AIR POLLUTION AND HEALTH (JD KAUFMAN, SECTION EDITOR)

# Ambient Coarse Particulate Matter and Human Health: A Systematic Review and Meta-Analysis

**Sara D. Adar · Paola A. Filigrana · Nicholas Clements · Jennifer L. Peel**

**Abstract** Airborne particles have been linked to increased mortality and morbidity. As most research has focused on fine particles ($PM_{2.5}$), the health implications of coarse particles ($PM_{10\text{-}2.5}$) are not well understood. We conducted a systematic review and meta-analysis of associations for short- and long-term $PM_{10\text{-}2.5}$ concentrations with mortality and hospital admissions. Using 23 mortality and 10 hospital admissions studies, we documented suggestive evidence of increased morbidity and mortality in relation to higher short-term $PM_{10\text{-}2.5}$ concentrations, with stronger relationships for respiratory than cardiovascular endpoints. Reported associations were highly heterogeneous, however, especially by geographic region and average $PM_{10\text{-}2.5}$ concentrations. Adjustment for $PM_{2.5}$ and publication bias resulted in weaker and less precise effect estimates, although positive associations remained for short-term $PM_{10\text{-}2.5}$ concentrations. Inconsistent relationships between effect estimates for $PM_{10\text{-}2.5}$ and correlations between $PM_{10\text{-}2.5}$ and $PM_{2.5}$ concentrations, however, indicate that $PM_{10\text{-}2.5}$ associations cannot be solely explained by co-exposure to $PM_{2.5}$. While suggestive evidence was found of increased mortality with long-term $PM_{10\text{-}2.5}$ concentrations, these associations were not robust to control for $PM_{2.5}$. Additional research is required to better understand sources of heterogeneity of associations between $PM_{10\text{-}2.5}$ and adverse health outcomes.

**Keywords** Air pollution · Coarse particulate matter · Health · Cardiovascular · Respiratory · Mortality · Hospitalizations · Time-series · Case-crossover

S. D. Adar (✉) · P. A. Filigrana
Department of Epidemiology, University of Michigan, School of Public Health, 1420 Washington Heights – SPHII-5539, Ann Arbor, MI 48109-2029, USA
e-mail: sadar@umich.edu

P. A. Filigrana
e-mail: paofilig@umich.edu

N. Clements
Department of Mechanical Engineering, University of Colorado, 135 30th St., Boulder, CO 80305, USA
e-mail: nsclements@gmail.com

J. L. Peel
Department of Environmental and Radiological Health Sciences, Colorado State University, Campus Delivery 1681, Fort Collins, CO 80523-1681, USA
e-mail: jennifer.peel@colostate.edu

## Introduction

Airborne particulate matter has been consistently linked to adverse health, including mortality and morbidity from respiratory and cardiovascular diseases [1]. As particles less than 10 μm in aerodynamic diameter ($PM_{10}$) can reach the tracheobronchial and alveolar regions of the respiratory tract [2], these particles have been of prime interest for epidemiology studies. $PM_{10}$ is comprised of two distinct types of particles with different morphologies and sources. Fine particles, < 2.5 μm ($PM_{2.5}$), are typically generated by combustion or photochemical reactions in the atmosphere and are thus generally comprised of organic carbon, elemental carbon, sulfate, nitrate, and metals. In contrast, coarse particles (typically classified as 2.5–10 μm, $PM_{10\text{-}2.5}$) are commonly formed by mechanical grinding and resuspension of solid material. This results in a primary composition of crustal elements, metals from suspended road dust, and organic debris [3–5]. These variations in composition, along with differential deposition in the body [2], suggest that $PM_{2.5}$ and $PM_{10\text{-}2.5}$ may differ in their impacts on human health.

To date, the vast majority of research has focused on $PM_{2.5}$ or $PM_{10}$; far less is known about the health implications of $PM_{10\text{-}2.5}$. This represents a critical gap in our understanding with direct policy implications. For example, the United States Environmental Protection Agency (EPA) has stated that $PM_{2.5}$

and $PM_{10-2.5}$ should be considered separately under the National Ambient Air Quality Standards (NAAQS), but a unique $PM_{10-2.5}$ standard has not yet been adopted. Rather, $PM_{10-2.5}$ is regulated through the $PM_{10}$ standard. This approach has been attributed in part due to the sparse epidemiological data available examining associations between exposures to $PM_{10-2.5}$ and health effects [5].

Over the past decade, an increasing number of epidemiological investigations have explored $PM_{10-2.5}$-related health effects. As reviewed by Brunekreef and Forsberg in 2005 [6], early evidence suggested the presence of associations for morbidity and mortality with short- but not long-term exposures to $PM_{10-2.5}$. Associations were noted to differ by location, with stronger associations in more arid locations. Associations with respiratory hospitalizations were also notably as strong or stronger for $PM_{10-2.5}$ than for $PM_{2.5}$. Since $PM_{10-2.5}$ associations were found to be sensitive to control for $PM_{2.5}$ in the few studies reporting adjusted results, the authors encouraged future research to report multi-pollutant models.

This manuscript extends the work of Brunekreef and Forsberg [6] by incorporating newly published studies on $PM_{10-2.5}$ with mortality and hospitalizations and conducting meta-analyses to generate summary estimates for relationships with $PM_{10-2.5}$. To better understand factors that may modify associations between $PM_{10-2.5}$ and health, we also explored heterogeneity by study location, lag period, ambient concentrations of pollution, the relative abundance of $PM_{10-2.5}$ to $PM_{2.5}$, and sampling methodology for $PM_{10-2.5}$. We further investigated the impact of $PM_{2.5}$ concentrations on associations with $PM_{10-2.5}$ by summarizing results from multi-pollutant models and exploring how the magnitude of association between $PM_{10-2.5}$ and health vary according to correlations between $PM_{2.5}$ and $PM_{10-2.5}$ concentrations.

## Methods

A systematic review was conducted to identify all published studies of short- and long-term exposures to $PM_{10-2.5}$ (or $PM_{15-2.5}$) that reported associations with mortality or hospital admissions. We also compiled data for emergency department visits but restricted these papers to sensitivity analyses to focus our estimates on the most severe health endpoints. Literature searches using the Web of Knowledge and Medline were conducted with the key words "coarse particulate matter" or "$PM_{10-2.5}$" and "health" through the end of December 2013. This approach was supplemented by a review of the reference lists of any identified publications, as well as earlier reviews by the Environmental Protection Agency [5] and Brunekreef and Forsberg [6].

Effect estimates and confidence intervals were extracted from each published report as well as descriptive information about the population, time period, outcome, and exposures.

When data or results were discussed but not quantified, we contacted the authors for additional information. Papers were excluded if they did not report or we could not obtain effect estimates for $PM_{10-2.5}$ with concurrent standard errors, confidence intervals, or t-values. When more than one study was available for the same population, we selected the report with the longest follow-up. Since associations for the case-crossover design are mathematically equivalent to those from time-series studies [7], we have used both designs in our meta-analyses, though we have restricted selection to papers employing a time-stratified referent selection strategy due to known bias with other designs [8]. When both case-crossover and time series approaches were presented, the time-series point estimates were included in our meta-analyses. Time-series analyses using non-parametric smoothing splines (except penalized splines) and generalized additive models in S-Plus were also excluded based on previously identified issues with model convergence and the underestimation of standard errors [9]. Citations were identified and summarized independently by two investigators.

