daily mortality were for the all-ages group, followed by the 65 + years group. For most populations the latter comprised a large proportion of the all-ages group so we confined our mortality analyses to the all-ages group. For hospital admissions we focused upon age-specific estimates in children and the elderly (ages 0–14 years and 65+ years, respectively). While the majority of studies were conducted in single cities, a substantial number reported findings from multicity studies.

Mortality

Summary estimates (95% CIs) per 10 $\mu g/m^3$ increment in $PM_{2.5}$ and all-age, all-cause and cause-specific mortality are presented in figure 1. All associations were positive and for all, except chronic COPD, lower CIs were above unity. For all-cause mortality, 23 single-city and multicity study estimates were selected for meta-analysis from the 43 estimates identified in the review (see online supplementary material, figure S1). The overall random effects summary estimate was 1.04% (95% CI 0.52% to 1.56%) per 10 $\mu g/m^3$ increment in $PM_{2.5}$. WHO region-specific summary estimates varied substantially (I^2=93%) from 0.25% to 2.08% (table 2).

While fewer estimates were available for cardiovascular (see online supplementary material, figure S2) and respiratory (see online supplementary material, figure S3) mortality, the overall summary estimate for all respiratory causes of death was larger than for all cardiovascular causes, 1.51% (95% CI 1.01% to 2.01%) versus 0.84% (95% CI 0.41% to 1.28%), respectively. For both causes of death, associations were positive in all WHO regions (table 2) and heterogeneous for cardiovascular deaths (I^2=76%) but not respiratory deaths (I^2=0%). Associations between $PM_{2.5}$ and death from ischaemic heart disease, stroke and COPD were 3.36% (0.68%, 6.10%), 1.85% (0.74%, 2.97%) and 2.86% (−0.12%, 5.93%) per 10 $\mu g/m^3$, respectively, although the evidence was restricted to a small number of single-city and multicity studies (see online supplementary material, table S3 and figures S4–S6).

Table 1 Time series studies of $PM_{2.5}$ and mortality and hospital admissions

Multicity study		Total		Multicity study		Single-city study	
Outcome		Mortality	Hospital admission	Mortality	Hospital admission	Mortality	Hospital admission
Total		68	54	17	11	51	43
Disease	Respiratory	33	43	7	9	26	34
	Cardiovascular	41	34	9	9	32	25
	All-cause	56	2	15	0	41	2
	Other	7	3	2	2	5	1
WHO region	American region A	33	31	13	8	20	23
	European region A	20	10	2	1	18	9
	Western Pacific region B	6	6	0	0	6	6
	American region B	6	2	0	0	6	2
	Western Pacific region A	4	4	3	2	1	2
	South-East Asia region D	0	1	0	0	0	1
Age group	All ages	54	21	16	1	40	20
	Elderly	26	28	5	9	21	19
	Not elderly	4	4	1	1	3	3
	Adult	1	2	0	0	1	2
	Young adult	0	9	0	2	0	7
	Children	1	18	0	3	1	15
	Other	2	3	0	0	2	3

Hospital admissions

Table 3 gives summary estimates for all-age, cardiovascular and respiratory causes of hospital admissions with individual study results presented in online supplementary material, figures S7 and S14.

$PM_{2.5}$ concentrations were positively associated with increases in risk of admission for cardiovascular diseases, 0.90% (95% CI 0.26% to 1.53%) and respiratory diseases, 0.96% (95% CI −0.63% to 2.58%) per 10 μg/m^3, respectively, with heterogeneity between WHO regions for respiratory diseases (I^2=80%) but not cardiovascular diseases (I^2=0%). Figure 2 illustrates summary estimates for specific cardiovascular diseases in ages 65+ years and for respiratory diseases in ages 65+ years and children aged 0–14 years. All associations were positive except for stroke and for all, except COPD including asthma, lower CIs exceeded 0%. Details of WHO-specific summary estimates are

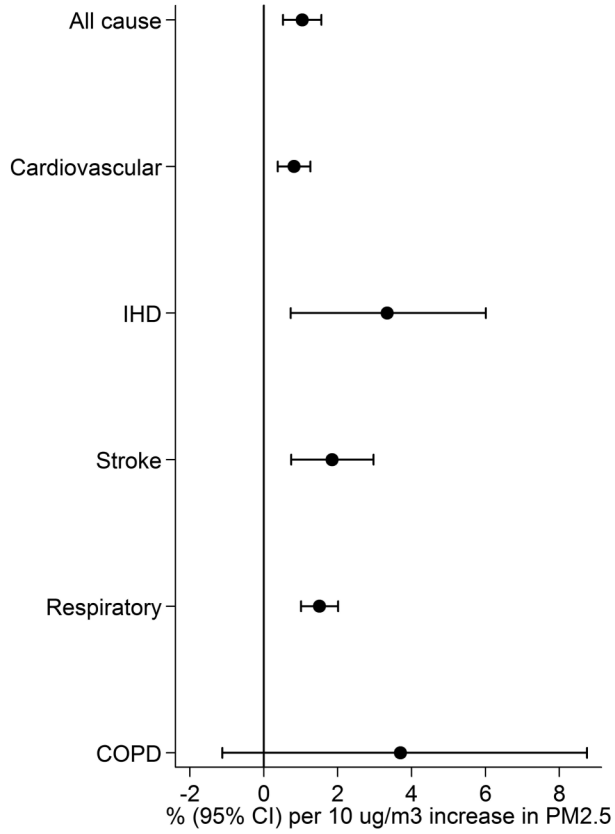

Figure 1 Summary estimates (95% confidence intervals) for all-cause and cause-specific mortality.

Table 2 Meta-analysis results for all-age, all-cause mortality and cause-specific mortality by WHO region

WHO region	All* (SC/MC)	Selected† (SC/MC)	RE (95% CI)‡	I^2 (%)§
All Cause				
AMR A	13/12	5/2	0.94 (0.73 to 1.16)	93
AMR B	4/0	2/0	2.08 (1.60 to 2.56)	
EUR A	12/1	9/1	1.23 (0.45 to 2.01)	
WPR A	0/1	0/1	0.90 (–0.70 to 2.53)	
WPR B	5/0	3/0	0.25 (0.06 to 0.44)	
Summary¶	–	4/4	1.04 (0.52 to 1.56)	
Cardiovascular				
AMR A	10/3	6/1	0.84 (0.47 to 1.20)	76
AMR B	3/0	2/0	0.13 (–0.71 to 0.98)	
EUR A	6/1	6/1	2.26 (1.23 to 3.29)	
WPR B	4/0	2/0	0.56 (0.31 to 0.81)	
Summary¶	–	4/2	0.84 (0.41 to 1.28)	
Respiratory				
AMR A	4/5	4/1	1.39 (0.62 to 2.16)	0
AMR B	3/0	2/0	0.88 (–1.88 to 3.71)	
EUR A	7/0	7/0	3.81 (0.57 to 7.16)	
WPR B	4/0	2/0	1.49 (0.04 to 2.96)	
Summary¶	–	4/1	1.51 (1.01 to 2.01)	

*Numbers of single-city(SC)/multicity (MC) estimates available from all studies.
†Numbers of single-city(SC)/multicity (MC) estimates selected for meta-analysis (see estimate selection protocol in Methods section).
‡Random effects summary estimate (95% CI) per 10 μg/m^3.
§I^2 statistic for heterogeneity.
¶Estimate numbers for 'Summary' refers to the number of pooled (from single-city estimates) and multicity estimates used to calculate the overall summary estimate across WHO regions.
AMR, Region of the Americas; EUR, European Region; WPR/SEAR, South East Asian Region.

Table 3 Meta-analysis results for all-age, cardiovascular and respiratory hospital admissions by WHO region

WHO region	All* (SC/MC)	Selected† (SC/MC	RE (95% CI)‡	I^2 (%)§
Cardiovascular				
AMR A	2/0	1/0	0.00 (−2.85 to 2.93)	0
EUR A	4/1	4/1	0.91 (0.17 to 1.66)	
WPR A	1/0	1/0	1.04 (−0.30 to 2.39)	
Summary¶	–	3/1	0.90 (0.26 to 1.53)	
Respiratory				
AMR A	1/0	1/0	−2.00 (−6.00 to 2.17)	80
EUR A	3/0	3/0	1.90 (−0.18 to 4.02)	
SEAR D	1/0	1/0	0.12 (0.08 to 0.16)	
WPR A	1/0	1/0	2.38 (1.04 to 3.73)	
Summary¶	–	4/0	0.96 (−0.63 to 2.58)	

*Numbers of single-city(SC)/multicity (MC) estimates available from all studies.
†Numbers of single-city(SC)/multicity (MC) estimates selected for meta-analysis (see estimate selection protocol in Methods section).
‡Random effects summary estimate (95% CI) per 10 μg/m^3.
§I^2 statistic for heterogeneity.
¶Estimate numbers for 'Summary' refers to the number of pooled (from single-city estimates) and multicity estimates used to calculate the overall summary estimate across WHO regions.

given in online supplementary material, tables S4 and S5, and study-specific estimates in online supplementary material, figures S7–S13 and S15–S20.

Small study bias

The impact of adjustments for small study bias in single-city studies within WHO regions and between the pooled single-city and multicity estimates for all-age, all-cause and cause-specific mortality are shown in table 4. We found evidence for small study bias in single-city mortality studies and in multicity studies of cardiovascular disease.

Figure 3 illustrates, for cardiovascular mortality, this adjustment using a funnel plot of individual study estimates and showing the random effects summary estimates with, and without, inclusion of the two 'filled' estimates identified by the 'trim and fill' procedure. We did not find evidence of small study bias in either single-city or multicity estimates for cardiovascular or respiratory hospital admissions (data not shown).

DISCUSSION

In this systematic review we identified 110 ecological time series studies of short-term exposure to outdoor $PM_{2.5}$ and daily mortality and hospital admissions indexed in medical databases up to May 2011. Our meta-analysis of effect estimates from these studies indicated positive associations with daily all-cause and cause-specific mortality and cause-specific and age-specific hospital admissions, with some evidence of heterogeneity. We also found evidence for small study bias in single-city estimates and between pooled and multicity estimates.

There are a number of plausible biomedical explanations for associations between short-term exposure to fine particles and adverse health outcomes.[5 6] It is hypothesised that small effects cause clinical events when experienced by individuals who are already vulnerable due to existing chronic or acute disease. Our review indicates that such effects are observed even at the relatively low levels of fine particles found in developed countries. Our results reinforce the public health importance of fine particles on health. While the estimates are small, the impact is substantial because the entire population is exposed. Impact

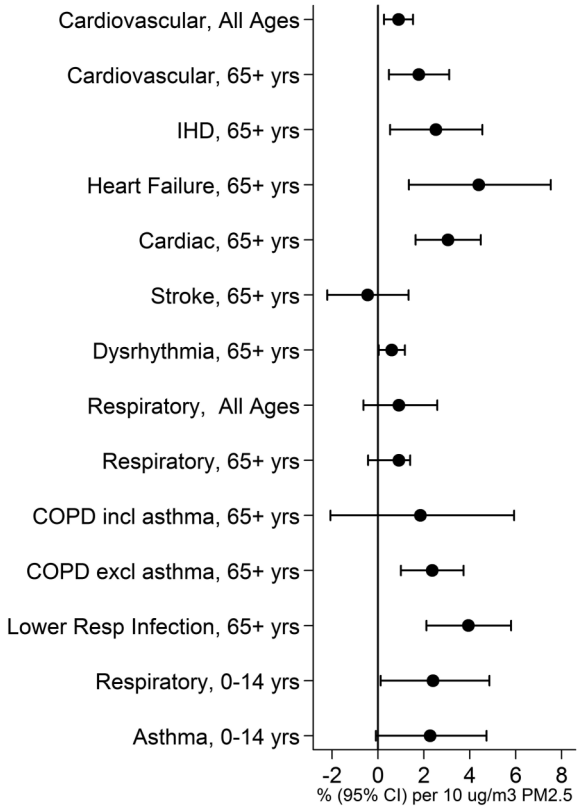

Figure 2 Summary estimates (95% confidence intervals) for cardiovascular and respiratory hospital admissions.

assessments of $PM_{2.5}$ on mortality are based on cohort rather than time-series evidence because this enables years of life lost to be estimated.[18 19] However, most cohort evidence is from North America or Western Europe. Our finding that short-term associations occur worldwide supports the generalisation of cohort based estimates globally[19] while at the same time indicating that there may also be some heterogeneity.

Our study extends the literature reviewing the evidence for health effects of short-term exposure to $PM_{2.5}$ derived from time series studies. The numbers of single-city and multicity studies have increased substantially in recent years, from 55 in 2005[11] to 110 identified in this review. In 2009 the Environmental Protection Agency (EPA) summarised evidence from studies of mainly US populations[5] published between 2002 and May 2009. Also in 2009, the American Heart Association issued an updated statement on the effects of particulate air pollution on cardiovascular disease including evidence from time series studies published to March 2009.[6] A more recent review in 2012[8] focused upon studies of $PM_{2.5}$ components indexed in the Science Citation Database up to October 2010. Our study complements these previous reviews by providing a meta-analysis for a much larger, more recent (indexed in medical databases to May 2011) and broader literature incorporating studies irrespective of geographical location and disease outcome.

Across the five WHO regions studied, our summary estimates for all-age, all-cause mortality ranged from 0.25% to 2.08% with an overall estimate of 1.04%, comparable with the summary estimate of 1.2% derived from seven studies by Levy *et al*.[8] While we found evidence of statistical heterogeneity across region-specific estimates both values are consistent with a mortality hazard from short-term exposure to fine particulate

Table 4 Assessment of bias in single-city studies and in pooled estimates for all-cause mortality and cause-specific mortality

	All-cause	Cardiovascular			Respiratory
No Adjustment*	1.04 (0.52 to 1.56)	0.84 (0.41 to 1.28)			1.51 (1.01 to 2.01)
Single-city bias†					
WHO region	Amr A	Amr A	Amr B	Eur A	Amr B
p Value Begg	0.14	0.57	0.32	0.35	0.32
p Value Egger	0.003	0.42	NA	0.32	NA
# Estimates	5	6	2	6	2
#Trim and fill	8	7	3	7	3
Single-city‡	0.97 (0.46 to 1.48)	0.78 (0.35 to 1.21)			1.00 (0.73 to 1.27)
Multicity bias§					
p Value Begg	0.81	0.09			0.46
p Value Egger	0.36	0.32			0.52
# Estimates	8	6			8
# Trim and fill	8	8			8
Pooled single and multicity¶	0.97 (0.46 to 1.48)	0.57 (0.09 to 1.05)			1.00 (0.73 to 1.27)

*Random effects summary estimate (95% CI) per 10 $\mu g/m^3$ without adjustment for small study bias.
†Analysis of bias in single-city studies by WHO region (where found): Begg's test p value, Egger's test p value, number of estimates prior to application of 'trim and fill' technique, number of estimates after application of 'trim and fill' technique.
‡Overall summary estimate calculated after application of 'trim and fill' technique to single-city estimates by WHO region.
§Bias between pooled single-city estimates and multicity estimates, Begg's test p value, Egger's test p value, number of estimates prior to application of the trim and fill' technique, number of estimates after application of the 'trim and fill' technique.
¶Overall summary estimate after application of the 'trim and fill' technique to single-city estimates within WHO region and between pooled single-city estimates and multicity estimates.

matter. The reasons for this variability in effect estimates between WHO regions warrant further investigation but may reflect variations in population vulnerability and/or differential toxicity of sources, pollutant mixtures and pollution monitoring.

Our finding that the association for respiratory mortality (1.51%) was larger than for cardiovascular mortality (0.84%)—a finding observed within all WHO regions—was also reported by the EPA in their review.[5] However, the EPA noted the coherence in associations between $PM_{2.5}$ and cardiovascular mortality and morbidity outcomes and the lack of such coherence for respiratory diseases. We were only able to assess the extent of coherence by comparing associations for mortality and admissions. For cardiovascular diseases our overall summary estimates for $PM_{2.5}$ and admissions and mortality were comparable confirming the coherence reported by the EPA although we note substantial disagreement between region-specific summary estimates for each outcome including North America. We also note the negative, although statistically not significant, associations observed in three single-city studies in Europe and the Western Pacific region for hospital admissions for stroke in adults over the age of 65 years. For respiratory diseases, we found that the overall summary estimates for $PM_{2.5}$ and mortality and admissions were broadly comparable although for respiratory admissions the summary estimate was approximately two-thirds that for mortality and the CI for the summary estimate straddled 0% due to the negative association reported in a single-city study from North America. We note however that while the same ICD codes are used for mortality and admissions, the way they are used is different—underlying cause of death for the former and immediate cause of admission for the latter. This might affect comparability of certain categories such as pneumonia or heart failure though they would still fall within the broad cardiovascular or respiratory rubric.