To be included in our quantitative meta-analysis, five or more studies were required for a particular health endpoint. We identified associations a priori with the previous day (Lag 1), current day (Lag 0), and two days prior (Lag 2) as our primary analyses for total mortality, cardiovascular endpoints, and respiratory endpoints, respectively. When these exact lags were unavailable, we selected the next closest time point. All associations were standardized to a difference of 10 μg/m³ and summarized across investigations using meta-analysis (STATA v13, Stata Corp, College Station, TX). To account for heterogeneity across studies, we employed the DerSimonian and Liard random effects approach and report the $I^2$ statistic as an indicator of the fraction of the variability due to true between-study differences as opposed to chance [10]. Publication bias was also explored using funnel plots, Egger's test of asymmetry [11], and the "trim and fill" approach to estimate the associations that might have been observed in the absence of publication bias [12].

To explore possible causes for heterogeneity in effect estimates, we conducted analyses stratified by geographic location and lag period. We also examined non-linearity of the dose-response relationship through stratification by $PM_{10-2.5}$ concentrations and meta-regression. Differences in associations by $PM_{2.5}$ concentrations and the ratio of $PM_{10-2.5}$ to $PM_{10}$ were similarly explored to assess if $PM_{10-2.5}$ from regions with more urban/industrial pollution from combustion had greater toxicity than $PM_{10-2.5}$ from other settings. In addition, we summarized all available associations with $PM_{10-2.5}$ adjusted for $PM_{2.5}$ and investigated if $PM_{10-2.5}$ associations were greater in locations with higher correlations between $PM_{10-2.5}$ and $PM_{2.5}$ concentrations. Finally, we explored if sampling methods suspected to have more (i.e., tapered element

**Table 1** Descriptive information for short-term exposure studies included in the meta-analysis

| Study | Location | Time Period | Study Design | Restrictions | Reported or Estimated # of Events (Short-Term) or # of Participants (Long-Term) | Estimated Incidence Rate Ratios (95 % CI) per 10 μg/m³ of PM$_{10-2.5}$ | Estimated Incidence Rate Ratios (95 % CI) per 10 μg/m³ of PM$_{2.5}$ | Median or Mean† PM$_{10-2.5}$ | Median or Mean† PM$_{2.5}$ | Correlation of PM$_{10-2.5}$ and PM$_{2.5}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Short-Term Associations With Non-Accidental Mortality | | | | | | | | | | |
| Atkinson et al. 2010 | London, United Kingdom | 2000–2005 | Time-Series | | 278,545 | 1.018 (1.007, 1.030) | 1.000 (0.996, 1.004) | 7.0 | 15 | 0.22 |
| Burnett et al. 2004 | 12 Cities, Canada | 1981–1999 | Time-Series | | 1,450,251 | 1.006 (0.999, 1.014) | 1.005 (0.991, 1.020) | 11.4† | 12.8† | |
| Chen et al. 2011 | 3 Cities, China | 2004–2008* | Time-Series | | 308,904 | 1.003 (1.001, 1.004) | 1.003 (1.002, 1.004) | 49–101† | 55–94† | 0.28–0.53 |
| Chock et al. 2000 | Allegheny County, United States | 1989–1991 | Time-Series | <75 years | 25,609 | 1.003 (0.993, 1.013) | 1.010 (0.992, 1.028) | | | |
| Chock et al. 2000 | Allegheny County, United States | 1989–1991 | Time-Series | >75 years | 25,109 | 1.005 (0.995, 1.015) | 1.006 (0.988, 1.025) | | | |
| Cifuentes et al. 2000 | Santiago metropolitan area, Chile | 1988–1996 | Time-Series | | 165,668 | 1.006 (1.001, 1.012) | 1.005 (1.003, 1.008) | 44.3 | 42.6 | 0.52 |
| Fairley 1999/HEI 2003 | Santa Clara, United States | 1986–1996 | Time-Series | | 58,440 | 0.978 (0.922, 1.037) | 0.984 (0.962, 1.007) | 11† | 9† | 0.51 |
| Janssen et al. 2013 | All Cities, Netherlands | 2008–2009 | Time-Series | | 258,159 | 0.998 (0.987, 1.010) | 1.008 (1.003, 1.012) | 7.2 | 13.1 | 0.29 |
| Klemm et al. 2004 | Atlanta, United States | 1998–2000 | Time-Series | >65 years | 10,841 | 1.006 (0.999, 1.014) | 1.003 (1.001, 1.005) | 9.3 | 18.1 | 0.42 |
| Lippmann et al. 2000/HEI 2003 | Detroit, United States | 1992–1994 | Time-Series | | 25,970 | 1.011 (0.991, 1.032) | 1.008 (0.993, 1.023) | 12 | 15 | 0.55 |
| Lopez-Villarrubia et al. 2012 | Las Palmas de Gran Canaria, Canary Islands | 2001–2004 | Time-Series | | 10,811 | 1.004 (0.981, 1.028) | 0.994 (0.959, 1.029) | 14.6 | 12.7 | 0.55 |
| Lopez-Villarrubia et al. 2012 | Santa Cruz de Tenerife, Canary Islands | 2001–2004 | Time-Series | | 6,428 | 1.004 (0.981, 1.028) | 0.994 (0.959, 1.029) | 20.3 | 11.3 | -0.03–0.35 |
| Malig et al. 2009 | 15 California Counties, United States | 1999–2005 | Case-Crossover | | 107,188 | 1.000 (0.989, 1.012) | | 10.6–46.5† | 11.1–17.3† | 0.27, 0.18†† |
| Mallone et al. 2011 | Rome, Italy | 2001–2004 | Case-Crossover | | 80,423 | 1.027 (1.011, 1.044) | 1.010 (0.995, 1.025) | 13.6, 18.3†† | 20.9, 24†† | 0.27 |
| Meister et al. 2012 | Stockholm, Sweden | 2000–2008 | Time-Series | | 93,398 | 1.017 (1.002, 1.032) | 1.015 (1.001, 1.028) | 7.1† | 8.6† | 0.33 |
| Perez et al. 2008 | Barcelona, Spain | 2003–2004 | Case-Crossover | | 24,850 | 1.027 (1.008, 1.046) | 1.040 (1.023, 1.057) | 12.9 | 22.4 | 0.19–0.68 |
| Samoli et al. 2013 | 8 metropolitan areas, European Mediterranean | 2001–2010* | Time-Series | | 578,191 | 1.003 (0.999, 1.007) | 1.006 (1.003, 1.008) | 8.0–15.8 | 13.6–27.7 | 0.23–0.69 |
| Schwartz et al. 1996/HEI 2003 | 6 Cities, United States | 1979–1988 | Time-Series | >65 years | 103,841 | 1.001 (0.995, 1.007) | 1.008 (1.004, 1.013) | 9 | 14.7 | |
| Tobias et al. 2011 | Madrid, Spain | 2003–2005 | Case-Crossover | Dust Days | 12,993 | 1.005 (0.987, 1.026) | 1.008 (0.980, 1.040) | 22 | 24 | 0.46 |
| Tobias et al. 2011 | Madrid, Spain | 2003–2005 | Case-Crossover | Dust-Free Days | 53,997 | 1.021 (1.007, 1.035) | 1.030 (1.015, 1.043) | 12 | 16 | |
| Villeneuve et al. 2003 | Vancouver, Canada | 1986–1998 | Time-Series | >65 years | 28,210 | 0.990 (0.964, 1.016) | 1.013 (0.983, 1.044) | 7.8† | 10.7† | |
| Zanobetti et al. 2009 | 47 Cities, United States | 1999–2005 | Time-Series | | 5,609,349 | 1.005 (1.002, 1.007) | 1.010 (1.008, 1.012) | 3.7–33.1† | 6.7–21.7† | |
| Short-Term Associations With Respiratory Mortality | | | | | | | | | | |
| Atkinson et al. 2010 | London, United Kingdom | 2000–2005 | Time-Series | | 42,262 | 1.001 (0.972, 1.031) | 1.009 (0.999, 1.019) | 7.0 | 15 | 0.22 |
| Chen et al. 2011 | 3 Cities, China | 2004–2008* | Time-Series | | 33,871 | 1.002 (0.996, 1.008) | 1.002 (0.999, 1.005) | 49–101† | 55–94† | 0.28–0.53 |
| Halonen et al. 2009 | Helsinki metropolitan area, Finland | 1998–2004 | Time-Series | | 3,701 | 1.005 (0.958, 1.054) | 1.000 (0.952, 1.051) | 7.5 | 9.5 | 0.25 |
| Janssen et al. 2013 | All Cities, Netherlands | 2008–2009 | Time-Series | | 27,759 | 1.038 (1.006, 1.072) | 1.016 (1.004, 1.029) | 7.2 | 13.1 | 0.29 |
| Lippmann et al 2000/HEI 2003 | Detroit, United States | 1992–1994 | Time-Series | | 12,250 | 1.025 (0.959, 1.096) | 1.012 (0.960, 1.067) | 12 | 15 | 0.42 |
| Lopez-Villarrubia et al. 2012 | Las Palmas de Gran Canaria, Canary Islands | 2001–2004 | Time-Series | | 979 | 1.060 (0.987, 1.137) | 1.059 (0.948, 1.184) | 14.6 | 12.7 | 0.55 |
| Lopez-Villarrubia et al. 2012 | Santa Cruz de Tenerife, Canary Islands | 2001–2004 | Time-Series | | 584 | 1.060 (0.987, 1.137) | 1.059 (0.948, 1.184) | 20.3 | 11.3 | 0.55 |
| Mallone et al. 2011 | Rome, Italy | 2001–2004 | Case-Crossover | | 4,574 | 1.117 (1.011, 1.233) | 1.002 (0.922, 1.089) | 13.6, 18.3†† | 20.9, 24†† | 0.27, 0.18†† |
| Perez et al. 2012 | Barcelona, Spain | 2003–2007 | Case-Crossover | Dust Days | 540 | 1.035 (0.918, 1.167) | 1.020 (0.909, 1.145) | 11.5 | 17.3 | 0.01 |
| Perez et al. 2012 | Barcelona, Spain | 2003–2007 | Case-Crossover | Dust-Free Days | 5,812 | 1.048 (1.013, 1.085) | 1.028 (0.994, 1.062) | 12.4 | 19.2** | 0.01** |

**Table 1** (continued)

| Study | Location | Time Period | Study Design | Restrictions | Reported or Estimated # of Events (Short-Term) or # of Participants (Long-Term) | Estimated Incidence Rate Ratios (95 % CI) per 10 μg/m³ of $PM_{10-2.5}$ | Estimated Incidence Rate Ratios (95 % CI) per 10 μg/m³ of $PM_{2.5}$ | Median or Mean† $PM_{10-2.5}$ | Median or Mean† $PM_{2.5}$ | Correlation of $PM_{10-2.5}$ and $PM_{2.5}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Samoli et al. 2013 | 8 metropolitan areas, European Mediterranean | 2001–2010* | Time-Series | | 58,440 | 1.007 (0.997, 1.018) | 1.016 (1.006, 1.027) | 8.0–15.8 | 13.6–27.7** | 0.19–0.68** |
| Villeneuve et al. 2003 | Vancouver, Canada | 1986–1998 | Time-Series | >65 years | 3,765 | 1.001 (0.942, 1.063) | 1.002 (0.919, 1.092) | 7.8† | 10.7† | 0.46 |
| Zanobetti et al. 2009 | 47 Cities, United States | 1999–2005 | Time-Series | | 547,660 | 1.012 (1.004, 1.019) | 1.017 (1.010, 1.023) | 3.7–33.1† | 6.7–21.7† | |
| **Short-Term Associations With Cardiovascular Mortality** | | | | | | | | | | |
| Atkinson et al. 2010 | London, United Kingdom | 2000–2005 | Time-Series | | 103,734 | 0.996 (0.977, 1.015) | 1.001 (0.994, 1.007) | 7.0 | 15 | 0.22 |
| Chen et al. 2011 | 3 Cities, China | 2004–2008* | Time-Series | | 126,988 | 1.001 (1.000, 1.003) | 1.005 (1.004, 1.007) | 49–101† | 55–94† | 0.28–0.53 |
| Halonen et al. 2009 | Helsinki metropolitan area, Finland | 1998–2004 | Time-Series | | 16,233 | 1.000 (0.979, 1.021) | 1.012 (0.989, 1.035) | 7.5 | 9.5 | 0.25 |
| Janssen et al. 2013 | All Cities, Netherlands | 2008–2009 | Time-Series | | 78,675 | 0.981 (0.961, 1.001) | 1.011 (1.002, 1.019) | 7.2 | 13.1 | 0.29 |
| Lippmann et al. 2000/ HEI 2003 | Detroit, United States | 1992–1994 | Time-Series | | 1,960 | 1.024 (0.994, 1.055) | 1.008 (0.986, 1.030) | 12 | 15 | 0.42 |
| Lopez-Villarrubia et al. 2012 | Las Palmas de Gran Canaria, Canary Islands | 2001–2004 | Time-Series | | 2,338 | 1.023 (0.976, 1.072) | 1.026 (0.956, 1.101) | 14.6 | 12.7 | 0.55 |
| Lopez-Villarrubia et al. 2012 | Santa Cruz de Tenerife, Canary Islands | 2001–2004 | Time-Series | | 1,315 | 1.023 (0.976, 1.072) | 1.026 (0.956, 1.101) | 20.3 | 11.3 | 0.55 |
| Malig et al. 2009 | 15 California Counties, United States | 1999–2005 | Case-Crossover | | 45,036 | 1.003 (0.988, 1.017) | | 10.6–46.5† | 11.1–17.3† | -0.03–0.35 |
| Mallone et al. 2011 | Rome, Italy | 2001–2004 | Case-Crossover | | 24,773 | 1.034 (1.007, 1.062) | 1.011 (0.987, 1.035) | 13.6, 18.3†† | 20.9, 24†† | 0.27, 0.18 |
| Mar et al 2000/2003 | Maricopa County, United States | 1995–1997 | Time-Series | | 4,182 | 1.024 (1.003, 1.046) | 1.040 (0.984, 1.100) | 33.5† | 13.0† | 0.5–0.59 |
| Ostro et al. 2000/2003 | Coachella Valley, United States | 1989–1998 | Time-Series | | 8,073 | 1.011 (1.002, 1.020) | 0.944 (0.882, 1.010) | 30.5† | 16.8† | 0.28 |
| Perez et al. 2012 | Barcelona, Spain | 2003–2007 | Case-Crossover | Dust Days | 1,650 | 1.104 (1.031, 1.181) | 1.041 (0.968, 1.122) | 11.5 | 17.3** | 0.01** |
| Perez et al. 2012 | Barcelona, Spain | 2003–2007 | Case-Crossover | Dust-Free Days | 16,513 | 1.041 (1.018, 1.066) | 1.030 (1.006, 1.054) | 12.4 | 19.2** | 0.01** |
| Samoli et al. 2013 | 8 metropolitan areas, European Mediterranean | 2001–2010* | Time-Series | | 213,306 | 1.003 (0.996, 1.009) | 1.006 (1.001, 1.011) | 8.0–15.8 | 13.6–27.7 | 0.19–0.68 |
| Villeneuve et al. 2003 | Vancouver, Canada | 1986–1998 | Time-Series | >65 years | 11,518 | 1.053 (1.010, 1.098) | 0.990 (0.942, 1.041) | 7.8† | 10.7† | 0.46 |
| Zanobetti et al. 2009 | 47 Cities, United States | 1999–2005 | Time-Series | | 1,787,078 | 1.003 (1.000, 1.006) | 1.009 (1.005, 1.012) | 3.7–33.1† | 6.7–21.7† | |
| **Short-Term Associations With Respiratory Hospitalizations** | | | | | | | | | | |
| Alessandrini et al. 2013 | Rome, Italy | 2001–2004 | Time-Series | <14 years | 11,157 | 0.986 (0.935, 1.038) | 0.999 (0.958, 1.041) | 14.6 to 20.7†† | 23.4 to 25.6†† | 0.25 |
| Alessandrini et al. 2013 | Rome, Italy | 2001–2004 | Time-Series | >35 years | 20,463 | 1.041 (1.004, 1.079) | 0.997 (0.969, 1.025) | 14.6 to 20.7†† | 23.4 to 25.6†† | 0.25 |
| Atkinson et al. 2010 | London, United Kingdom | 2000–2005 | Time-Series | <14 years | 67,235 | 0.998 (0.973, 1.024) | 1.017 (1.009, 1.025) | 7.0 | 15 | 0.22 |
| Atkinson et al. 2010 | London, United Kingdom | 2000–2005 | Time-Series | >65 years | 121,023 | 1.007 (0.988, 1.026) | 1.009 (1.003, 1.016) | 7.0 | 15 | 0.22 |
| Chen et al. 2005 | Vancouver, Canada | 1995–1999 | Time-Series | >65 years | 12,880 | 1.123 (1.048, 1.201) | 1.051 (0.975, 1.157) | 5.6† | 7.7† | 0.38 |
| Halonen et al. 2009 | Helsinki metropolitan area, Finland | 1998–2004 | Time-Series | >65 years | 26,095 | 0.999 (0.981, 1.017) | 1.023 (1.004, 1.042) | 7.5 | 9.5 | 0.25 |
| Host et al. 2008 | 6 French cities, France | 2000–2003* | Time-Series | <14 years | 56,387 | 1.062 (1.004, 1.123) | 1.004 (0.988, 1.020) | 7.0–11.0† | 13.8–18.8† | 0.28–0.73 |
| Host et al. 2008 | 6 French cities, France | 2000–2003* | Time-Series | 15–64 years | 57,589 | 1.026 (0.995, 1.058) | 1.008 (0.993, 1.023) | 7.0–11.0† | 13.8–18.8† | 0.28–0.73 |
| Host et al. 2008 | 6 French cities, France | 2000–2003* | Time-Series | >65 years | 56,267 | 1.019 (0.981, 1.059) | 1.005 (0.980, 1.030) | 7.0–11.0† | 13.8–18.8† | 0.28–0.73 |
| Peng et al. 2008 | 108 Counties, United States | 1999–2005 | Time-Series | >65 years | 1.4 M | 0.999 (0.994, 1.005) | 1.004 (1.001, 1.008) | 13.5 | 9.8 | 0.12 |
| Qiu et al. 2012 | Hong Kong, Special Administrative Region of China | 2000–2005 | Time-Series | | 518,864 | 1.009 (1.004, 1.014) | | 14.5 | 34.8 | 0.68 |
| Stafoggia et al. 2013 | 6 metropolitan areas, European Mediterranean | 2001–2010 | Time-Series | >15 years | 459,261 | 1.012 (0.989, 1.036) | 1.011 (1.000, 1.021) | 9.3–17.5† | 17.2–34.4† | 0–>0.5 |

**Table 1** (continued)

| Study | Location | Time Period | Study Design | Restrictions | Reported or Estimated # of Events (Short-Term) or # of Participants (Long-Term) | Estimated Incidence Rate Ratios (95 % CI) per 10 µg/m³ of PM$_{10-2.5}$ | Estimated Incidence Rate Ratios (95 % CI) per 10 µg/m³ of PM$_{2.5}$ | Median or Mean† PM$_{10-2.5}$ | Median or Mean† PM$_{2.5}$ | Correlation of PM$_{10-2.5}$ and PM$_{2.5}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Yang et al. 2004 | Vancouver, Canada | 1995–1999 | Case-Control | <3 years | 1,610 | 1.048 (0.885, 1.255) | | 4.8 | 7 | 0.39 |
| Short-Term Associations With Cardiovascular Hospitalizations | | | | | | | | | | |
| Atkinson et al. 2010 | London, United Kingdom | 2000–2005 | Time-Series | | 293,913 | 1.002 (0.990, 1.014) | 1.004 (0.999, 1.008) | 7.0 | 15 | 0.22 |
| Halonen et al. 2009 | Helsinki metropolitan area, Finland | 1998–2004 | Time-Series | | 61,571 | 1.010 (0.998, 1.021) | 0.997 (0.985, 1.009) | 7.5 | 9.5 | 0.25 |
| Host et al. 2008 | 6 French cities, France | 2000–2003* | Time-Series | | 251,397 | 1.005 (0.988, 1.023) | 1.009 (1.001, 1.018) | 7.0–11.0† | 13.8–18.8† | 0.28–0.73 |
| Peng et al. 2008 | 108 Counties, United States | 1999–2005 | Time-Series | >65 years | 3.7 M | 1.004 (1.001, 1.007) | 1.007 (1.005, 1.010) | 13.5 | 9.8 | 0.12 |
| Qiu et al. 2013 | Hong Kong, Special Administrative Region of China | 2000–2005 | Time-Series | | 338,123 | 1.007 (1.000, 1.013) | 1.006 (1.003, 1.009) | 14.5 | 34.8 | 0.68 |
| Stafoggia et al. 2013 | 6 metropolitan areas, European Mediterranean | 2001–2010 | Time-Series | >15 years | 727,579 | 1.007 (1.002, 1.013) | 1.005 (1.001, 1.009) | 9.3–17.5† | 17.2–34.4† | 0–>0.5 |

* Years differed by city, ** PM$_1$ reported instead of PM$_{2.5}$, † Mean, †† Dust day, dust-free day

oscillating microbalance, TEOM) or less measurement error (i.e., dichotomous sampler) for PM$_{10-2.5}$ [13] were found to impact associations.