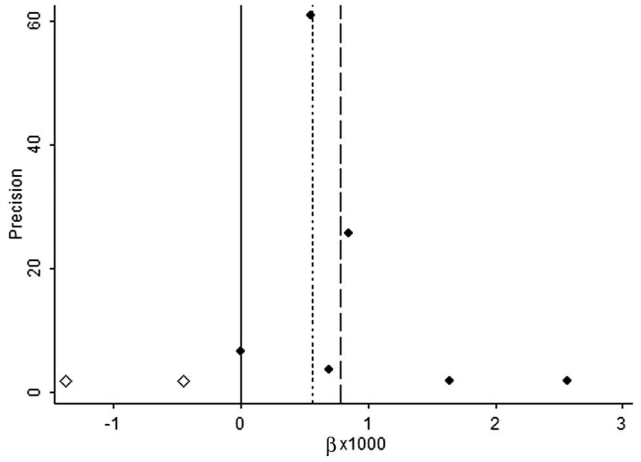

Figure 3 Funnel plot of pooled single-city and multi-city summary estimates for cardiovascular mortality including 'filled' estimates. Random effects summary estimates without (long-dash line) and with (short-dash line) adjustment using the Trim & Fill procedure.

The main strengths of our study are: (1) a protocol driven approach to the identification, coding and selection of effect estimates for meta-analysis to minimise selection bias throughout the review process; (2) inclusion of all health outcomes for which sufficient estimates were available for meta-analysis; (3) no limitations on study location or language, and (4) stratification of results by WHO region. However, in common with other reviews, our study is limited by: (1) the need for numerical, rather than graphical, presentation of data to facilitate quantitative meta-analysis; (2) the authors' choice of results to publish; and (3) having no assessment of the 'grey' literature. It is therefore important to assess the extent to which the inferences and quantitative estimates presented here have been affected by small study bias, a process that leads to the published literature being unrepresentative of the totality of evidence.[20]

Our analysis of small study effects, a generic term also encompassing publication bias and a range of other potential biases,[21] suggests that this may be an important issue in the meta-analysis of single-city and multicity estimates. The former has been noted previously in relation to time series studies of PM_{10}[11] but the observation that meta-analysis of multicity estimates can be similarly affected is new. Sterne *et al* suggested that the greater

investment of time and money in larger studies (such as multicity time-series studies) meant such studies would be more likely to be of high methodological quality and published even if their results are negative.[21] Sterne *et al* also noted that the 'trim and fill' procedure detects 'missing' studies in a substantial proportion of meta-analyses, even in the absence of bias. Thus, there is a danger that the application of the procedure could mean adding and adjusting for non-existent studies in response to funnel plot asymmetry arising from nothing more than random variation. Our finding that the 'trim and fill' adjustment substantially reduced the magnitude and precision of the associations between $PM_{2.5}$ and cardiovascular mortality should therefore be interpreted with some caution, especially so given the unremarkable p values from the Begg and Egger tests and the funnel plot presented in figure 3.

Other potential sources of bias in our study methodology could be: (1) the selection of estimates from the individual papers; and (2) the selection of study estimates for meta-analysis. Bias arising from the former is possible given the tendency of investigators to assess associations at different time lags between exposure and health event. To address this we used a protocol for estimate selection that was independent of the direction of an association. In previous work this has been shown not to introduce bias but increase between-estimate heterogeneity[11] so we believe that it is unlikely that we are overstating the magnitude of associations. Our protocol for the selection of estimates (from those available) for meta-analysis similarly did not consider direction of associations, instead basing the selection upon geographical coverage, publication date and length of study period. It also ensured that no single location appeared more than once in a summary estimate. While our approach was just one of many analytical strategies that could have been adopted, we believe that the resulting summary estimates were unlikely to be systematically biased since none of our selection criteria included the direction or magnitude, of the individual study effect estimates. The relevance of these issues cannot be overstated since results from meta-analyses can be important in underpinning the use of more limited cohort data in worldwide health impact assessments.[19]

Our review points to adverse associations between short-term exposure to daily concentrations of $PM_{2.5}$ and daily mortality and hospital admissions across a range of diseases and age groups which supports continued policy measures to control $PM_{2.5}$ levels worldwide. However, we note that the evidence for these associations is concentrated in a small number of geographical regions of the world and also limited to the broader categories of disease. Further studies from other developed countries, in particular Asia and Eastern Europe, are needed to confirm the observed associations. Also, new studies including specific, rather than broad, categories of diseases would increase understanding of the populations at risk and may also add to our understanding of mechanism of effect. In addition, the reasons for the heterogeneity in effect estimates in different regions of the world require further research as they may be relevant to the formulation of policy measures. Our findings also suggest that, for the purpose of health impact assessment, some consideration of, and adjustment for, small study bias in results from multicity as well as single-city studies should be undertaken.

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Competing interests None.

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Epidemiological time series studies of $PM_{2.5}$ and daily mortality and hospital admissions – a systematic review and meta-analysis

RW Atkinson[1], S Kang[1], HR Anderson[1,2], IC Mills[3], HA Walton[2,4]

Supplementary Material

Contents

Methods

Search String

The following search string was used (with minor amendments for the specific databases) to identify potential studies published in peer reviewed journals and indexed in PubMed, EMBASE or Web of Science (which includes the Science Citation Index):

(air pollution OR pollution OR smog OR particle*OR particulate*) AND (timeseries OR time series OR time-series OR daily OR case-crossover) AND (mortality OR death* OR dying OR hospital admission* OR admission* OR emergency room OR visit* OR attendance* OR 'a&e' OR 'a and e' OR accident and emergency OR general pract* OR physician* OR consultation* OR emergency department*)

Study Selection criteria

The selection criteria used were that the study provided: 1) estimates for $PM_{2.5}$; 2) at least one year of daily data relating to a general population; 3) a reasonable attempt to control for important confounding factors such as season, long-term temporal trends and meteorological conditions and 4) sufficient information for the calculation of a regression estimate and standard error for comparison in the quantitative analysis. No limitation was placed upon language. We also cross-checked our search results against publications selected for other reviews.

Lag selection protocol

The short-term relationships between air pollution and health effects are characterised by the time lag (in days) between exposure and health events and investigators vary in which lags they study and report. This means that the use of any particular lag would result in the exclusion of many other studies. In the absence of a standard method of reporting the lag, we therefore adopted the following approach for selecting lag results for inclusion in the database. If only one lagged estimate for a given pollutant/outcome pair was presented (either because only one was analysed or only one was reported in the paper), this estimate was recorded in the Access database for the outcome–pollutant pair. If more than one lag measure was presented, we selected one for meta-analysis according to the following algorithm: 1) the lag that the author focused on or stated a priori; 2) the lag that was the most statistically significant (positive or

negative) and 3) the lag with the largest effect estimate (positive or negative). For options 2) and 3) results for single lags were selected ahead of results for cumulative/distributed lags.

Estimate selection protocol

Furthermore, numerous multi-city studies have incorporated the same cities more than once. Inclusion of results from a single-city more than once in a meta-analysis was not appropriate as the study populations will be correlated and the over-representation of a single-city may bias the summary estimate. Hence, we selected estimates from single-city studies only if they did not appear in multi-city studies. If a city was the subject of a single-city study on more than one occasion we took the result for the most recent publication. Where results from more than one multi-city study within a WHO Region were available we selected, in order of priority, the multi-city study: 1) with the most cities/greatest geographical coverage; 2) the most recently published; and 3) the longest study period.

Table S1 List of countries by WHO Region and mortality strata
(Source**:** *The World Health Report 2002)*

Mortality strata
A. Very low child, very low adult
B. Low child, low adult
C. Low child, high adult
D. High child, high adult
E. High child, very high adult

African Region	Eastern Mediterranean Region	European Region	Region of the Americas	South-East Asian Region	Western Pacific Region
AFR D • Algeria • Angola • Benin • Burkina Faso • Cameroon • Cape Verde • Chad • Equatorial Guinea • Gabon • Gambia • Ghana • Guinea	**EMR B** • Bahrain • Cyprus • Iran, Islamic Republic of • Jordan • Kuwait • Lebanon • Libyan Arab Jamahiriya • Oman • Qatar • Saudi Arabia • Syrian Arab	**EUR A** • Andorra • Austria • Belgium • Croatia • Czech Republic • Denmark • Finland • France • Germany • Greece • Iceland • Ireland • Israel	**AMR A** • Canada • Cuba • United States of America **AMR B** • Antigua and Barbuda • Argentina • Bahamas • Barbados • Belize	**SEAR B** • Indonesia • Sri Lanka • Thailand • Timor-Leste **SEAR D** • Bangladesh • Bhutan • Democratic People's Republic of Korea	**WPR A** • Australia • Brunei Darussalam • Japan • New Zealand • Singapore **WPR B** • Cambodia • China • Cook Islands • Fiji

• Guinea-Bissau • Liberia • Madagascar • Mali • Mauritania • Mauritius • Niger • Nigeria • Sao Tome and Principe • Senegal • Seychelles • Sierra Leone • Togo **AFR E** • Botswana • Burundi • Central African Republic • Congo • Côte d'Ivoire • Democratic Republic of Congo • Eritrea • Ethiopia • Kenya • Lesotho • Malawi • Mozambique	Republic • Tunisia • United Arab Emirates **EMR D** • Afghanistan • Djibouti • Egypt • Iraq • Morocco • Pakistan • Somalia • Sudan • Yemen	• Italy • Luxembourg • Malta • Monaco • Netherlands • Norway • Portugal • San Marino • Slovenia • Spain • Sweden • Switzerland • United Kingdom **EUR B** • Albania • Armenia • Azerbaijan • Bosnia and Herzegovina • Bulgaria • Georgia • Kyrgyzstan • Poland • Romania • Slovakia • Tajikistan • The former Yugoslav Republic of	• Brazil • Chile • Colombia • Costa Rica • Dominica • Dominican Republic • El Salvador • Grenada • Guyana • Honduras • Jamaica • Mexico • Panama • Paraguay • Saint Kitts and Nevis • Saint Lucia • Saint Vincent and the Grenadines • Suriname • Trinidad and Tobago • Uruguay • Venezuela, Bolivarian Republic of **AMR D** • Bolivia	• India • Maldives • Myanmar • Nepal	• Kiribati • Lao People’s Democratic Republic • Malaysia • Marshall Islands • Micronesia, Federated States of • Mongolia • Nauru • Niue • Palau • Papua New Guinea • Philippines • Republic of Korea • Samoa • Solomon Islands • Tonga • Tuvalu • Vanuatu • Viet Nam

• Namibia • Rwanda • South Africa • Swaziland • Uganda • United Republic of Tanzania • Zambia • Zimbabwe		Macedonia • Turkey • Turkmenistan • Uzbekistan • Yugoslavia **EUR C** • Belarus • Estonia • Hungary • Kazakhstan • Latvia • Lithuania • Republic of Moldova • Russian Federation • Ukraine	• Ecuador • Guatemala • Haiti • Nicaragua • Peru		

Source: http://www.who.int/choice/demography/regions/en/ (accessed 27th March 2014)

Table S2 List of time series studies of $PM_{2.5}$ and mortality and hospital admissions

Goldberg, M.S., Burnett, R.T., Bailar, J.C., Brook, J., Bonvalot, Y., Tamblyn, R., Singh, R., & Valois, M.F. 2001. The association between daily mortality and ambient air particle pollution in Montreal, Quebec 1. Nonaccidental mortality. *Environmental Research*, 86, (1) 12-25
Ref ID: 19

Burnett, R.T., Smith-Doiron, M., Stieb, D., Raizenne, M.E., Brook, J.R., Dales, R.E., Leech, J.A., Cakmak, S., & Krewski, D. 2001. Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. *American Journal of Epidemiology*, 153, (5) 444-452
Ref ID: 57

Anderson, H.R., Bremner, S.A., Atkinson, R.W., Harrison, R.M., & Walters, S. 2001. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occupational and Environmental Medicine*, 58, (8) 504-510
Ref ID: 69

Chen, Y., Yang, Q.Y., Krewski, D., Burnett, R.T., Shi, Y.L., & McGrail, K.M. 2005. The effect of coarse ambient particulate matter on first, second, and overall hospital admissions for respiratory disease among the elderly. *Inhalation Toxicology*, 17, (12) 649-655 available from: ISI:000231082600002
Ref ID: 73

Ostro, B., Roth, L., Malig, B., & Marty, M. 2009. The Effects of Fine Particle Components on Respiratory Hospital Admissions in Children. *Environmental Health Perspectives*, 117, (3) 475-480 available from: ISI:000263933600038
Ref ID: 95

Chimonas, M.A.R. & Gessner, B.D. 2007. Airborne particulate matter from primarily geologic, non-industrial sources at levels below National Ambient Air Quality Standards is associated with outpatient visits for asthma and quick-relief medication prescriptions among children less than 20 years old enrolled in Medicaid in Anchorage, Alaska. *Environmental Research*, 103, (3) 397-404 available from: ISI:000244903200014
Ref ID: 100

Lin, M., Chen, Y., Burnett, R.T., Villeneuve, P.J., & Krewski, D. 2002. The influence of ambient coarse particulate matter on asthma hospitalization in children: Case-crossover and time series analyses. *Environmental Health Perspectives*, 110, (6) 575-581
Ref ID: 103

Zanobetti, A. & Schwartz, J. 2006. Air pollution and emergency admissions in Boston, MA. *Journal of Epidemiology and Community Health*, 60, (10) 890-895 available from: ISI:000240495000015
Ref ID: 105

Lee, S.L., Wong, W.H.S., & Lau, Y.L. 2006. Association between air pollution and asthma admission among children in Hong Kong. *Clinical and Experimental Allergy*, 36, (9) 1138-1146 available from: ISI:000240311900005
Ref ID: 126

Simpson, R., Williams, G., Petroeschevsky, A., Best, T., Morgan, G., Denison, L., Hinwood, A., Neville, G., & Neller, A. 2005. The short-term effects of air pollution on daily mortality in four Australian cities. *Australian and New Zealand Journal of Public Health*, 29, (3) 205-212 available

from: ISI:000229854700003
Ref ID: 133

Burnett, R.T., Brook, J., Dann, T., Delocla, C., Philips, O., Cakmak, S., Vincent, R., Goldberg, M.S., & Krewski, D. 2000. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. *Inhalation Toxicology*, 12, 15-39
Ref ID: 135

Moolgavkar, S.H. 2000. Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. *Inhalation Toxicology*, 12, 75-90
Ref ID: 136

Ostro, B.D., Broadwin, R., & Lipsett, M.J. 2000. Coarse and fine particles and daily mortality in the Coachella Valley, California: a follow-up study. *Journal of Exposure Analysis and Environmental Epidemiology*, 10, (5) 412-419
Ref ID: 144

Kan, H., Jia, J., & Chen, B.H. 2004. The association of daily diabetes mortality and outdoor air pollution in Shanghai, China. *Journal of Environmental Health*, 67, (3) 21-25 available from: ISI:000224044900004
Ref ID: 150

Ito, K., Christensen, W.F., Eatough, D.J., Henry, R.C., Kim, E., Laden, F., Lall, R., Larson, T.V., Neas, L., Hopke, P.K., & Thurston, G.D. 2006. PM source apportionment and health effects: 2. An investigation of intermethod variability in associations between source-apportioned fine particle mass and daily mortality in Washington, DC. *Journal of Exposure Science and Environmental Epidemiology*, 16, (4) 300-310 available from: ISI:000239389600002
Ref ID: 159

Moolgavkar, S.H. 2003. Air pollution and daily mortality in two U. S. counties: Season-specific analyses and exposure-response relationships. *Inhalation Toxicology*, 15, (9) 877-907 available from: ISI:000184470900002
Ref ID: 162

Moolgavkar, S.H. 2000. Air pollution and daily mortality in three US counties. *Environmental Health Perspectives*, 108, (8) 777-784
Ref ID: 163

Klemm, R.J. & Mason, R.M. 2000. Aerosol Research and Inhalation Epidemiological Study (ARIES): Air quality and daily mortality statistical modeling - Interim results. *Journal of the Air & Waste Management Association*, 50, (8) 1433-1439
Ref ID: 176

Chock, D.P. & Winkler, S.L. 2000. A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. *Journal of the Air & Waste Management Association*, 50, (8) 1481-1500
Ref ID: 177

Lipfert, F.W., Morris, S.C., & Wyzga, R.E. 2000. Daily mortality in the Philadelphia metropolitan area and size- classified particulate matter. *Journal of the Air & Waste Management Association*, 50, (8) 1501-1513
Ref ID: 178

Loomis, D.P., Castillejos, M., Gold, D.R., McDonnell, W., & Borja-Aburto, V.H. 1999. Air pollution and infant mortality in Mexico City. *Epidemiology*, 10, (2) 118-123
Ref ID: 210

Peters, A., Skorkovsky, J., Kotesovec, F., Brynda, J., Spix, C., Wichmann, H.E., & Heinrich, J. 2000. Associations between mortality and air pollution in Central Europe. *Environmental Health Perspectives*, 108, (4) 283-287
Ref ID: 212

Borja-Aburto, V.H., Castillejos, M., Gold, D.R., Bierzwinski, S., & Loomis, D. 1998. Mortality and ambient fine particles in southwest Mexico City, 1993-1995. *Environmental Health Perspectives*, 106, (12) 849-855
Ref ID: 214

Burnett, R.T., Cakmak, S., Raizenne, M.E., Stieb, D., Vincent, R., Krewski, D., Brook, J.R., Philips, O., & Ozkaynak, H. 1998. The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. *Journal of the Air & Waste Management Association*, 48, (8) 689-700
Ref ID: 224

Slaughter, J.C., Kim, E., Sheppard, L., Sullivan, J.H., Larson, T.V., & Claiborn, C. 2005. Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. *Journal of Exposure Analysis and Environmental Epidemiology*, 15, (2) 153-159 available from: ISI:000227541800005
Ref ID: 230

Halonen, J.I., Lanki, T., Yli-Tuomi, T., Tiittanen, P., Kulmala, M., & Pekkanen, J. 2009. Particulate Air Pollution and Acute Cardiorespiratory Hospital Admissions and Mortality Among the Elderly. *Epidemiology*, 20, (1) 143-153 available from: ISI:000261930800023
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Schreuder, A.B., Larson, T.V., Sheppard, L., & Claiborn, C.S. 2006. Ambient woodsmoke and associated respiratory emergency department visits in Spokane, Washington. *International Journal of Occupational and Environmental Health*, 12, (2) 147-153 available from: ISI:000237477200008
Ref ID: 239

Cancado, J.E., Saldiva, P.H.N., Pereira, L.A.A., Lara, L.B.L.S., Artaxo, P., Martinelli, L.A., Arbex, M.A., Zanobetti, A., & Braga, A.L.F. 2006. The impact of sugar cane-burning emissions on the respiratory system of children and the elderly. *Environmental Health Perspectives*, 114, (5) 725-729 available from: ISI:000237308500040
Ref ID: 248

Schwartz, J., Dockery, D.W., & Neas, L.M. 1996. Is daily mortality associated specifically with fine particles? *Journal of the Air & Waste Management Association*, 46, (10) 927-939
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Ostro, B.D. 1995. Fine particulate air pollution and mortality in two Southern California counties. *Environmental Research*, 70, (2) 98-104
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Perez, L., Tobias, A., Querol, X., Kunzli, N., Pey, J., Alastuey, A., Viana, M., Valero, N., Gonzalez-Cabre, M., & Sunyer, J. 2008. Coarse Particles From Saharan Dust and Daily Mortality.

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Dockery, D.W., Schwartz, J., & Spengler, J.D. 1992. Air pollution and daily mortality: associations with particulates and acid aerosols. *Environmental Research*, 59, (2) 362-373
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Ueda, K., Nitta, H., & Ono, M. 2009. Effects of fine particulate matter on daily mortality for specific heart diseases in Japan. *Circulation Journal*, 73, (7) 1248-1254 available from: ISI:000267584400016
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Peng, R.D., Chang, H.H., Bell, M.L., McDermott, A., Zeger, S.L., Samet, J.M., & Dominici, F. 2008. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among medicare patients. *Jama-Journal of the American Medical Association*, 299, (18) 2172-2179 available from: ISI:000255790000024
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Ref ID: 889

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Mar, T.F., Norris, G.A., Koenig, J.Q., & Larson, T.V. 2000. Associations between air pollution and mortality in Phoenix, 1995- 1997. *Environmental Health Perspectives*, 108, 347-353
Ref ID: 1120

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Ref ID: 1181

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Ref ID: 1182

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Ref ID: 1196

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Table S3 Meta-analysis results for cause-specific mortality by WHO region and overall

WHO Region	All[a] (SC/MC)	Selected[b] (SC/MC	RE (95% CI)[c]	I^2 (%)[d]
Ischaemic Heart Disease				
AMR A	1/2	1/1	1.27 (0.60, 1.94)	90
EUR A	2/0	2/0	5.90 (3.88, 7.95)	
WPR A	0/1	0/1	5.40 (0.20, 10.87)	
Summary[e]	-	2/2	3.36 (0.68, 6.10)	
Stroke				
AMR A	0/3	0/1	1.78 (0.96, 2.61)	50
EUR A	2/0	2/0	5.44 (1.52, 9.52)	
WPR A	1/0	1/0	1.30 (0.20, 2.41)	
Summary[e]	-	2/1	1.85 (0.74, 2.97)	
COPD (excl. Asthma)				
AMR A	2/1	1/1	1.81 (-0.57, 4.23)	72
EUR A	1/0	1/0	9.00 (5.11, 13.03)	
Summary[e]	-	2/1	2.86 (-0.12, 5.93)	

Notes: a - Numbers of single-city(SC)/multi-city (MC) estimates available from all studies and b-Numbers of single-city(SC)/multi-city (MC) estimates selected for meta-analysis (see estimate selection protocol in Methods section); c - Random effects summary estimate (95% confidence interval) per 10 μg/m^3; d -I^2 statistic for heterogeneity; e - Estimate numbers for 'Summary' refers to the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Region

Table S4 Meta-analysis results for ages 65+ yrs. for cardiovascular admissions by WHO region and overall

WHO Region	All[a] (SC/MC)	Selected[b] (SC/MC	RE (95% CI)[c]	I^2 (%)[d]
Cardiovascular				
AMR A	0/3	0/1	0.71 (0.45, 0.97)	
EUR A	2/1	2/1	1.91 (0.92, 2.91)	85
WPR A	2/1	0/1	3.46 (1.59, 5.36)	
Summary[e]	-	1/3	1.78 (0.48, 3.10)	
Cardiac				
AMR A	1/1	0/1	1.89 (1.34, 2.44)	72
EUR A	1/1	1/1	3.69 (0.31, 7.19)	
WPR A	1/1	0/1	5.08 (2.65, 7.56)	
Summary[e]	-	1/3	3.05 (1.64, 4.48)	
Ischaemic Heart Disease				
AMR A	3/2	1/1	0.47 (0.06, 0.89)	
EUR A	3/1	3/1	2.79 (-0.38, 6.07)	86
WPR A	1/1	0/1	7.26 (3.46, 11.21)	
Summary[e]	-	2/3	2.52 (0.53, 4.55)	
Stroke				
AMR A	2/1	1/1	0.81 (0.31, 1.31)	
EUR A	2/0	2/0	-1.58 (-3.59, 0.47)	79
WPR A	1/0	1/0	-3.06 (-6.31, 0.31)	
Summary[e]	-	3/1	-0.45 (-2.21, 1.33)	
Heart Failure				
AMR A	3/2	2/1	2.78 (-0.33, 5.98)	65
EUR A	1/0	1/0	3.58 (0.16, 7.11)	
WPR A	0/1	0/1	9.75 (4.81, 14.93)	
Summary[e]	-	2/2	4.39 (1.35, 7.53)	
Dysrhythmias				
AMR A	1/1	0/1	0.57 (-0.01, 1.15)	
EUR A	1/0	1/0	1.33 (-1.66, 4.40)	0
Summary[e]	-	1/1	0.60 (0.03, 1.17)	

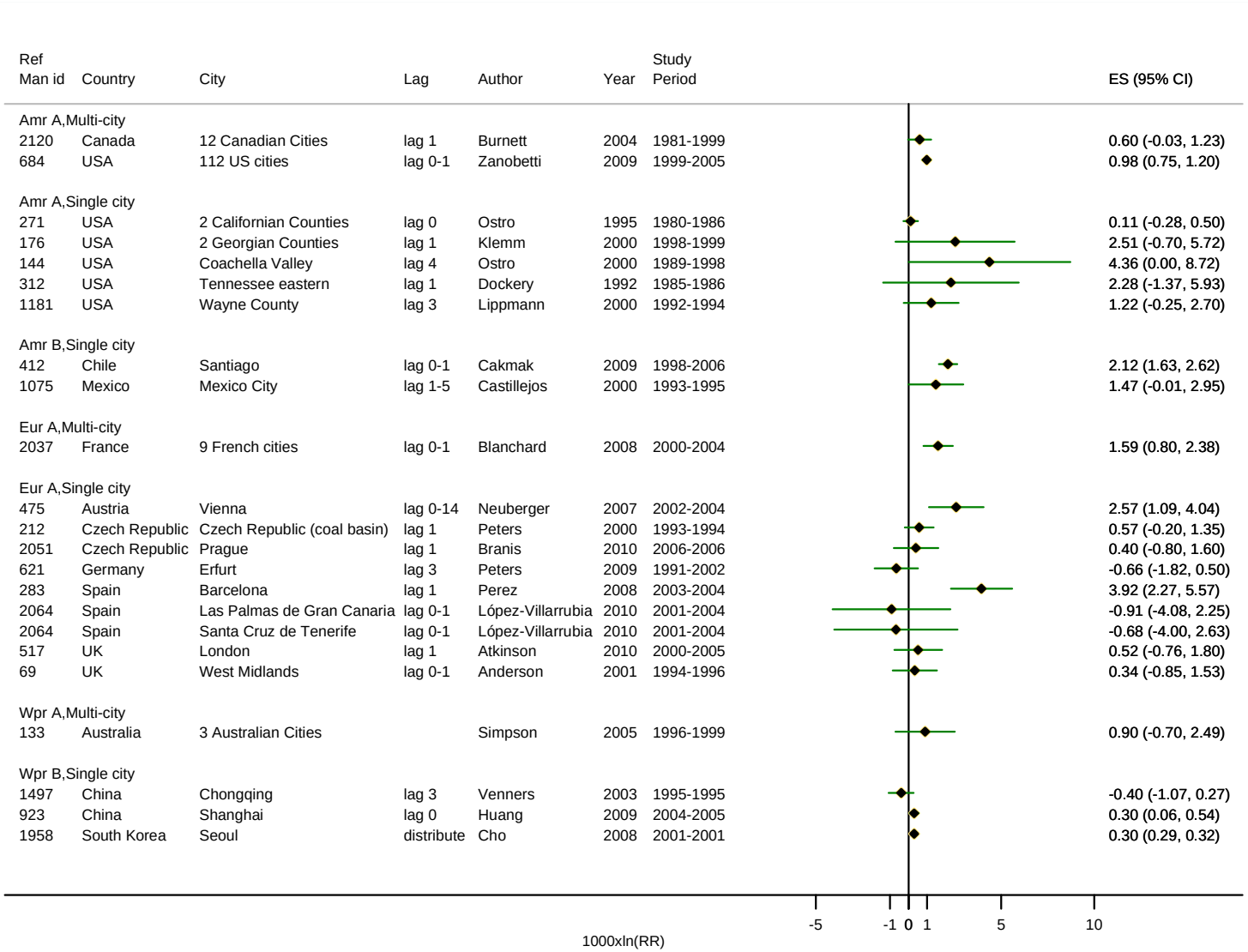
Notes: a - Numbers of single-city(SC)/multi-city (MC) estimates available from all studies and b-Numbers of single-city(SC)/multi-city (MC) estimates selected for meta-analysis (see estimate selection protocol in Methods section); c - Random effects summary estimate (95% confidence interval) per 10 $\mu g/m^3$; d -I^2 statistic for heterogeneity; e - Estimate numbers for 'Summary' refers to the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Region

Table S5 Meta-analysis results for ages 65+ years & 0-14 years for respiratory admissions by WHO region and overall

WHO Region	All[a] (SC/MC)	Selected[b] (SC/MC	RE (95% CI)[c]	I^2 (%)[d]
Respiratory, 65+ years				
AMR A	2/4	1/1	0.90 (0.39, 1.1)	
EUR A	4/1	4/1	0.99 (-0.90, 2.92)	80
WPR A	1/0	1/0	1.23 (-1.30, 3.82)	
Summary[e]	-	3/2	0.91 (0.43, 1.40)	
COPD (incl. asthma), 65+ years				
AMR A	1/1	1/1	7.48 (-6.91, 24.10)	4
EUR A	2/0	2/0	-0.49 (-3.80, 2.93)	
Summary[e]	-	2/1	1.85 (-2.07, 5.93)	
COPD (excl. asthma), 65+ years				
AMR A	3/0	2/0	1.90 (0.37, 3.46)	32
EUR A	2/0	2/0	3.93 (1.06, 6.89)	
Summary[e]	-	2/0	2.36 (1.0, 3.73)	
Lower Respiratory Infection, 65+ years				
AMR A	3/0	2/0	3.88 (1.62, 6.20)	
EUR A	2/0	2/0	4.05 (0.97, 7.22)	0
Summary[e]	-	2/0	3.94 (2.11, 5.80)	
Respiratory, 0-14 years				
AMR A	0/1	0/1	2.74 (1.14, 4.36)	
AMR B	2/0	2/0	10.84 (-2.54, 26.05)	76
EUR A	2/1	2/1	0.32 (-1.18, 1.84)	
WPR A	0/1	0/1	6.44 (2.65, 10.37)	
Summary[e]	-	2/3	2.45 (0.12, 4.85)	
Asthma, 0-14 years				
AMR A	4/1	3/1	-1.67 (-9.88, 7.28)	
EUR A	2/0	2/0	12.27 (-10.64, 41.06)	
WPR A	1/1	1/1	5.08 (2.28, 7.95)	33
WPR B	2/0	1/0	2.40 (1.30, 3.51)	
Summary[e]	-	4/2[c]	2.29 (-0.09, 4.73)	

Notes: a - Numbers of single-city(SC)/multi-city (MC) estimates available from all studies and b-Numbers of single-city(SC)/multi-city (MC) estimates selected for meta-analysis (see estimate selection protocol in Methods section); c - Random effects summary estimate (95% confidence interval) per 10 $\mu g/m^3$; d -I^2 statistic for heterogeneity; e - Estimate numbers for 'Summary' refers to the number of pooled (from single-city estimates) and multi-city estimates used to calculate the overall summary estimate across WHO Region

Figure S1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Lag
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Year
Study Period
ES (95% CI)
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684 USA 112 US cities lag 0-1 Zanobetti 2009 1999-2005 0.98 (0.75, 1.20)
Amr A,Single city
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176 USA 2 Georgian Counties lag 1 Klemm 2000 1998-1999 2.51 (-0.70, 5.72)
144 USA Coachella Valley lag 4 Ostro 2000 1989-1998 4.36 (0.00, 8.72)
312 USA Tennessee eastern lag 1 Dockery 1992 1985-1986 2.28 (-1.37, 5.93)
1181 USA Wayne County lag 3 Lippmann 2000 1992-1994 1.22 (-0.25, 2.70)
Amr B,Single city
412 Chile Santiago lag 0-1 Cakmak 2009 1998-2006 2.12 (1.63, 2.62)
1075 Mexico Mexico City lag 1-5 Castillejos 2000 1993-1995 1.47 (-0.01, 2.95)
Eur A,Multi-city
2037 France 9 French cities lag 0-1 Blanchard 2008 2000-2004 1.59 (0.80, 2.38)
Eur A,Single city
475 Austria Vienna lag 0-14 Neuberger 2007 2002-2004 2.57 (1.09, 4.04)
212 Czech Republic Czech Republic (coal basin) lag 1 Peters 2000 1993-1994 0.57 (-0.20, 1.35)
2051 Czech Republic Prague lag 1 Branis 2010 2006-2006 0.40 (-0.80, 1.60)
621 Germany Erfurt lag 3 Peters 2009 1991-2002 -0.66 (-1.82, 0.50)
283 Spain Barcelona lag 1 Perez 2008 2003-2004 3.92 (2.27, 5.57)
2064 Spain Las Palmas de Gran Canaria lag 0-1 López-Villarrubia 2010 2001-2004 -0.91 (-4.08, 2.25)
2064 Spain Santa Cruz de Tenerife lag 0-1 López-Villarrubia 2010 2001-2004 -0.68 (-4.00, 2.63)
517 UK London lag 1 Atkinson 2010 2000-2005 0.52 (-0.76, 1.80)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 0.34 (-0.85, 1.53)
Wpr A,Multi-city
133 Australia 3 Australian Cities Simpson 2005 1996-1999 0.90 (-0.70, 2.49)
Wpr B,Single city
1497 China Chongqing lag 3 Venners 2003 1995-1995 -0.40 (-1.07, 0.27)
923 China Shanghai lag 0 Huang 2009 2004-2005 0.30 (0.06, 0.54)
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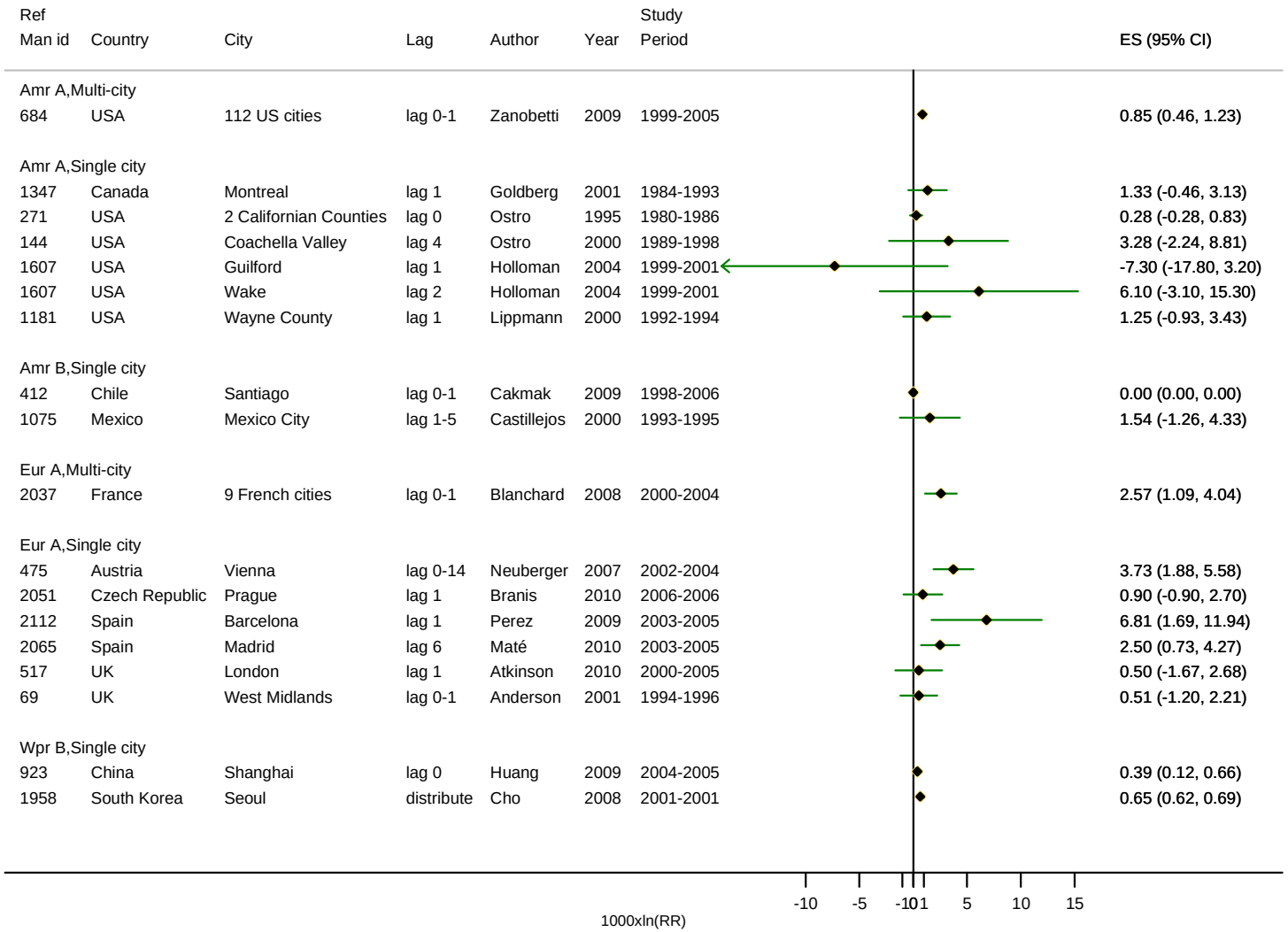
-1
0
1
5
10
1000xln(RR)