## Results

Papers Identified with Short-Term PM$_{10-2.5}$ Exposures

A total of 34 published studies were identified that presented associations between short-term fluctuations in PM$_{10-2.5}$ concentrations and mortality. Of these investigations, we excluded three manuscripts with incomplete reporting of numerical results [14–16]. An additional nine papers were excluded for use of non-parametric smoothing splines in GAM. Of these, seven [17–23] were replaced by later re-analysis of the same data [9], but two were without replication [24, 25]. Similarly, three papers were superseded by longer time series from the same populations [22, 26, 27], and one was excluded, as it was a sensitivity analysis of another report [28]. One final paper was excluded as it only explore stroke mortality [29]. This resulted in 23 studies for inclusion in this meta-analysis—19, 11, and 14 total cases of non-accidental [9, 30–32, 33••, 34, 35, 36••, 37, 38, 39••, 40–45], respiratory, [9, 33••, 34, 36••, 37, 38, 39••, 41, 42, 46, 47], and cardiovascular mortality [9, 33••, 34, 35, 36••, 37, 38, 39••, 41, 42, 46, 47], respectively. No other cause-specific mortality had sufficient counts to be included.

For hospital admissions, we identified 23 studies and one scientific report with published associations for short-term exposures to PM$_{10-2.5}$. Of these investigations, we excluded eight manuscripts for using non-parametric smoothing splines in GAM or case-crossover reference strategies inconsistent with current recommendations [18, 24, 48–53]. Two of these investigations [18, 53] were re-analyzed [9], and therefore included in our analysis. An additional study was excluded for using an ordinary least squares approach for time-series [54], two as sensitivity analyses of primary results presented elsewhere [55, 56] and another four for including health outcomes with insufficient counts for meta-analysis [18, 52, 57, 58]. After these exclusions, there were a total of 10 papers for meta-analysis, resulting in sufficient counts to explore respiratory (n=9) [42, 47, 59–61, 62••, 63••, 64, 65•] and cardiovascular hospitalizations (n=6) [42, 47, 61, 62••, 64, 66]. An additional 12 papers [15, 35, 67–76] and one report [77] were identified on emergency department visits, although these included some extensions of earlier papers and some unique health outcomes that were not reported in a sufficient number of studies to support meta-analysis.

Table 1 summarizes the studies included in this meta-analysis. Across all of the investigations of short-term exposures to PM$_{10-2.5}$, a total of 9.3 million non-accidental deaths, 0.75 million respiratory deaths, and 2.4 million cardiovascular deaths were enumerated. Additionally there were 2.8 and 5.4

million hospital admissions for respiratory and cardiovascular causes, respectively. Most of these investigations (80 %) utilized a time-series design and were conducted in either North America or Europe. In the regions studied, concentrations of $PM_{10-2.5}$ and $PM_{2.5}$ ranged from lows of 3.7 and 6.7 $\mu g/m^3$ in the United States to highs of 101 and 94 $\mu g/m^3$ in China, respectively. Correlations between these two pollutants were generally modest and ranged from -0.03 in the United States to 0.73 in France.

Associations Between Short-Term $PM_{10-2.5}$ Exposures, Mortality, and Hospital Admissions

The vast majority of short-term studies linked higher mortality and morbidity with higher $PM_{10-2.5}$ concentrations (Fig. 1). Mortality and hospital admissions due to respiratory causes had the largest associations with random-effects summary estimates of 1.4 % (95 % CI: 0.5–2.4 %) and 1.0 % (95 % CI: 0.1–1.8 %) higher rates per 10 $\mu g/m^3$, respectively (Table 2). These estimates were approximately two to three times higher than the observed associations for total mortality, cardiovascular mortality, and cardiovascular hospital admissions, although the confidence intervals were also much wider. Sensitivity analyses of cause-specific hospital visits (including estimates from emergency department studies) provided consistent evidence of increased rates with increasing levels of $PM_{10-2.5}$ for outcomes including asthma, chronic obstructive pulmonary disease, and ischemic heart disease (results not presented). In general, the inclusion of emergency department visits resulted in a slight weakening of the respiratory but not cardiovascular summary estimates, though the results were qualitatively the same. Exclusion of childhood respiratory admissions also did not substantially alter our findings (results not presented).

Single pollutant associations for $PM_{10-2.5}$ were generally similar to those reported for $PM_{2.5}$ in studies with paired single pollutant estimates (Table 2). Estimates for $PM_{10-2.5}$, however, showed more evidence of possible publication bias as shown by statistically significant findings of asymmetry using Egger's regression test. Adjustment for asymmetry using a "trim and fill" approach resulted in a weakening, though not elimination, of most associations with $PM_{10-2.5}$. Associations for $PM_{2.5}$ were generally more robust to adjustment for possible publication bias.

All outcomes except cardiovascular disease hospital admissions showed moderate ($I^2$=51–68 %) and statistically significant heterogeneity in the point estimates for $PM_{10-2.5}$ (Table 2). As shown in Figs. 2 and 3, location appeared to be an important explanatory factor for this heterogeneity with stratified analyses indicating that European cities consistently had larger $PM_{10-2.5}$ associations than North America for all outcomes except for cardiovascular mortality. Although there was no clear evidence of heterogeneity by $PM_{2.5}$

concentrations, there was some evidence of lower rate ratios with higher $PM_{10-2.5}$ concentrations for both mortality and hospital admissions. Lower rate ratios were also found when $PM_{10-2.5}$ was more than half of the reported $PM_{10}$ concentrations for hospital admissions but not mortality (meta-regression p-value: 0.06). There was also a suggestion of weaker associations with total mortality among studies using TEOMs and stronger associations among studies using dichotomous samplers but the sample size was small and the differences were not large (results not shown). There were insufficient numbers to examine these relationships with outcomes other than cardiovascular and respiratory mortality and admissions.