Figure S2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Author
Year
Study Period
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Amr A,Single city
1347 Canada Montreal lag 1 Goldberg 2001 1984-1993 1.33 (-0.46, 3.13)
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144 USA Coachella Valley lag 4 Ostro 2000 1989-1998 3.28 (-2.24, 8.81)
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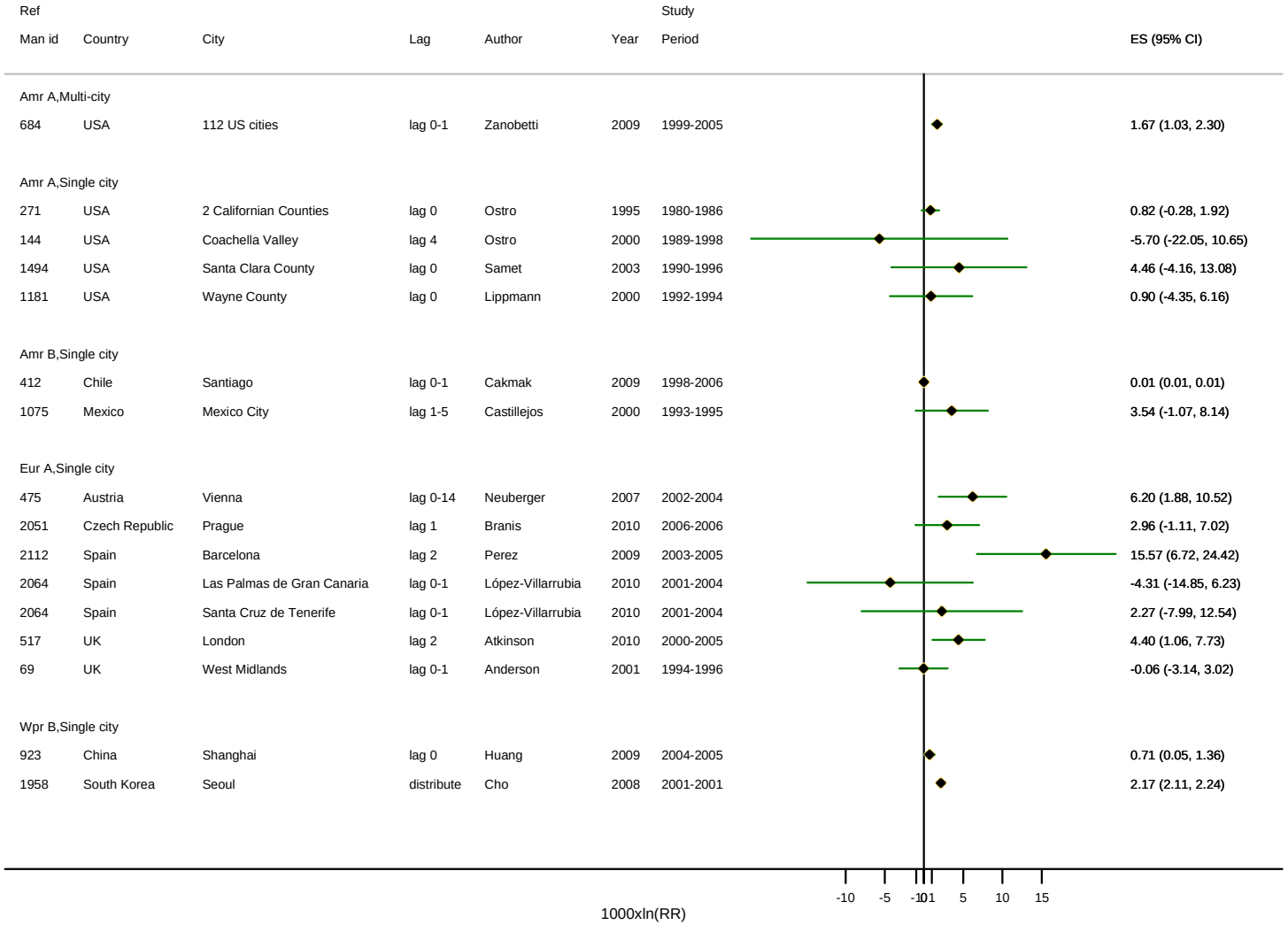
1607 USA Wake lag 2 Holloman 2004 1999-2001 6.10 (-3.10, 15.30)
1181 USA Wayne County lag 1 Lippmann 2000 1992-1994 1.25 (-0.93, 3.43)
Amr B,Single city
412 Chile Santiago lag 0-1 Cakmak 2009 1998-2006 0.00 (0.00, 0.00)
1075 Mexico Mexico City lag 1-5 Castillejos 2000 1993-1995 1.54 (-1.26, 4.33)
Eur A,Multi-city
2037 France 9 French cities lag 0-1 Blanchard 2008 2000-2004 2.57 (1.09, 4.04)
Eur A,Single city
475 Austria Vienna lag 0-14 Neuberger 2007 2002-2004 3.73 (1.88, 5.58)
2051 Czech Republic Prague lag 1 Branis 2010 2006-2006 0.90 (-0.90, 2.70)
2112 Spain Barcelona lag 1 Perez 2009 2003-2005 6.81 (1.69, 11.94)
2065 Spain Madrid lag 6 Maté 2010 2003-2005 2.50 (0.73, 4.27)
517 UK London lag 1 Atkinson 2010 2000-2005 0.50 (-1.67, 2.68)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 0.51 (-1.20, 2.21)
Wpr B,Single city
923 China Shanghai lag 0 Huang 2009 2004-2005 0.39 (0.12, 0.66)
1958 South Korea Seoul distribute Cho 2008 2001-2001 0.65 (0.62, 0.69)
-10
-5
-1
0
1
5
10
15
1000xln(RR)

Figure S3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ES (95% CI)
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Amr A,Single city
271 USA 2 Californian Counties lag 0 Ostro 1995 1980-1986 0.82 (-0.28, 1.92)
144 USA Coachella Valley lag 4 Ostro 2000 1989-1998 -5.70 (-22.05, 10.65)
1494 USA Santa Clara County lag 0 Samet 2003 1990-1996 4.46 (-4.16, 13.08)
1181 USA Wayne County lag 0 Lippmann 2000 1992-1994 0.90 (-4.35, 6.16)
Amr B,Single city
412 Chile Santiago lag 0-1 Cakmak 2009 1998-2006 0.01 (0.01, 0.01)
1075 Mexico Mexico City lag 1-5 Castillejos 2000 1993-1995 3.54 (-1.07, 8.14)
Eur A,Single city
475 Austria Vienna lag 0-14 Neuberger 2007 2002-2004 6.20 (1.88, 10.52)
2051 Czech Republic Prague lag 1 Branis 2010 2006-2006 2.96 (-1.11, 7.02)
2112 Spain Barcelona lag 2 Perez 2009 2003-2005 15.57 (6.72, 24.42)
2064 Spain Las Palmas de Gran Canaria lag 0-1 López-Villarrubia 2010 2001-2004 -4.31 (-14.85, 6.23)
2064 Spain Santa Cruz de Tenerife lag 0-1 López-Villarrubia 2010 2001-2004 2.27 (-7.99, 12.54)
517 UK London lag 2 Atkinson 2010 2000-2005 4.40 (1.06, 7.73)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 -0.06 (-3.14, 3.02)
Wpr B,Single city
923 China Shanghai lag 0 Huang 2009 2004-2005 0.71 (0.05, 1.36)
1958 South Korea Seoul distribute Cho 2008 2001-2001 2.17 (2.11, 2.24)
-10
-5
-1
0
1
5
10
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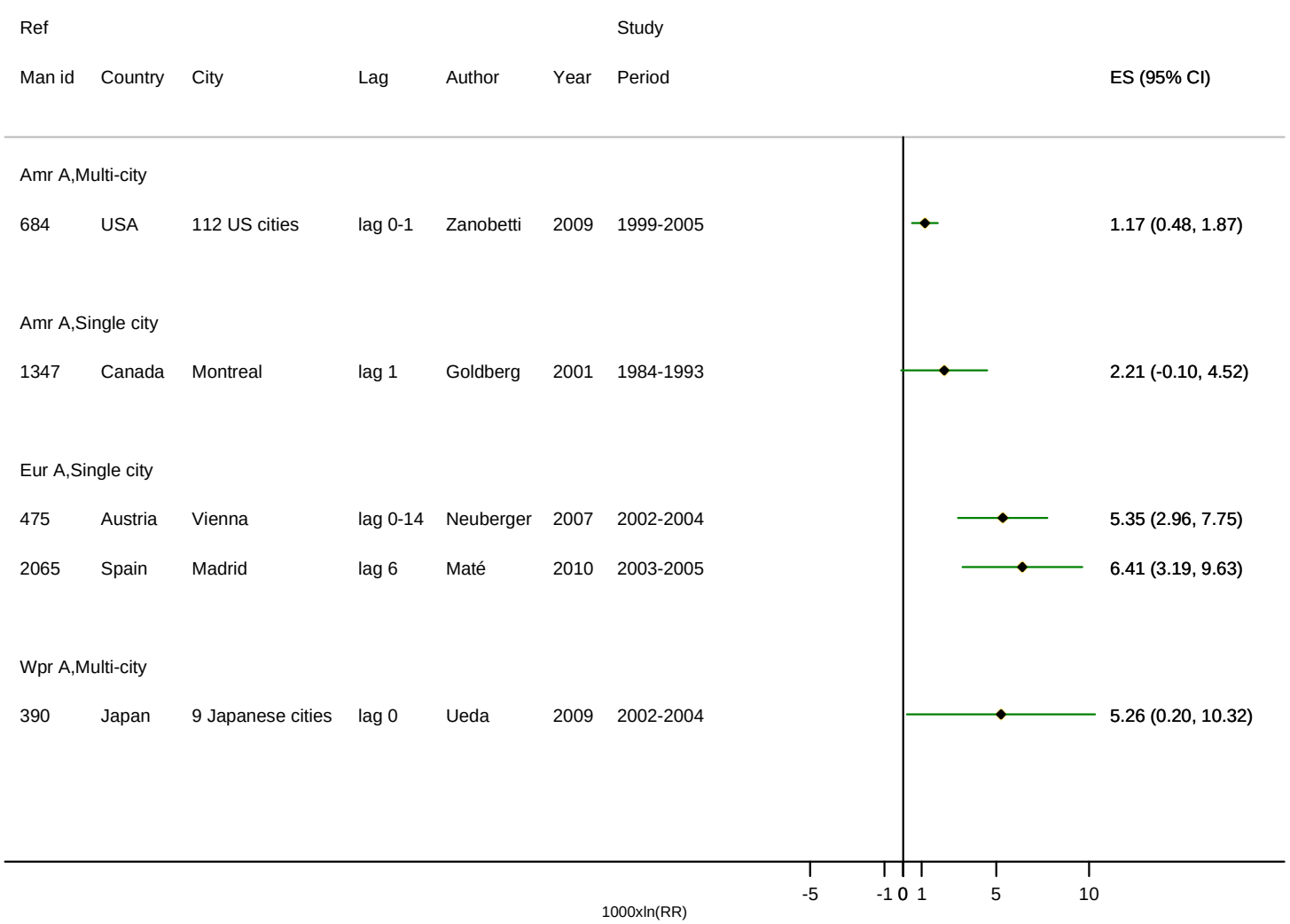
1000xln(RR)

Figure S4


Ref
Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
684
USA
112 US cities
lag 0-1
Zanobetti
2009
1999-2005
1.17 (0.48, 1.87)
Amr A,Single city
1347
Canada
Montreal
lag 1
Goldberg
2001
1984-1993
2.21 (-0.10, 4.52)
Eur A,Single city
475
Austria
Vienna
lag 0-14
Neuberger
2007
2002-2004
5.35 (2.96, 7.75)
2065
Spain
Madrid
lag 6
Maté
2010
2003-2005
6.41 (3.19, 9.63)
Wpr A,Multi-city
390
Japan
9 Japanese cities
lag 0
Ueda
2009
2002-2004
5.26 (0.20, 10.32)
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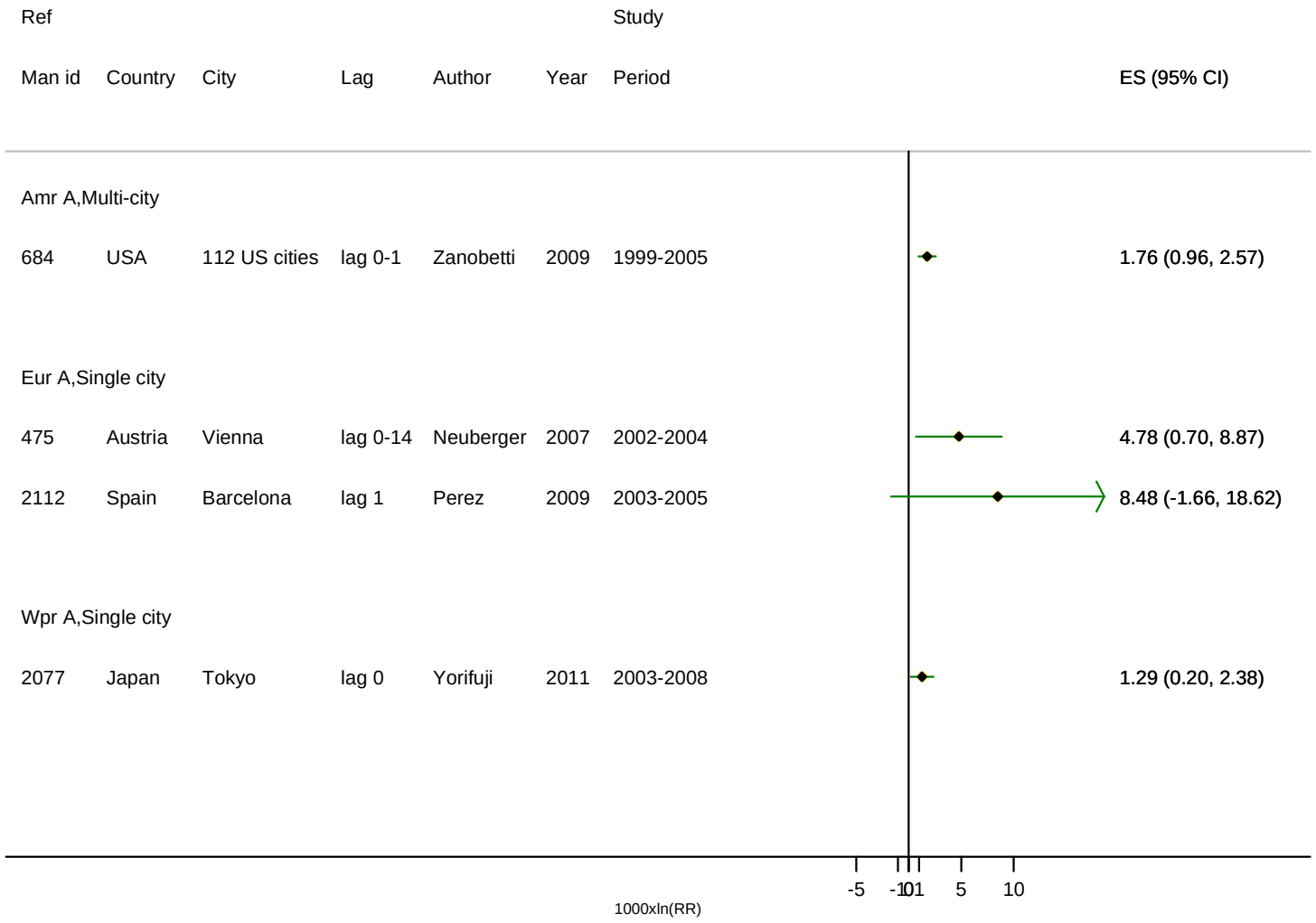
0
1
5
10
1000xln(RR)

Figure S5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Author
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USA
112 US cities
lag 0-1
Zanobetti
2009
1999-2005
1.76 (0.96, 2.57)
Eur A,Single city
475
Austria
Vienna
lag 0-14
Neuberger
2007
2002-2004
4.78 (0.70, 8.87)
2112
Spain
Barcelona
lag 1
Perez
2009
2003-2005
8.48 (-1.66, 18.62)
Wpr A,Single city
2077
Japan
Tokyo
lag 0
Yorifuji
2011
2003-2008
1.29 (0.20, 2.38)
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-1
0
1
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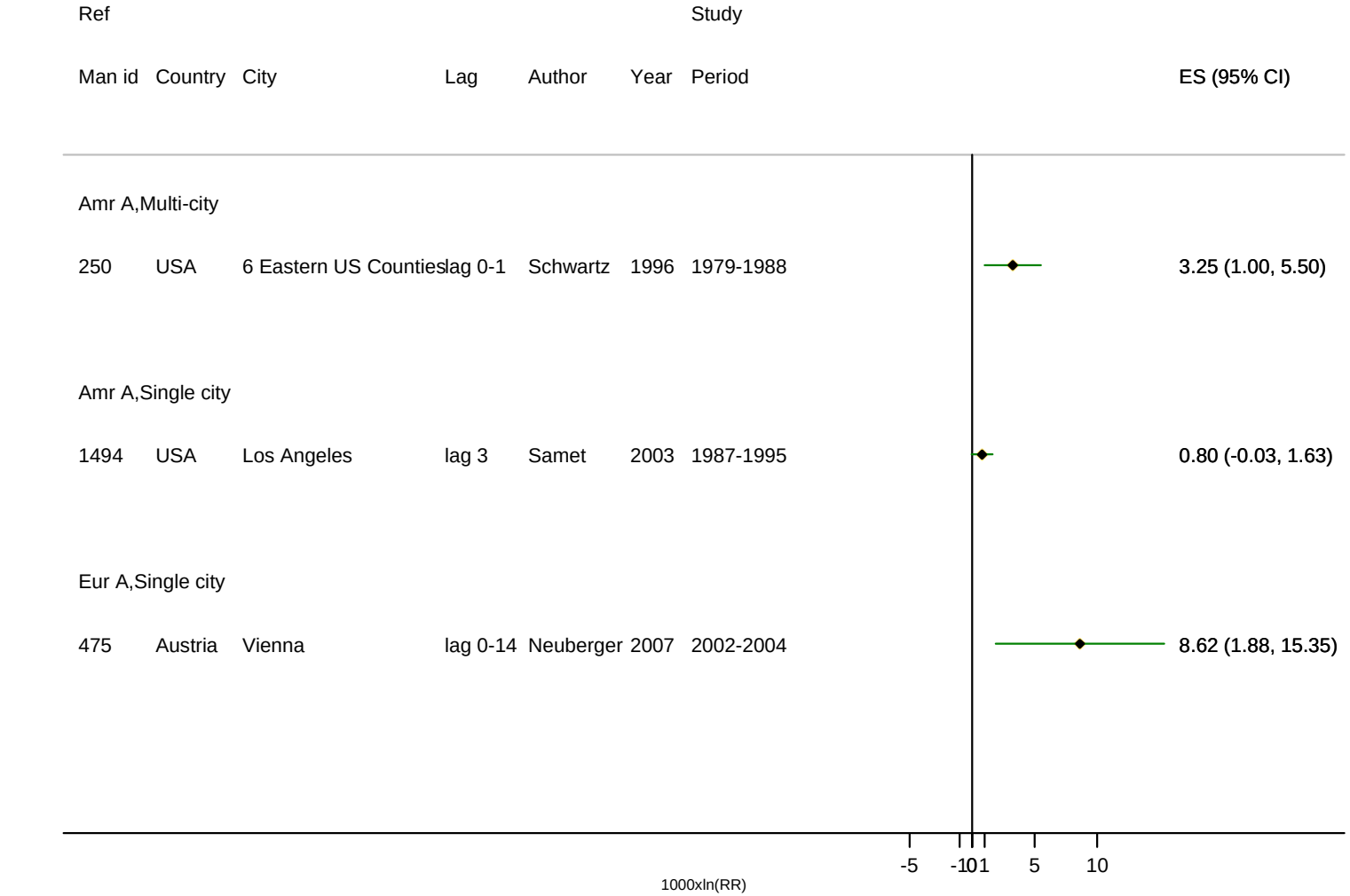
10
1000xln(RR)

Figure S6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Study
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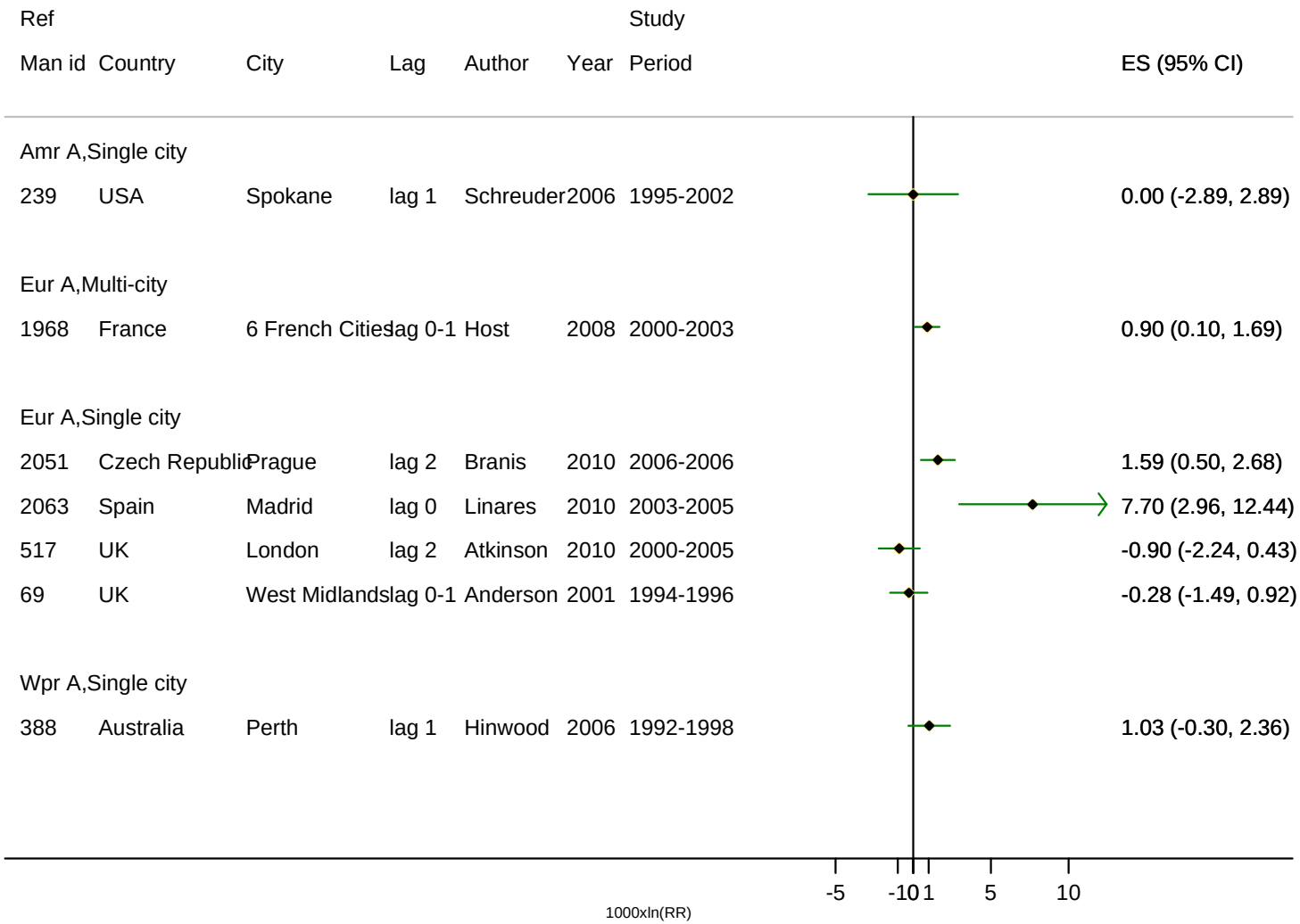
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
250
USA
6 Eastern US Counties
lag 0-1
Schwartz
1996
1979-1988
3.25 (1.00, 5.50)
Amr A,Single city
1494
USA
Los Angeles
lag 3
Samet
2003
1987-1995
0.80 (-0.03, 1.63)
Eur A,Single city
475
Austria
Vienna
lag 0-14
Neuberger
2007
2002-2004
8.62 (1.88, 15.35)
-5
-1
0
1
5
10
1000xln(RR)

Figure S7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City
Lag
Author
Year
Study Period
ES (95% CI)
Amr A,Single city
239 USA Spokane lag 1 Schreuder 2006 1995-2002 0.00 (-2.89, 2.89)
Eur A,Multi-city
1968 France 6 French Cities lag 0-1 Host 2008 2000-2003 0.90 (0.10, 1.69)
Eur A,Single city
2051 Czech Republic Prague lag 2 Branis 2010 2006-2006 1.59 (0.50, 2.68)
2063 Spain Madrid lag 0 Linares 2010 2003-2005 7.70 (2.96, 12.44)
517 UK London lag 2 Atkinson 2010 2000-2005 -0.90 (-2.24, 0.43)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 -0.28 (-1.49, 0.92)
Wpr A,Single city
388 Australia Perth lag 1 Hinwood 2006 1992-1998 1.03 (-0.30, 2.36)
-5
-10
1
5
10
1000xln(RR)

Figure S8

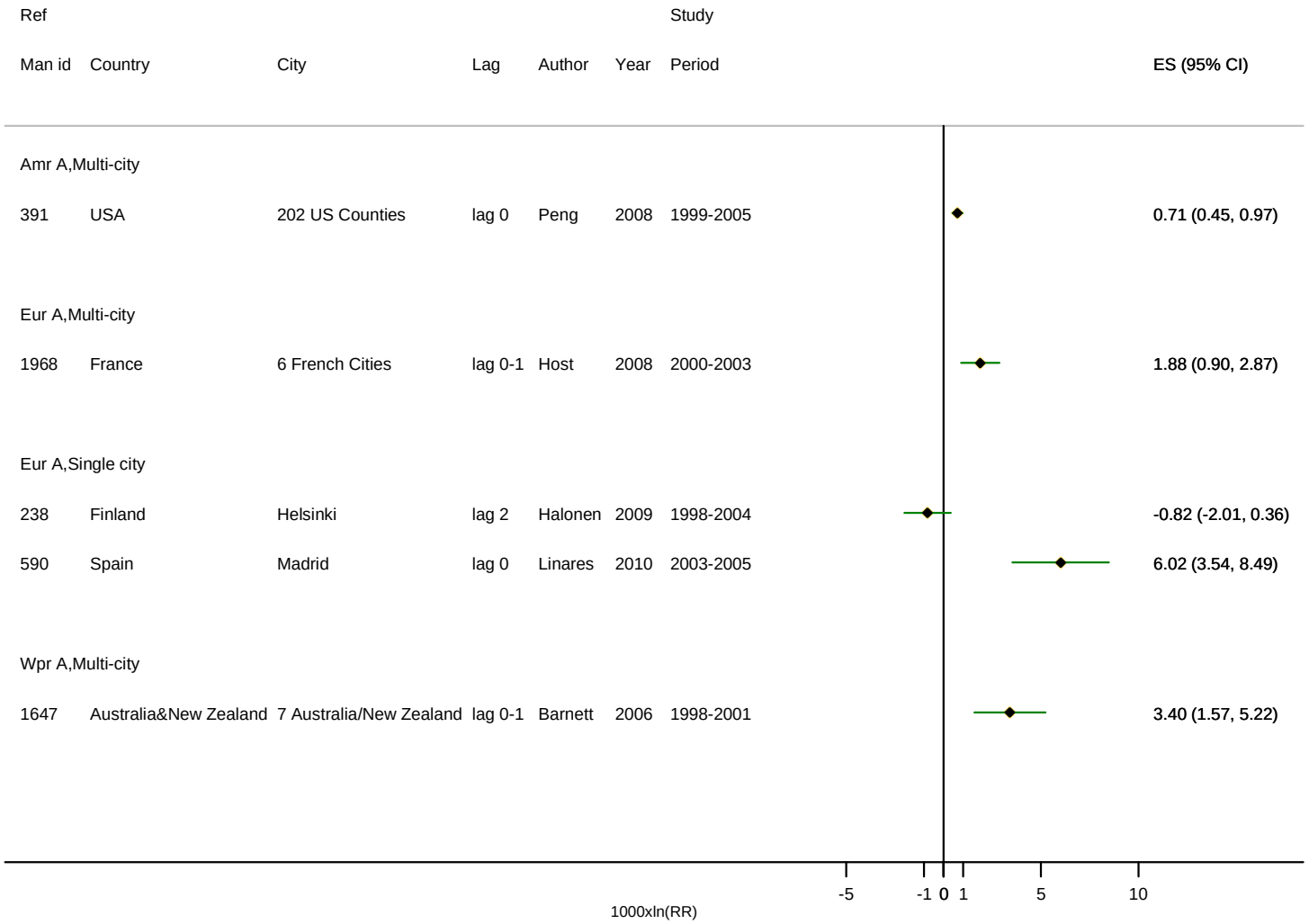
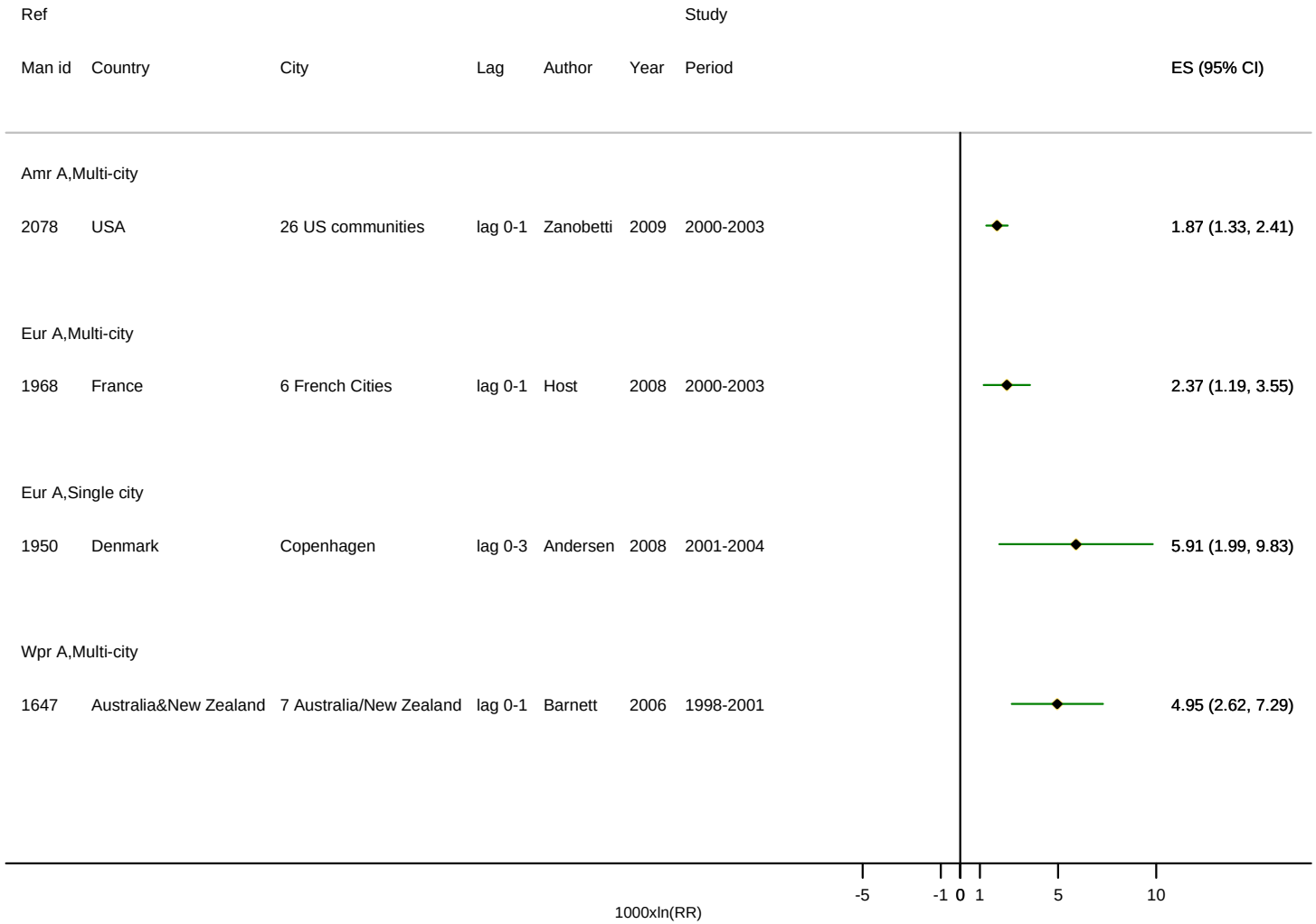