As shown in Fig. 2, associations between short-term $PM_{10-2.5}$ concentrations and mortality were sensitive to control for $PM_{2.5}$ in two-pollutant models, with a weakening of associations that resulted in a loss of statistical significance in all scenarios. This was especially true for cardiovascular mortality, for which the $PM_{10-2.5}$ association was fully eliminated by control for $PM_{2.5}$ (results not shown). Although there were too few hospital admission studies with multi-pollutant estimates for a formal meta-analysis, these results appeared to be generally less sensitive to control for $PM_{2.5}$. In spite of the observed sensitivity in $PM_{10-2.5}$ associations to control for $PM_{2.5}$, we did not observe a consistent pattern of increasing associations with $PM_{10-2.5}$ with increasing correlations between $PM_{2.5}$ and $PM_{10-2.5}$ concentrations when $PM_{2.5}$ was associated with adverse health (Fig. 4). Nor did we find consistent evidence of smaller associations with $PM_{10-2.5}$ with increasing correlations between $PM_{10-2.5}$ and $PM_{2.5}$ concentrations when $PM_{2.5}$ concentrations were associated with improved health. Associations with $PM_{2.5}$ were less sensitive to control for $PM_{10-2.5}$ concentrations (Fig. 2)

Papers Identified with Long-Term Exposures to $PM_{10-2.5}$

Estimates of associations between long-term $PM_{10-2.5}$ concentrations and all-cause mortality were available from five American cohort studies [78••, 79, 80••, 81••, 82] and one multicenter study in Europe that combined data from 19 study populations (Table 3) [83]. Additional studies on infant mortality[84] and fatal coronary heart disease [85] were identified but ultimately not included because the number of studies was insufficient to support a meta-analysis. As summarized in Tables 3, these cohort studies collectively followed approximately 780,000 participants over a range of $PM_{10-2.5}$ (4.0 to 27.3 $\mu g/m^3$) and $PM_{2.5}$ concentrations (6.6 to 31.9 $\mu g/m^3$).