Ref
Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
391
USA
202 US Counties
lag 0
Peng
2008
1999-2005
0.71 (0.45, 0.97)
Eur A,Multi-city
1968
France
6 French Cities
lag 0-1
Host
2008
2000-2003
1.88 (0.90, 2.87)
Eur A,Single city
238
Finland
Helsinki
lag 2
Halonen
2009
1998-2004
-0.82 (-2.01, 0.36)
590
Spain
Madrid
lag 0
Linares
2010
2003-2005
6.02 (3.54, 8.49)
Wpr A,Multi-city
1647
Australia&New Zealand
7 Australia/New Zealand
lag 0-1
Barnett
2006
1998-2001
3.40 (1.57, 5.22)
-5
-1
0
1
5
10
1000xln(RR)

Figure S9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Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
2078
USA
26 US communities
lag 0-1
Zanobetti
2009
2000-2003
1.87 (1.33, 2.41)
Eur A,Multi-city
1968
France
6 French Cities
lag 0-1
Host
2008
2000-2003
2.37 (1.19, 3.55)
Eur A,Single city
1950
Denmark
Copenhagen
lag 0-3
Andersen
2008
2001-2004
5.91 (1.99, 9.83)
Wpr A,Multi-city
1647
Australia&New Zealand
7 Australia/New Zealand
lag 0-1
Barnett
2006
1998-2001
4.95 (2.62, 7.29)
-5
-1
0
1
5
10
1000xln(RR)

Figure S10

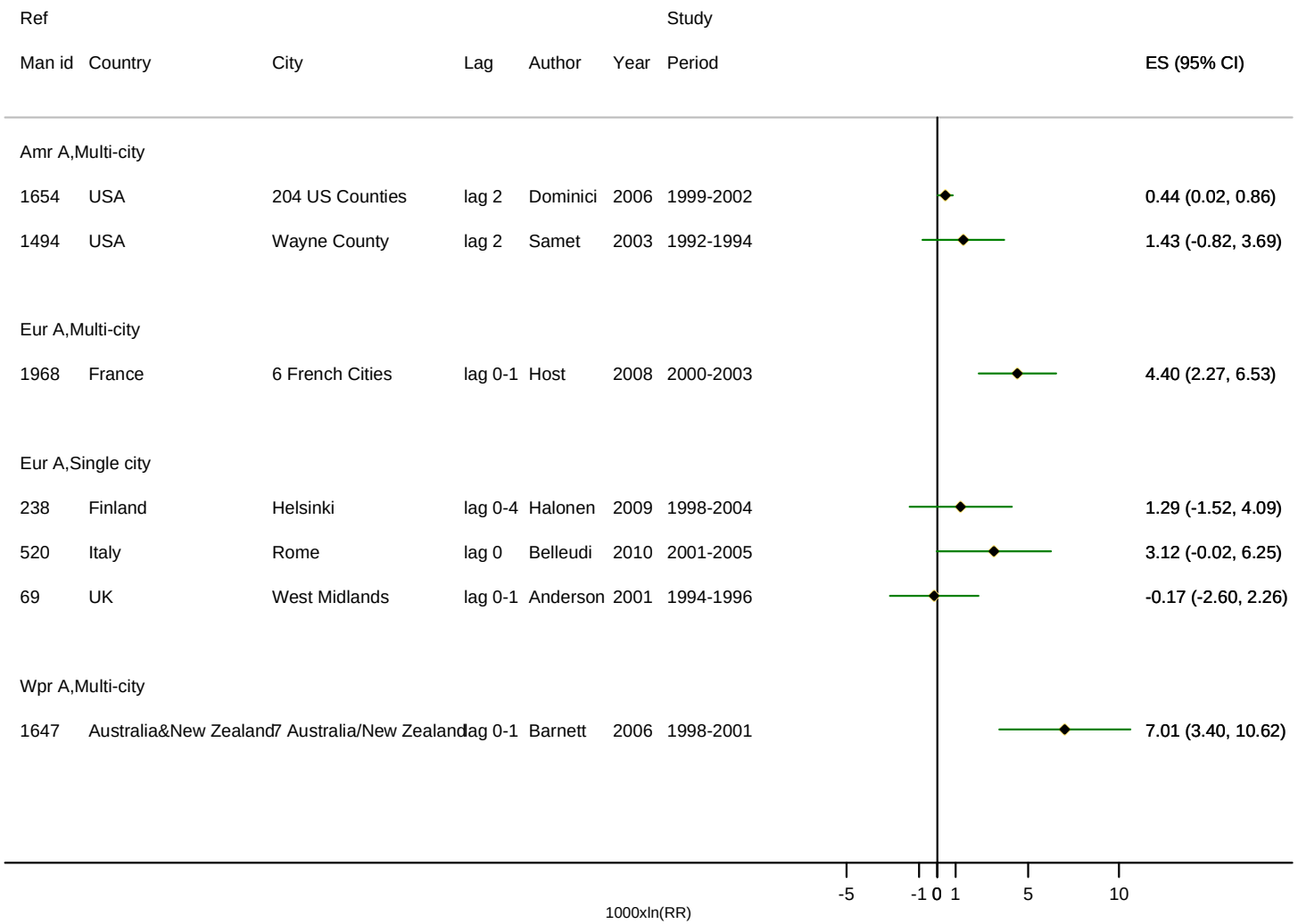

Ref
Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
1654 USA 204 US Counties lag 2 Dominici 2006 1999-2002 0.44 (0.02, 0.86)
1494 USA Wayne County lag 2 Samet 2003 1992-1994 1.43 (-0.82, 3.69)
Eur A,Multi-city
1968 France 6 French Cities lag 0-1 Host 2008 2000-2003 4.40 (2.27, 6.53)
Eur A,Single city
238 Finland Helsinki lag 0-4 Halonen 2009 1998-2004 1.29 (-1.52, 4.09)
520 Italy Rome lag 0 Belleudi 2010 2001-2005 3.12 (-0.02, 6.25)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 -0.17 (-2.60, 2.26)
Wpr A,Multi-city
1647 Australia&New Zealand 7 Australia/New Zealand lag 0-1 Barnett 2006 1998-2001 7.01 (3.40, 10.62)
-5
-1
0
1
5
10
1000xln(RR)

Figure S11

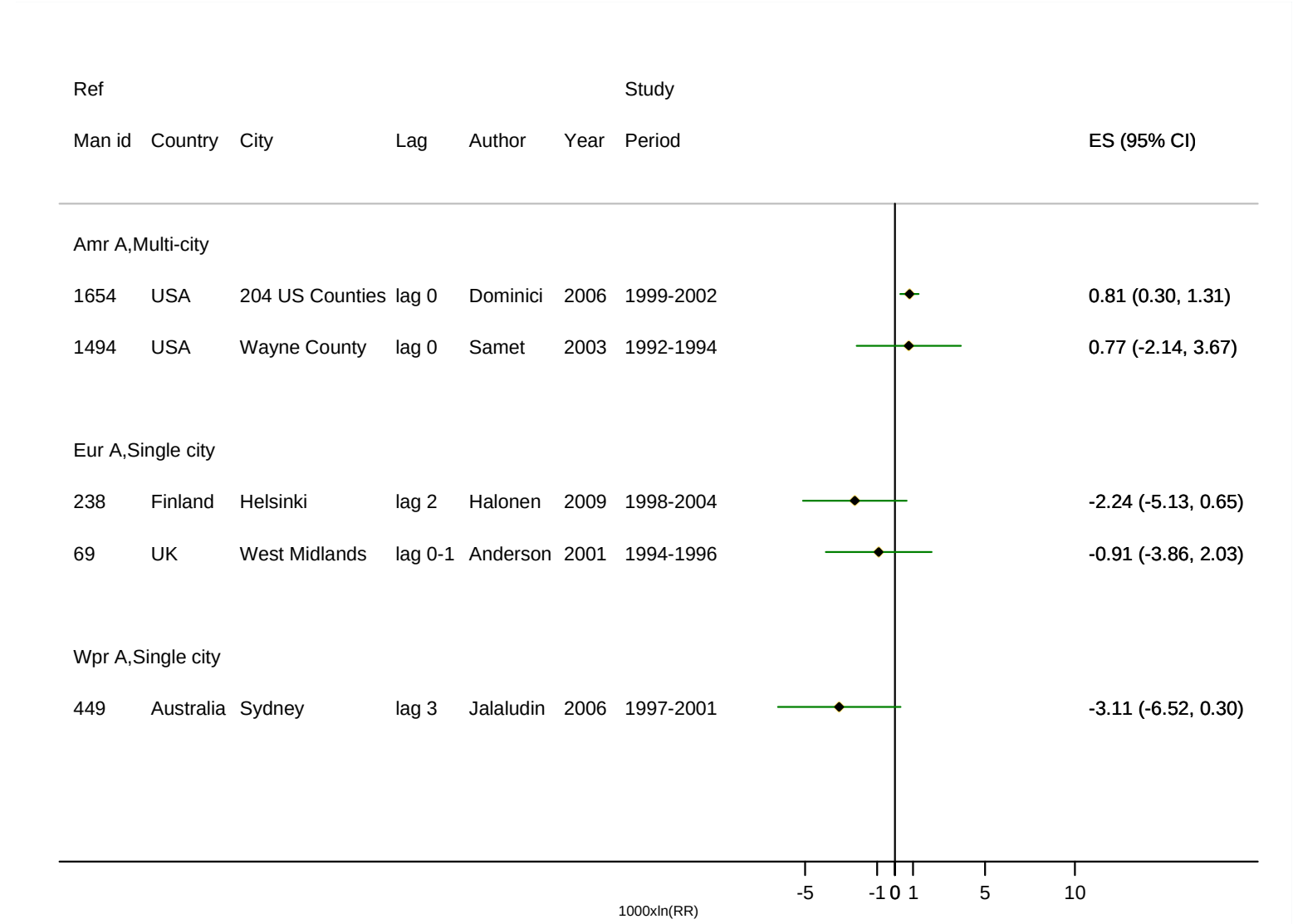
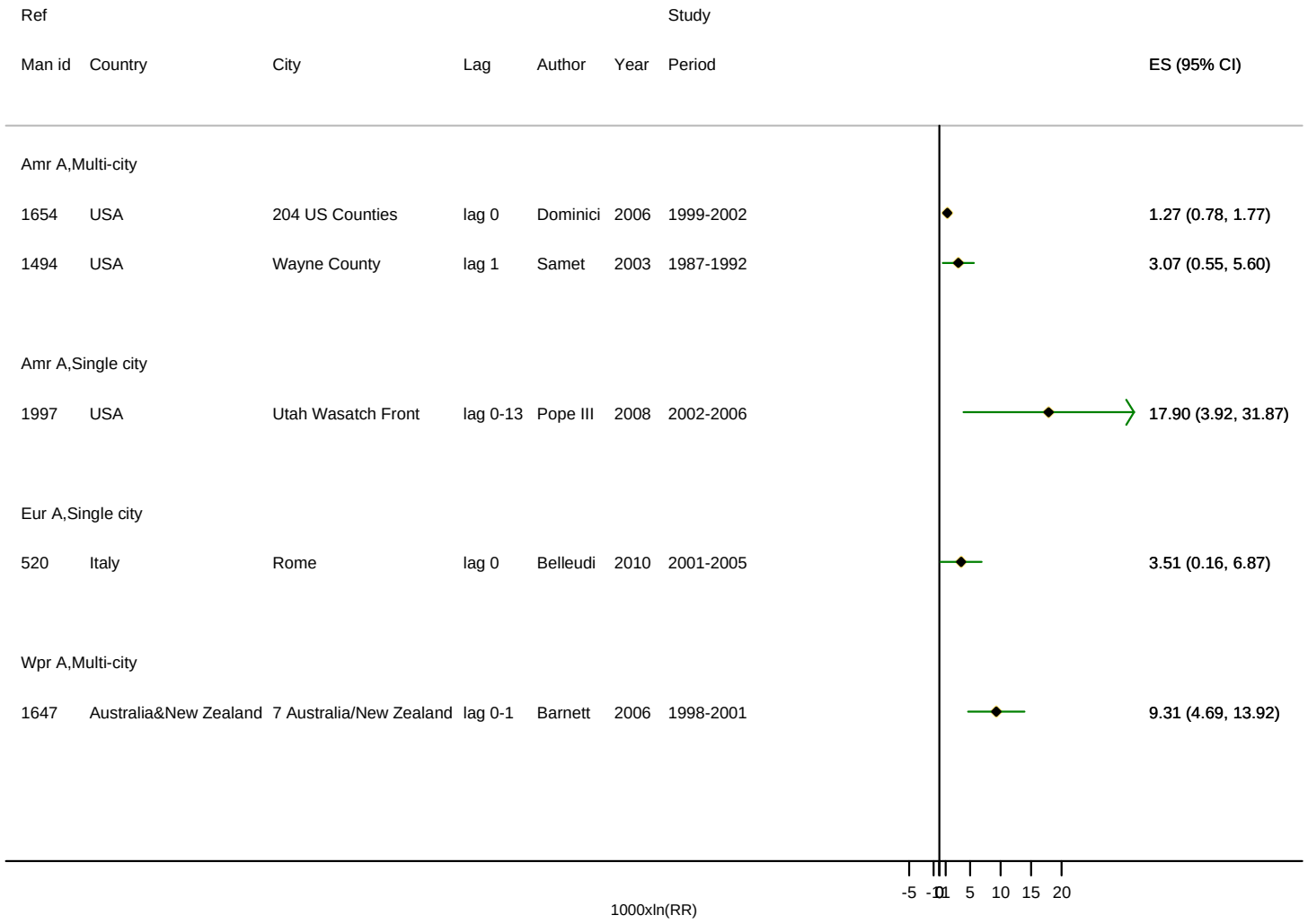

Ref
Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
1654 USA 204 US Counties lag 0 Dominici 2006 1999-2002 0.81 (0.30, 1.31)
1494 USA Wayne County lag 0 Samet 2003 1992-1994 0.77 (-2.14, 3.67)
Eur A,Single city
238 Finland Helsinki lag 2 Halonen 2009 1998-2004 -2.24 (-5.13, 0.65)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 -0.91 (-3.86, 2.03)
Wpr A,Single city
449 Australia Sydney lag 3 Jalaludin 2006 1997-2001 -3.11 (-6.52, 0.30)
-5
-1
0
1
5
10
1000xln(RR)

Figure S12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Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
1654 USA 204 US Counties lag 0 Dominici 2006 1999-2002 1.27 (0.78, 1.77)
1494 USA Wayne County lag 1 Samet 2003 1987-1992 3.07 (0.55, 5.60)
Amr A,Single city
1997 USA Utah Wasatch Front lag 0-13 Pope III 2008 2002-2006 17.90 (3.92, 31.87)
Eur A,Single city
520 Italy Rome lag 0 Belleudi 2010 2001-2005 3.51 (0.16, 6.87)
Wpr A,Multi-city
1647 Australia&New Zealand 7 Australia/New Zealand lag 0-1 Barnett 2006 1998-2001 9.31 (4.69, 13.92)
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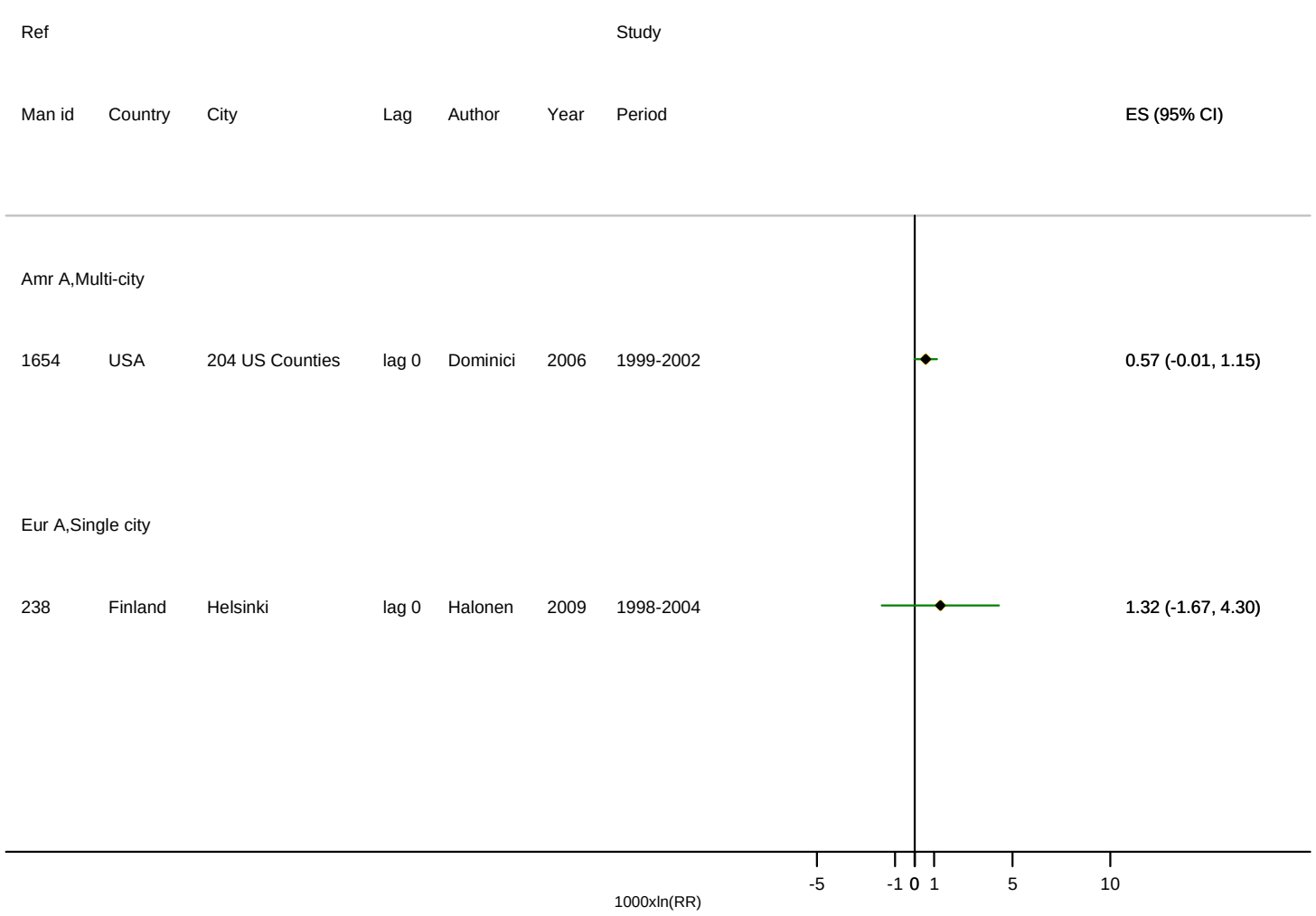
1000xln(RR)

Figure S13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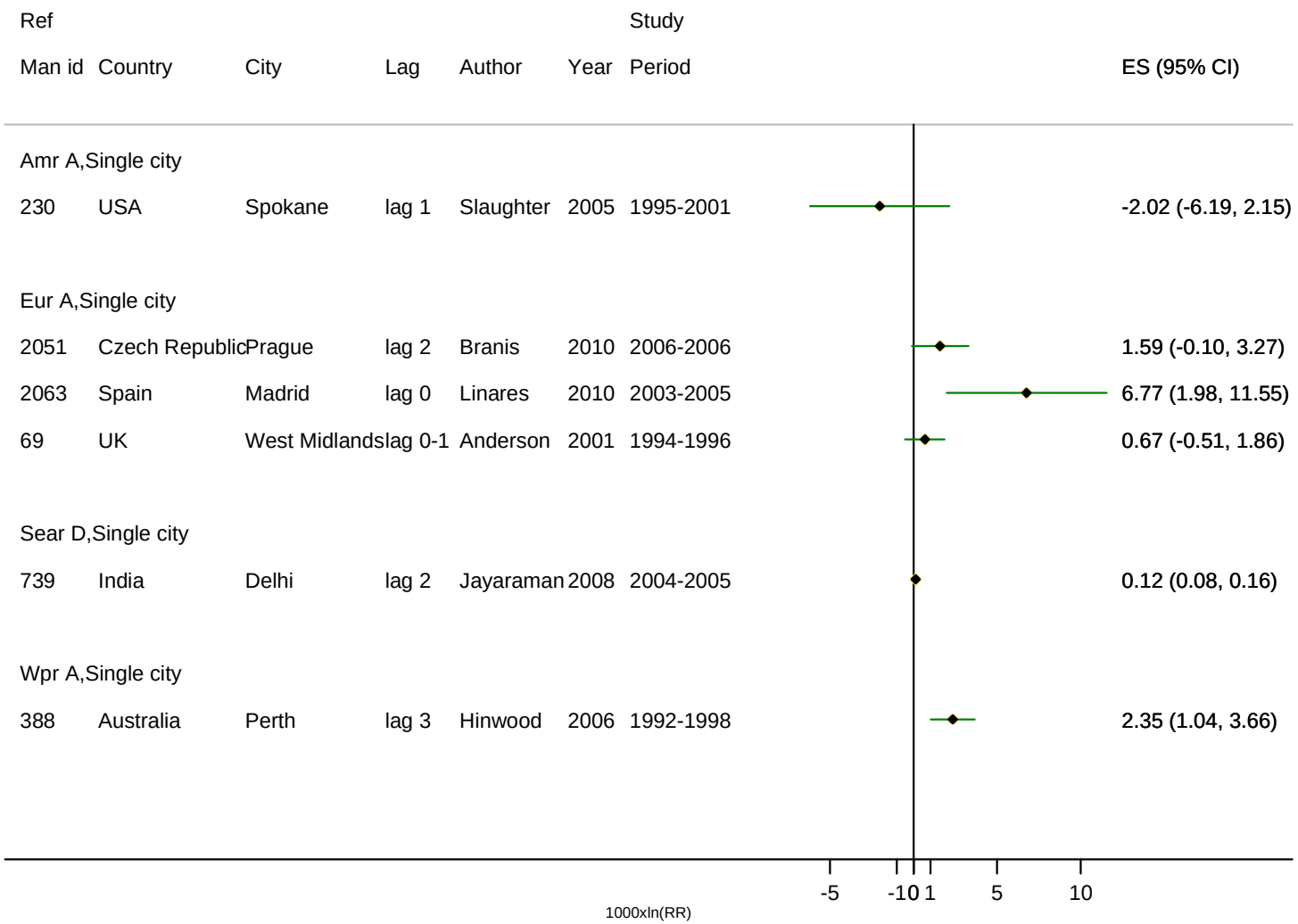
Study
Man id
Country
City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Multi-city
1654
USA
204 US Counties
lag 0
Dominici
2006
1999-2002
0.57 (-0.01, 1.15)
Eur A,Single city
238
Finland
Helsinki
lag 0
Halonen
2009
1998-2004
1.32 (-1.67, 4.30)
-5
-1
0
1
5
10
1000xln(RR)

Figure S14


Ref
Man id
Country
City
Lag
Author
Year
Study Period
ES (95% CI)
Amr A,Single city
230 USA Spokane lag 1 Slaughter 2005 1995-2001 -2.02 (-6.19, 2.15)
Eur A,Single city
2051 Czech Republic Prague lag 2 Branis 2010 2006-2006 1.59 (-0.10, 3.27)
2063 Spain Madrid lag 0 Linares 2010 2003-2005 6.77 (1.98, 11.55)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 0.67 (-0.51, 1.86)
Sear D,Single city
739 India Delhi lag 2 Jayaraman 2008 2004-2005 0.12 (0.08, 0.16)
Wpr A,Single city
388 Australia Perth lag 3 Hinwood 2006 1992-1998 2.35 (1.04, 3.66)
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-10
1
5
10
1000xln(RR)

Figure S15

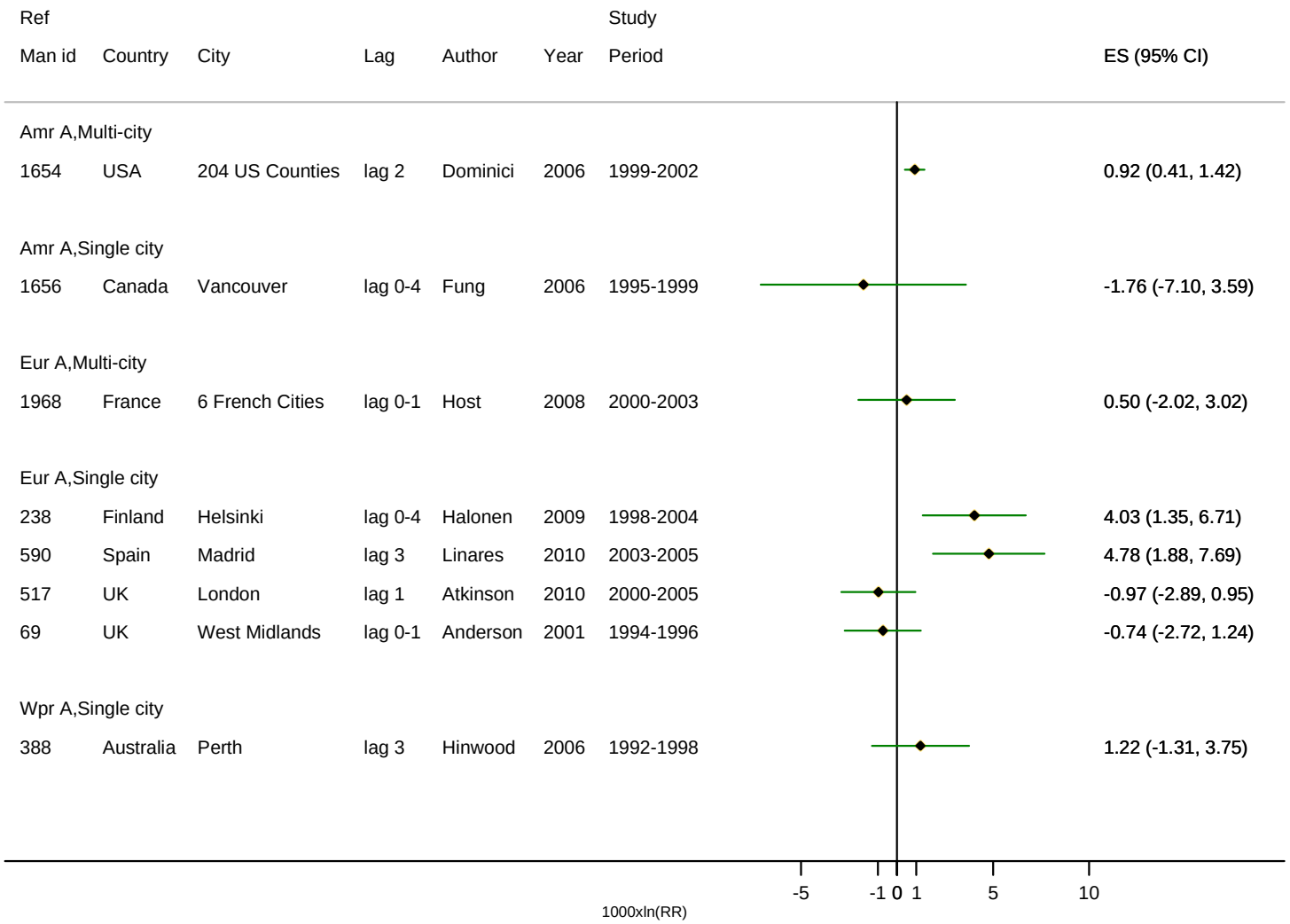
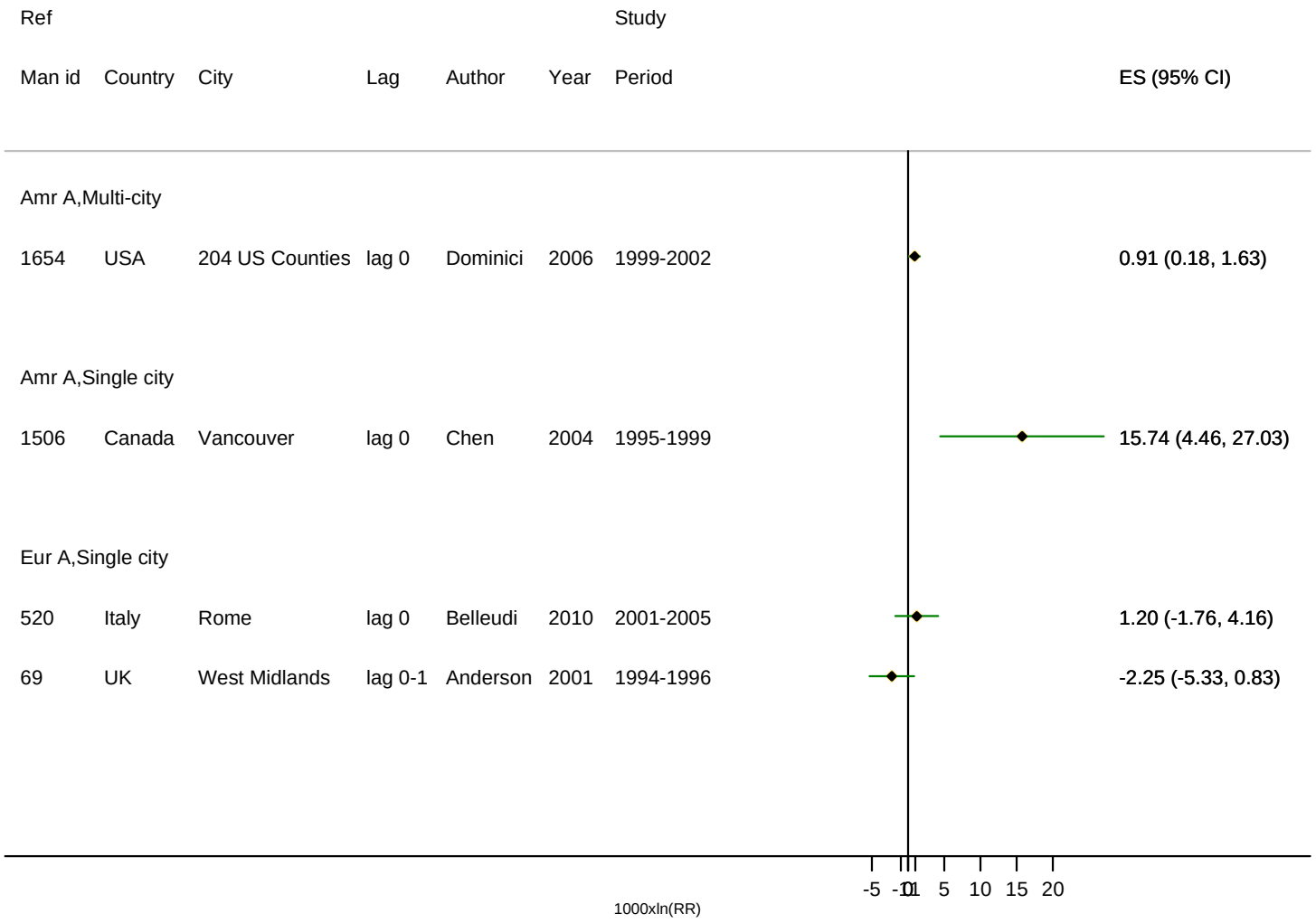

Ref
Man id
Country
City
Lag
Author
Year
Study Period
ES (95% CI)
Amr A,Multi-city
1654 USA 204 US Counties lag 2 Dominici 2006 1999-2002 0.92 (0.41, 1.42)
Amr A,Single city
1656 Canada Vancouver lag 0-4 Fung 2006 1995-1999 -1.76 (-7.10, 3.59)
Eur A,Multi-city
1968 France 6 French Cities lag 0-1 Host 2008 2000-2003 0.50 (-2.02, 3.02)
Eur A,Single city
238 Finland Helsinki lag 0-4 Halonen 2009 1998-2004 4.03 (1.35, 6.71)
590 Spain Madrid lag 3 Linares 2010 2003-2005 4.78 (1.88, 7.69)
517 UK London lag 1 Atkinson 2010 2000-2005 -0.97 (-2.89, 0.95)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 -0.74 (-2.72, 1.24)
Wpr A,Single city
388 Australia Perth lag 3 Hinwood 2006 1992-1998 1.22 (-1.31, 3.75)
-5
-1
0
1
5
10
1000xln(RR)