Associations Between Long-Term $PM_{10-2.5}$ Exposures and Mortality

Pooled random-effects analyses resulted in a summary estimate of a 2.1 % (95 % CI: -1.6 % to 5.8 %) increased mortality rates per 10 $\mu g/m^3$ higher long-term $PM_{10-2.5}$ concentration
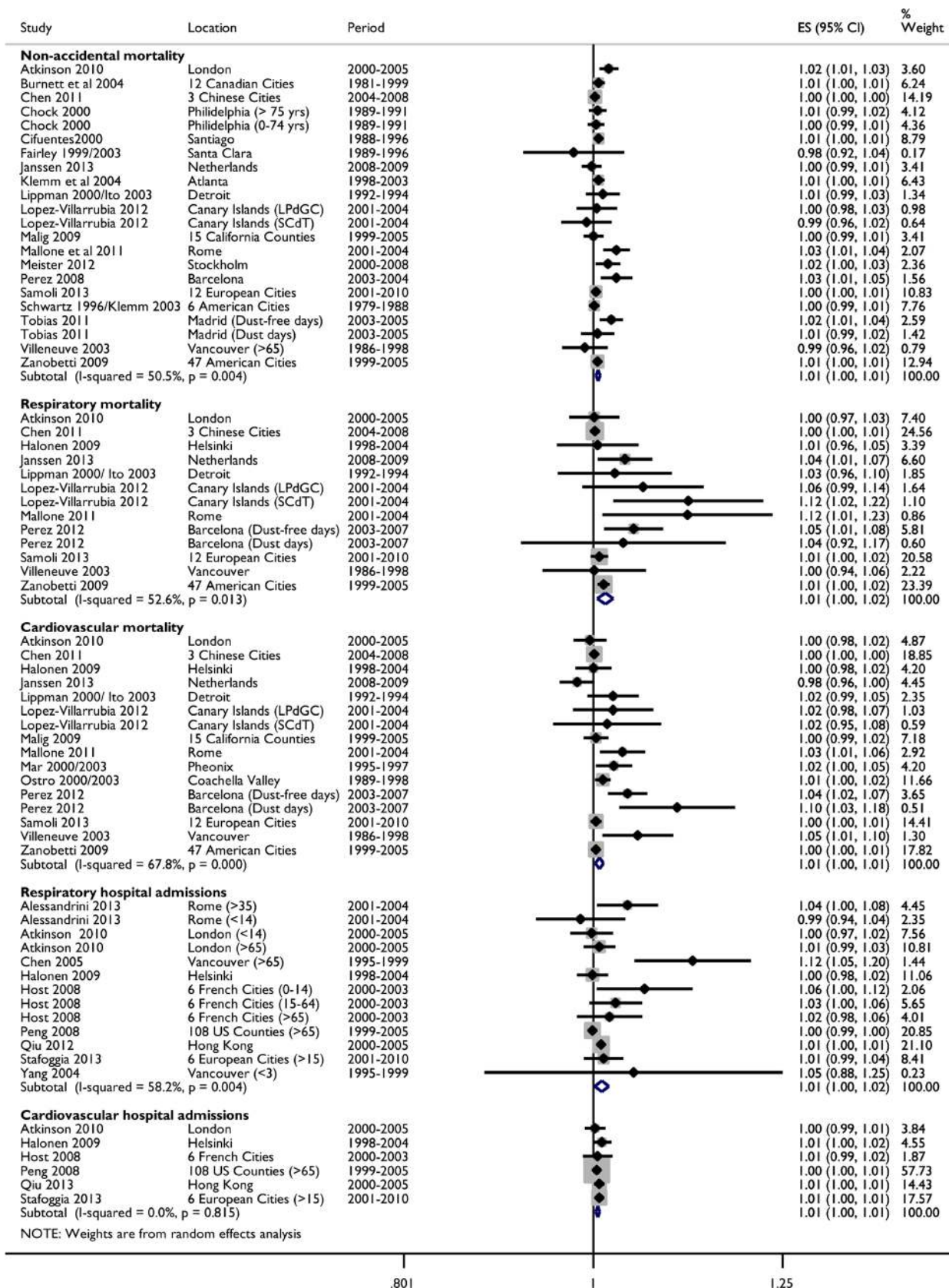
| Study | Location | Period | ES (95% CI) | % Weight |
|---|---|---|---|---|
| **Non-accidental mortality** | | | | |
| Atkinson 2010 | London | 2000-2005 | 1.02 (1.01, 1.03) | 3.60 |
| Burnett et al 2004 | 12 Canadian Cities | 1981-1999 | 1.01 (1.00, 1.01) | 6.24 |
| Chen 2011 | 3 Chinese Cities | 2004-2008 | 1.00 (1.00, 1.00) | 14.19 |
| Chock 2000 | Philidelphia (> 75 yrs) | 1989-1991 | 1.01 (0.99, 1.02) | 4.12 |
| Chock 2000 | Philidelphia (0-74 yrs) | 1989-1991 | 1.00 (0.99, 1.01) | 4.36 |
| Cifuentes2000 | Santiago | 1988-1996 | 1.01 (1.00, 1.01) | 8.79 |
| Fairley 1999/2003 | Santa Clara | 1989-1996 | 0.98 (0.92, 1.04) | 0.17 |
| Janssen 2013 | Netherlands | 2008-2009 | 1.00 (0.99, 1.01) | 3.41 |
| Klemm et al 2004 | Atlanta | 1998-2003 | 1.01 (1.00, 1.01) | 6.43 |
| Lippman 2000/Ito 2003 | Detroit | 1992-1994 | 1.01 (0.99, 1.03) | 1.34 |
| Lopez-Villarrubia 2012 | Canary Islands (LPdGC) | 2001-2004 | 1.00 (0.98, 1.03) | 0.98 |
| Lopez-Villarrubia 2012 | Canary Islands (SCdT) | 2001-2004 | 0.99 (0.96, 1.02) | 0.64 |
| Malig 2009 | 15 California Counties | 1999-2005 | 1.00 (0.99, 1.01) | 3.41 |
| Mallone et al 2011 | Rome | 2001-2004 | 1.03 (1.01, 1.04) | 2.07 |
| Meister 2012 | Stockholm | 2000-2008 | 1.02 (1.00, 1.03) | 2.36 |
| Perez 2008 | Barcelona | 2003-2004 | 1.03 (1.01, 1.05) | 1.56 |
| Samoli 2013 | 12 European Cities | 2001-2010 | 1.00 (1.00, 1.01) | 10.83 |
| Schwartz 1996/Klemm 2003 | 6 American Cities | 1979-1988 | 1.00 (0.99, 1.01) | 7.76 |
| Tobias 2011 | Madrid (Dust-free days) | 2003-2005 | 1.02 (1.01, 1.04) | 2.59 |
| Tobias 2011 | Madrid (Dust days) | 2003-2005 | 1.01 (0.99, 1.02) | 1.42 |
| Villeneuve 2003 | Vancouver (>65) | 1986-1998 | 0.99 (0.96, 1.02) | 0.79 |
| Zanobetti 2009 | 47 American Cities | 1999-2005 | 1.01 (1.00, 1.01) | 12.94 |
| Subtotal (I-squared = 50.5%, p = 0.004) | | | 1.01 (1.00, 1.01) | 100.00 |
| **Respiratory mortality** | | | | |
| Atkinson 2010 | London | 2000-2005 | 1.00 (0.97, 1.03) | 7.40 |
| Chen 2011 | 3 Chinese Cities | 2004-2008 | 1.00 (1.00, 1.01) | 24.56 |
| Halonen 2009 | Helsinki | 1998-2004 | 1.01 (0.96, 1.05) | 3.39 |
| Janssen 2013 | Netherlands | 2008-2009 | 1.04 (1.01, 1.07) | 6.60 |
| Lippman 2000/ Ito 2003 | Detroit | 1992-1994 | 1.03 (0.96, 1.10) | 1.85 |
| Lopez-Villarrubia 2012 | Canary Islands (LPdGC) | 2001-2004 | 1.06 (0.99, 1.14) | 1.64 |
| Lopez-Villarrubia 2012 | Canary Islands (SCdT) | 2001-2004 | 1.12 (1.02, 1.22) | 1.10 |
| Mallone 2011 | Rome | 2001-2004 | 1.12 (1.01, 1.23) | 0.86 |
| Perez 2012 | Barcelona (Dust-free days) | 2003-2007 | 1.05 (1.01, 1.08) | 5.81 |
| Perez 2012 | Barcelona (Dust days) | 2003-2007 | 1.04 (0.92, 1.17) | 0.60 |
| Samoli 2013 | 12 European Cities | 2001-2010 | 1.01 (1.00, 1.02) | 20.58 |
| Villeneuve 2003 | Vancouver | 1986-1998 | 1.00 (0.94, 1.06) | 2.22 |
| Zanobetti 2009 | 47 American Cities | 1999-2005 | 1.01 (1.00, 1.02) | 23.39 |
| Subtotal (I-squared = 52.6%, p = 0.013) | | | 1.01 (1.00, 1.02) | 100.00 |
| **Cardiovascular mortality** | | | | |
| Atkinson 2010 | London | 2000-2005 | 1.00 (0.98, 1.02) | 4.87 |
| Chen 2011 | 3 Chinese Cities | 2004-2008 | 1.00 (1.00, 1.00) | 18.85 |
| Halonen 2009 | Helsinki | 1998-2004 | 1.00 (0.98, 1.02) | 4.20 |
| Janssen 2013 | Netherlands | 2008-2009 | 0.98 (0.96, 1.00) | 4.45 |
| Lippman 2000/ Ito 2003 | Detroit | 1992-1994 | 1.02 (0.99, 1.05) | 2.35 |
| Lopez-Villarrubia 2012 | Canary Islands (LPdGC) | 2001-2004 | 1.02 (0.98, 1.07) | 1.03 |
| Lopez-Villarrubia 2012 | Canary Islands (SCdT) | 2001-2004 | 1.02 (0.95, 1.08) | 0.59 |
| Malig 2009 | 15 California Counties | 1999-2005 | 1.00 (0.99, 1.02) | 7.18 |
| Mallone 2011 | Rome | 2001-2004 | 1.03 (1.01, 1.06) | 2.92 |
| Mar 2000/2003 | Pheonix | 1995-1997 | 1.02 (1.00, 1.05) | 4.20 |
| Ostro 2000/2003 | Coachella Valley | 1989-1998 | 1.01 (1.00, 1.02) | 11.66 |
| Perez 2012 | Barcelona (Dust-free days) | 2003-2007 | 1.04 (1.02, 1.07) | 3.65 |
| Perez 2012 | Barcelona (Dust days) | 2003-2007 | 1.10 (1.03, 1.18) | 0.51 |
| Samoli 2013 | 12 European Cities | 2001-2010 | 1.00 (1.00, 1.01) | 14.41 |
| Villeneuve 2003 | Vancouver | 1986-1998 | 1.05 (1.01, 1.10) | 1.30 |
| Zanobetti 2009 | 47 American Cities | 1999-2005 | 1.00 (1.00, 1.01) | 17.82 |
| Subtotal (I-squared = 67.8%, p = 0.000) | | | 1.01 (1.00, 1.01) | 100.00 |
| **Respiratory hospital admissions** | | | | |
| Alessandrini 2013 | Rome (>35) | 2001-2004 | 1.04 (1.00, 1.08) | 4.45 |
| Alessandrini 2013 | Rome (<14) | 2001-2004 | 0.99 (0.94, 1.04) | 2.35 |
| Atkinson 2010 | London (<14) | 2000-2005 | 1.00 (0.97, 1.02) | 7.56 |
| Atkinson 2010 | London (>65) | 2000-2005 | 1.01 (0.99, 1.03) | 10.81 |
| Chen 2005 | Vancouver (>65) | 1995-1999 | 1.12 (1.05, 1.20) | 1.44 |
| Halonen 2009 | Helsinki | 1998-2004 | 1.00 (0.98, 1.02) | 11.06 |
| Host 2008 | 6 French Cities (0-14) | 2000-2003 | 1.06 (1.00, 1.12) | 2.06 |
| Host 2008 | 6 French Cities (15-64) | 2000-2003 | 1.03 (1.00, 1.06) | 5.65 |
| Host 2008 | 6 French Cities (>65) | 2000-2003 | 1.02 (0.98, 1.06) | 4.01 |
| Peng 2008 | 108 US Counties (>65) | 1999-2005 | 1.00 (0.99, 1.00) | 20.85 |
| Qiu 2012 | Hong Kong | 2000-2005 | 1.01 (1.00, 1.01) | 21.10 |
| Stafoggia 2013 | 6 European Cities (>15) | 2001-2010 | 1.01 (0.99, 1.04) | 8.41 |
| Yang 2004 | Vancouver (<3) | 1995-1999 | 1.05 (0.88, 1.25) | 0.23 |
| Subtotal (I-squared = 58.2%, p = 0.004) | | | 1.01 (1.00, 1.02) | 100.00 |
| **Cardiovascular hospital admissions** | | | | |
| Atkinson 2010 | London | 2000-2005 | 1.00 (0.99, 1.01) | 3.84 |
| Halonen 2009 | Helsinki | 1998-2004 | 1.01 (1.00, 1.02) | 4.55 |
| Host 2008 | 6 French Cities | 2000-2003 | 1.01 (0.99, 1.02) | 1.87 |
| Peng 2008 | 108 US Counties (>65) | 1999-2005 | 1.00 (1.00, 1.01) | 57.73 |
| Qiu 2013 | Hong Kong | 2000-2005 | 1.01 (1.00, 1.01) | 14.43 |
| Stafoggia 2013 | 6 European Cities (>15) | 2001-2010 | 1.01 (1.00, 1.01) | 17.57 |
| Subtotal (I-squared = 0.0%, p = 0.815) | | | 1.01 (1.00, 1.01) | 100.00 |