Figure S16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City
Lag
Author
Year
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Amr A,Multi-city
1654
USA
204 US Counties
lag 0
Dominici
2006
1999-2002
0.91 (0.18, 1.63)
Amr A,Single city
1506
Canada
Vancouver
lag 0
Chen
2004
1995-1999
15.74 (4.46, 27.03)
Eur A,Single city
520
Italy
Rome
lag 0
Belleudi
2010
2001-2005
1.20 (-1.76, 4.16)
69
UK
West Midlands
lag 0-1
Anderson
2001
1994-1996
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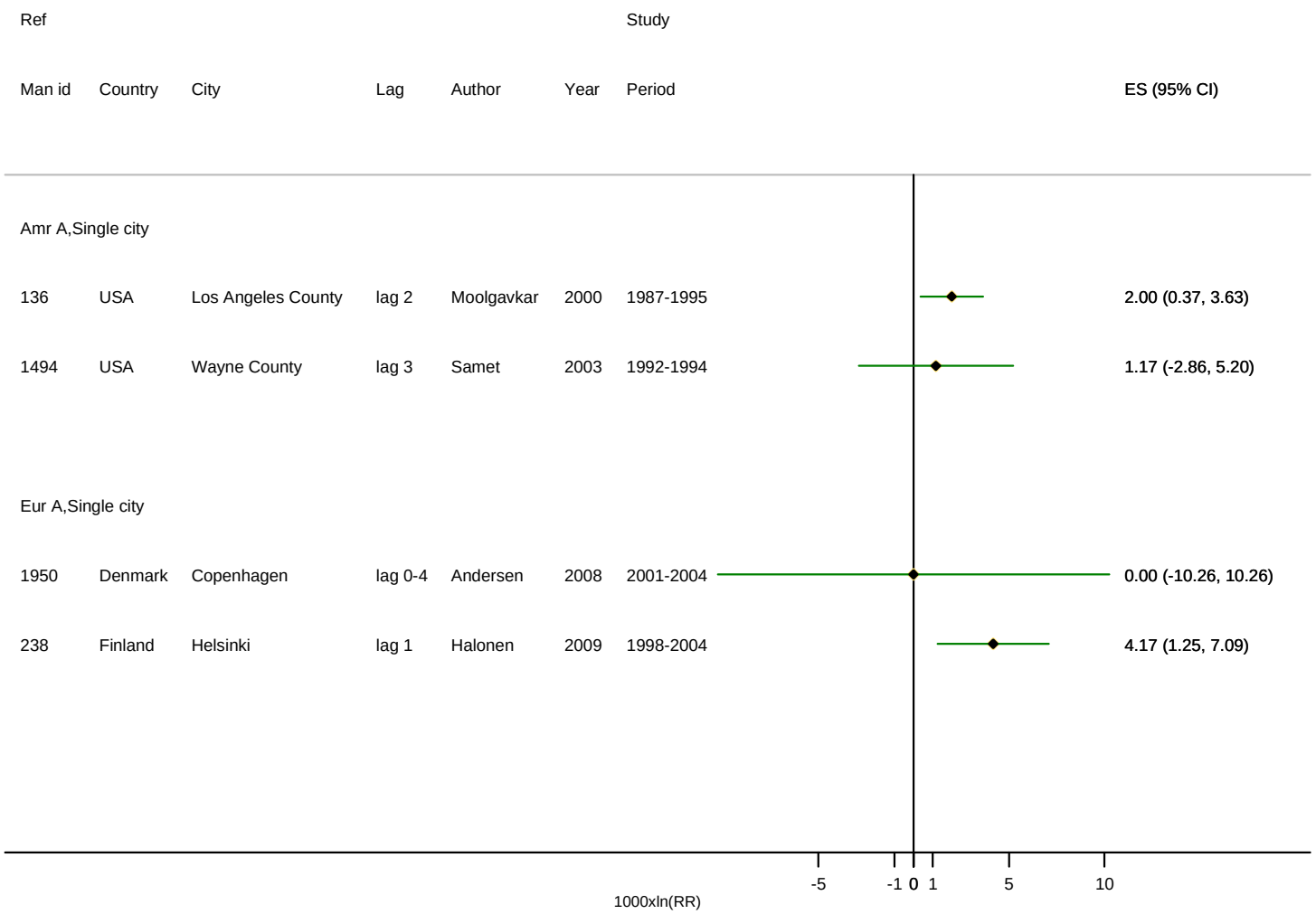
Figure S17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City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Single city
136
USA
Los Angeles County
lag 2
Moolgavkar
2000
1987-1995
2.00 (0.37, 3.63)
1494
USA
Wayne County
lag 3
Samet
2003
1992-1994
1.17 (-2.86, 5.20)
Eur A,Single city
1950
Denmark
Copenhagen
lag 0-4
Andersen
2008
2001-2004
0.00 (-10.26, 10.26)
238
Finland
Helsinki
lag 1
Halonen
2009
1998-2004
4.17 (1.25, 7.09)
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-1
0
1
5
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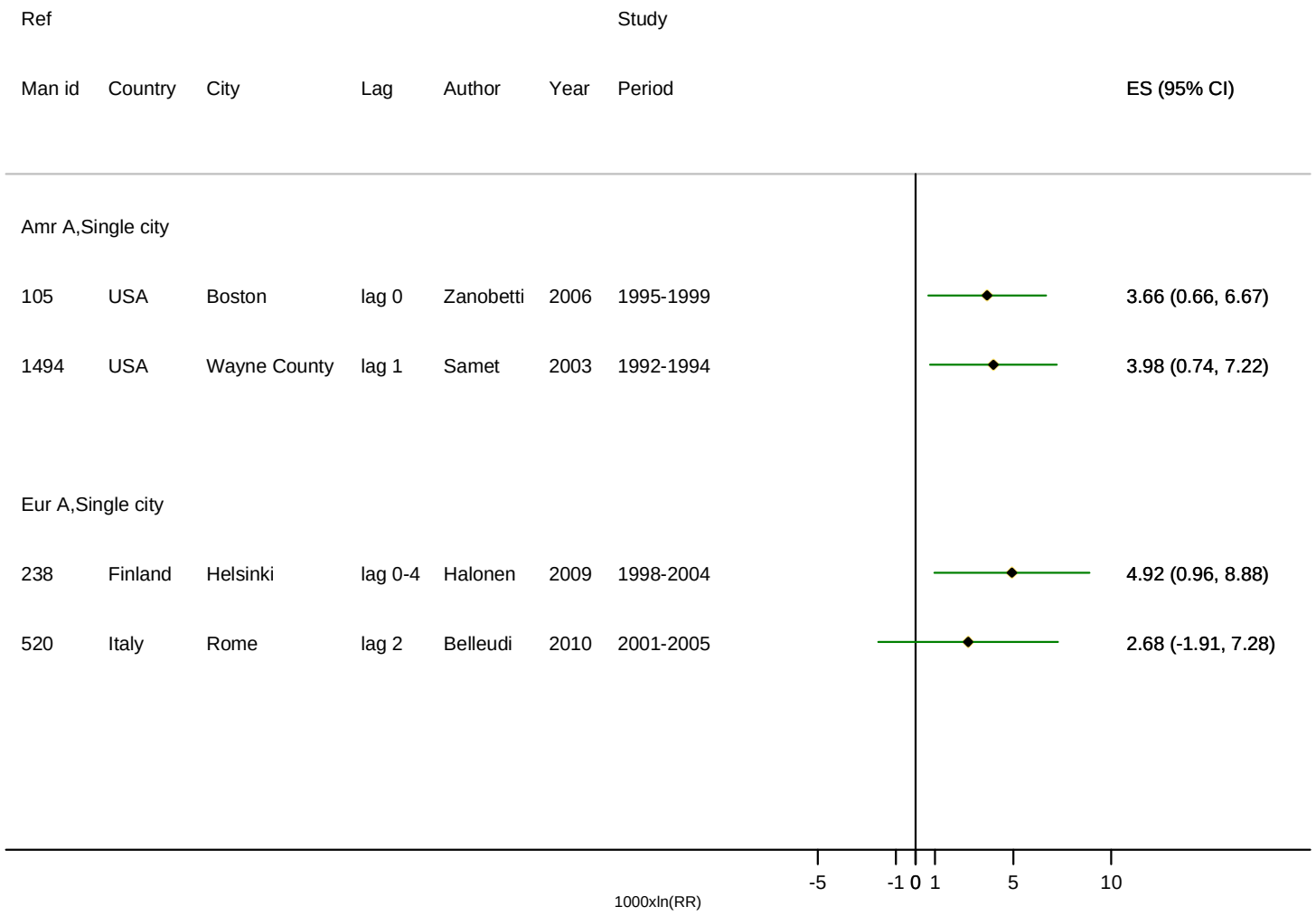
1000xln(RR)

Figure S18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City
Lag
Author
Year
Period
ES (95% CI)
Amr A,Single city
105 USA Boston lag 0 Zanobetti 2006 1995-1999 3.66 (0.66, 6.67)
1494 USA Wayne County lag 1 Samet 2003 1992-1994 3.98 (0.74, 7.22)
Eur A,Single city
238 Finland Helsinki lag 0-4 Halonen 2009 1998-2004 4.92 (0.96, 8.88)
520 Italy Rome lag 2 Belleudi 2010 2001-2005 2.68 (-1.91, 7.28)
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0
1
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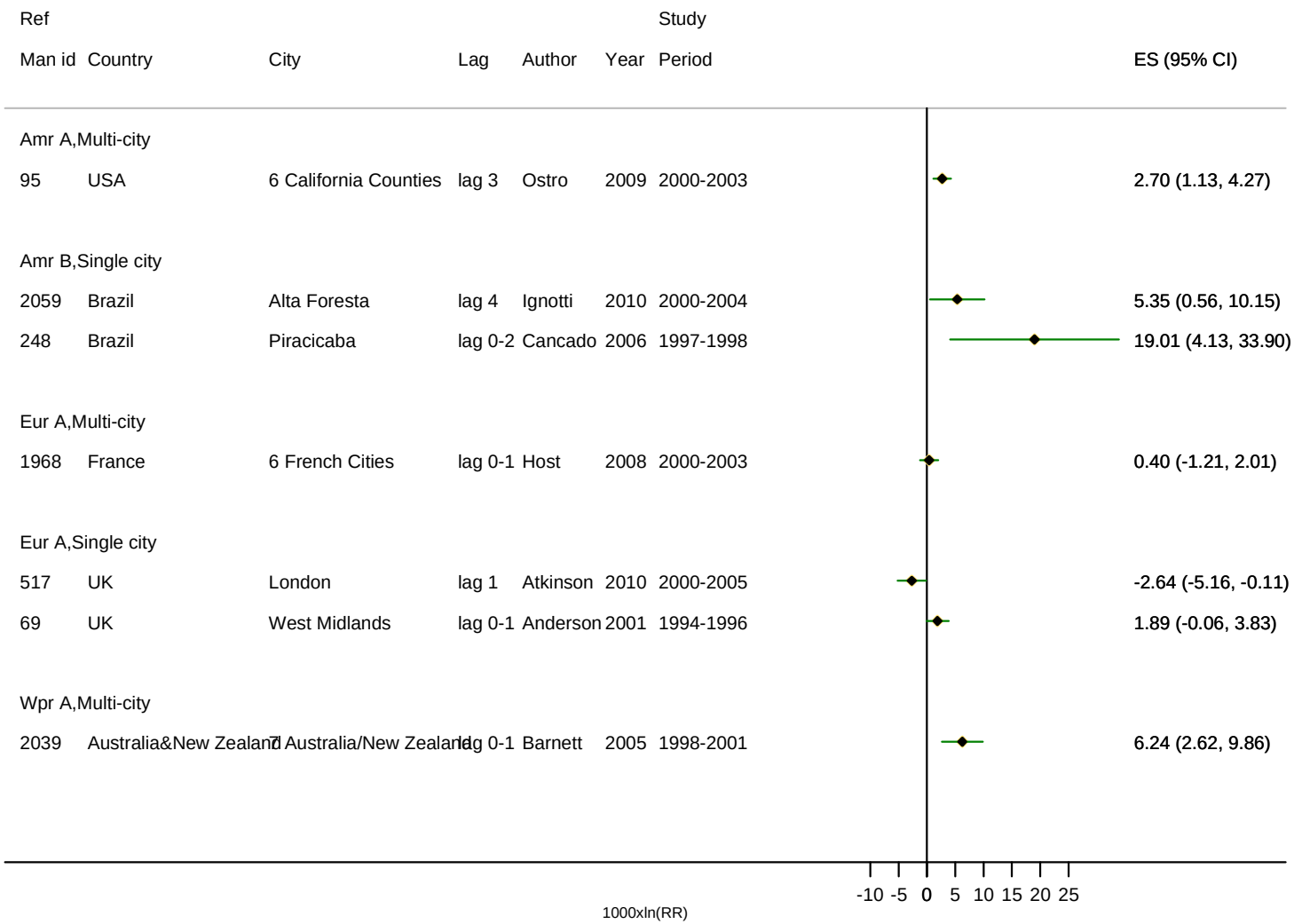
1000xln(RR)

Figure S19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City
Lag
Author
Year
Study Period
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Amr A,Multi-city
95 USA 6 California Counties lag 3 Ostro 2009 2000-2003 2.70 (1.13, 4.27)
Amr B,Single city
2059 Brazil Alta Foresta lag 4 Ignotti 2010 2000-2004 5.35 (0.56, 10.15)
248 Brazil Piracicaba lag 0-2 Cancado 2006 1997-1998 19.01 (4.13, 33.90)
Eur A,Multi-city
1968 France 6 French Cities lag 0-1 Host 2008 2000-2003 0.40 (-1.21, 2.01)
Eur A,Single city
517 UK London lag 1 Atkinson 2010 2000-2005 -2.64 (-5.16, -0.11)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 1.89 (-0.06, 3.83)
Wpr A,Multi-city
2039 Australia&New Zealand 7 Australia/New Zealand lag 0-1 Barnett 2005 1998-2001 6.24 (2.62, 9.86)
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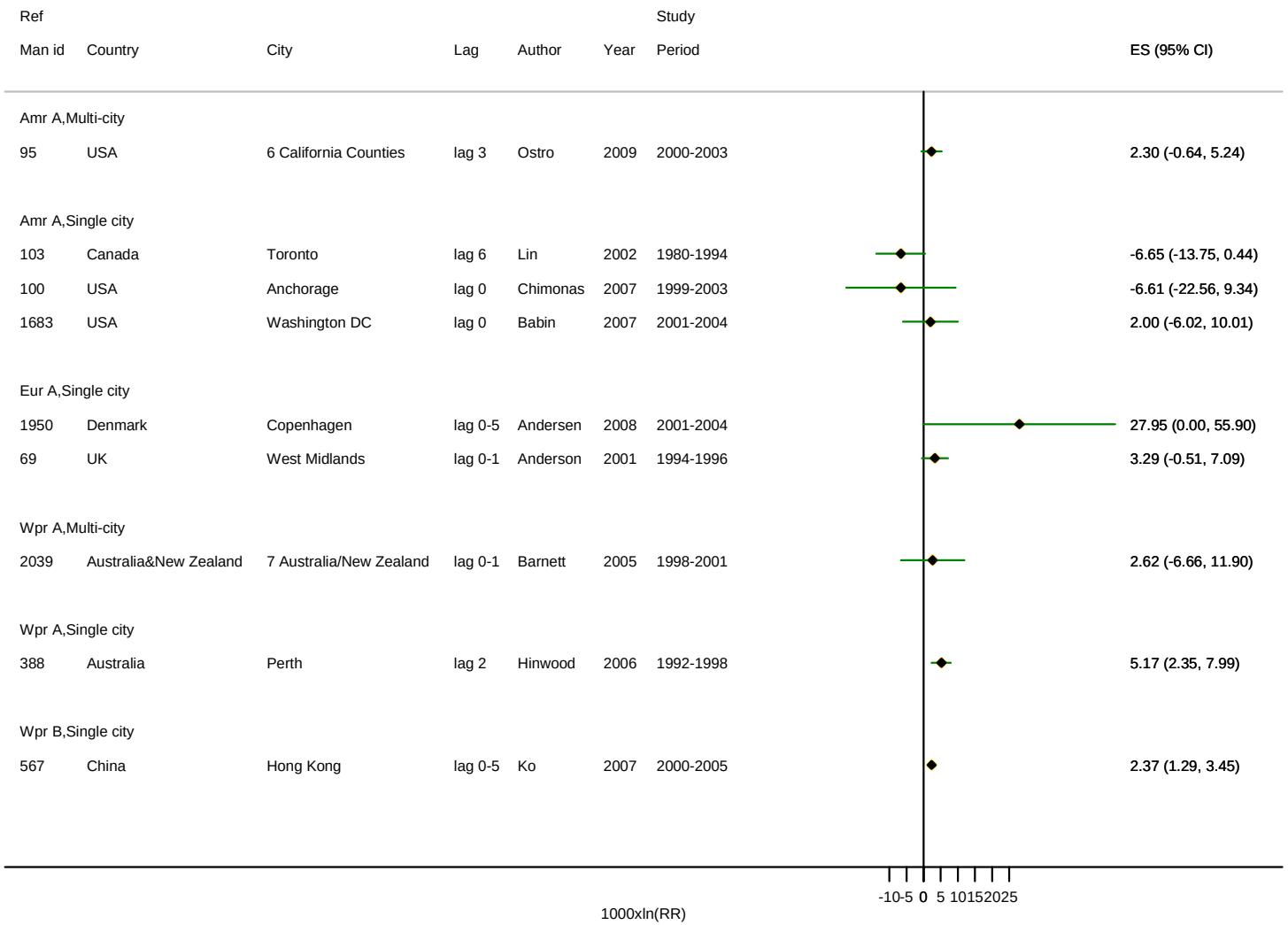
Figure S20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City
Lag
Author
Year
Study Period
ES (95% CI)
Amr A,Multi-city
95 USA 6 California Counties lag 3 Ostro 2009 2000-2003 2.30 (-0.64, 5.24)
Amr A,Single city
103 Canada Toronto lag 6 Lin 2002 1980-1994 -6.65 (-13.75, 0.44)
100 USA Anchorage lag 0 Chimonas 2007 1999-2003 -6.61 (-22.56, 9.34)
1683 USA Washington DC lag 0 Babin 2007 2001-2004 2.00 (-6.02, 10.01)
Eur A,Single city
1950 Denmark Copenhagen lag 0-5 Andersen 2008 2001-2004 27.95 (0.00, 55.90)
69 UK West Midlands lag 0-1 Anderson 2001 1994-1996 3.29 (-0.51, 7.09)
Wpr A,Multi-city
2039 Australia&New Zealand 7 Australia/New Zealand lag 0-1 Barnett 2005 1998-2001 2.62 (-6.66, 11.90)
Wpr A,Single city
388 Australia Perth lag 2 Hinwood 2006 1992-1998 5.17 (2.35, 7.99)
Wpr B,Single city
567 China Hong Kong lag 0-5 Ko 2007 2000-2005 2.37 (1.29, 3.45)
-10-5 0 5 10152025
1000xln(RR)