NOTE: Weights are from random effects analysis

.801   1   1.25

**Fig. 1** Forest plot of incidence rate ratios for mortality and hospital admissions per 10 μg/m$^3$ of short-term exposure to PM$_{10-2.5}$. Note: Overall estimates are from random-effects models without adjustment for possible publication bias

**Table 2** Summary rate ratios (RR) for mortality and hospital admissions per 10 μg/m³ of PM$_{10-2.5}$ and PM$_{2.5}$ concentrations

| | Total Mortality | Short-Term Exposures | | | | Long-Term Exposures |
| | | Respiratory Mortality | Cardiovascular Mortality | Respiratory Hospitalizations | Cardiovascular Hospitalizations | Total Mortality |
|---|---|---|---|---|---|---|
| **Coarse Particulate Matter** | | | | | | |
| Number of studies | 19 | 11 | 14 | 9 | 6 | 6 |
| Number of estimates[a] | 22 | 13 | 16 | 13 | 6 | 6 |
| Pooled RR (95 % CI)[b] | 1.006 (1.003–1.008) | 1.014 (1.005–1.024) | 1.007 (1.002–1.012) | 1.010 (1.001–1.018) | 1.005 (1.003–1.008) | 1.021 (0.984–1.058) |
| Heterogeneity | | | | | | |
| I² | 51 % | 53 % | 68 % | 58 % | 0 % | 38 % |
| p-value | 0.004 | 0.013 | <0.001 | 0.004 | 0.82 | 0.15 |
| Publication bias | | | | | | |
| Adjusted RR (95 % CI)[c] | 1.004 (1.001–1.007) | 1.007 (0.996–1.018) | 1.002 (0.997–1.008) | 1.006 (0.996–1.016) | 1.005 (1.003–1.007) | 0.994 (0.956–1.035) |
| Egger regression test, p-value | 0.05 | 0.01 | 0.01 | 0.07 | 0.45 | 0.66 |
| **Fine Particulate Matter** | | | | | | |
| Number of studies | 18 | 11 | 14 | 9 | 7 | 6 |
| Number of estimates[a] | 21 | 13 | 15 | 11 | 7 | 6 |
| Pooled RR (95 % CI)[b] | 1.007 (1.004–1.009) | 1.012 (1.005–1.020) | 1.006 (1.004–1.008) | 1.009 (1.005–1.013) | 1.006 (1.004–1.007) | 1.092 (1.009–1.182) |
| Heterogeneity | | | | | | |
| I² | 75 % | 62 % | 17 % | 27 % | 0 % | 76 % |
| p-value | <0.001 | 0.002 | 0.26 | 0.19 | 0.51 | 0.001 |
| Publication bias | | | | | | |
| Adjusted RR (95 % CI)[c] | 1.005 (1.002–1.008) | 1.006 (0.998–1.013) | 1.006 (1.004–1.008) | 1.009 (1.005–1.013) | 1.006 (1.004–1.007) | 1.061 (0.984–1.143) |
| Egger regression test, p-value | 0.08 | 0.06 | 0.20 | 0.39 | 0.28 | 0.32 |

Notes: [a] The number of estimates can differ from the number of studies due to reports stratified by age group and/or Saharan dust days

[b] Overall estimates are from random-effects models

[c] Models are adjusted for possible publication bias using a trim and fill approach

(Table 2, Fig. 5). There was limited evidence of heterogeneity among these point estimates ($I^2$=38 %, p=0.15) and no finding of publication bias among these five studies. A meta-analysis of multi-pollutant estimates from five studies [79, 80••, 81••, 82, 83] indicated no associations with $PM_{10-2.5}$ after adjustment for $PM_{2.5}$ (-1.2 %, 95 % CI: -5.1 to 2.8 % per 10 µg/m$^3$). In contrast, $PM_{2.5}$ associations were weakened after adjustment for $PM_{10-2.5}$ (3.7 %, 95 % CI: 0 to 7.6 % per 10 µg/m$^3$) but remained positive and statistically significant. Because there were only six studies identified, we did not investigate stratified analyses by study characteristics.

## Discussion

Although the health implications of $PM_{10-2.5}$ remain far less characterized than those for $PM_{2.5}$, there is a growing epidemiological literature for $PM_{10-2.5}$. In this meta-analysis we identified 23 and 10 studies of short-term associations with mortality and hospitalizations, respectively, as well as 6 papers

for long-term associations with mortality. Overall, we found suggestive evidence that higher short-term $PM_{10-2.5}$ concentrations are associated with greater rates of mortality and hospitalizations, with the strongest relationships for respiratory endpoints. There was high heterogeneity in these estimates, however, with stronger associations suggested for European locations as compared to North America and weaker associations for locations with the highest $PM_{10-2.5}$ levels. Adjustments for $PM_{2.5}$ and asymmetry due to possible publication bias resulted in positive associations for $PM_{10-2.5}$ that were weaker and less precise. Higher long-term exposures to $PM_{10-2.5}$ were also associated with larger mortality in single pollutant models but these associations were eliminated by control for $PM_{2.5}$. $PM_{2.5}$ associations in these studies were less sensitive to control for $PM_{10-2.5}$ and had less evidence of asymmetry.

$PM_{10-2.5}$ may plausibly impact health given their deposition in the lungs, high biological content, and, in urban areas, high content of heavy metals.[86] Toxicological studies have provided evidence of the inflammatory effects of $PM_{10-2.5}$, including some evidence that $PM_{10-2.5}$ may be
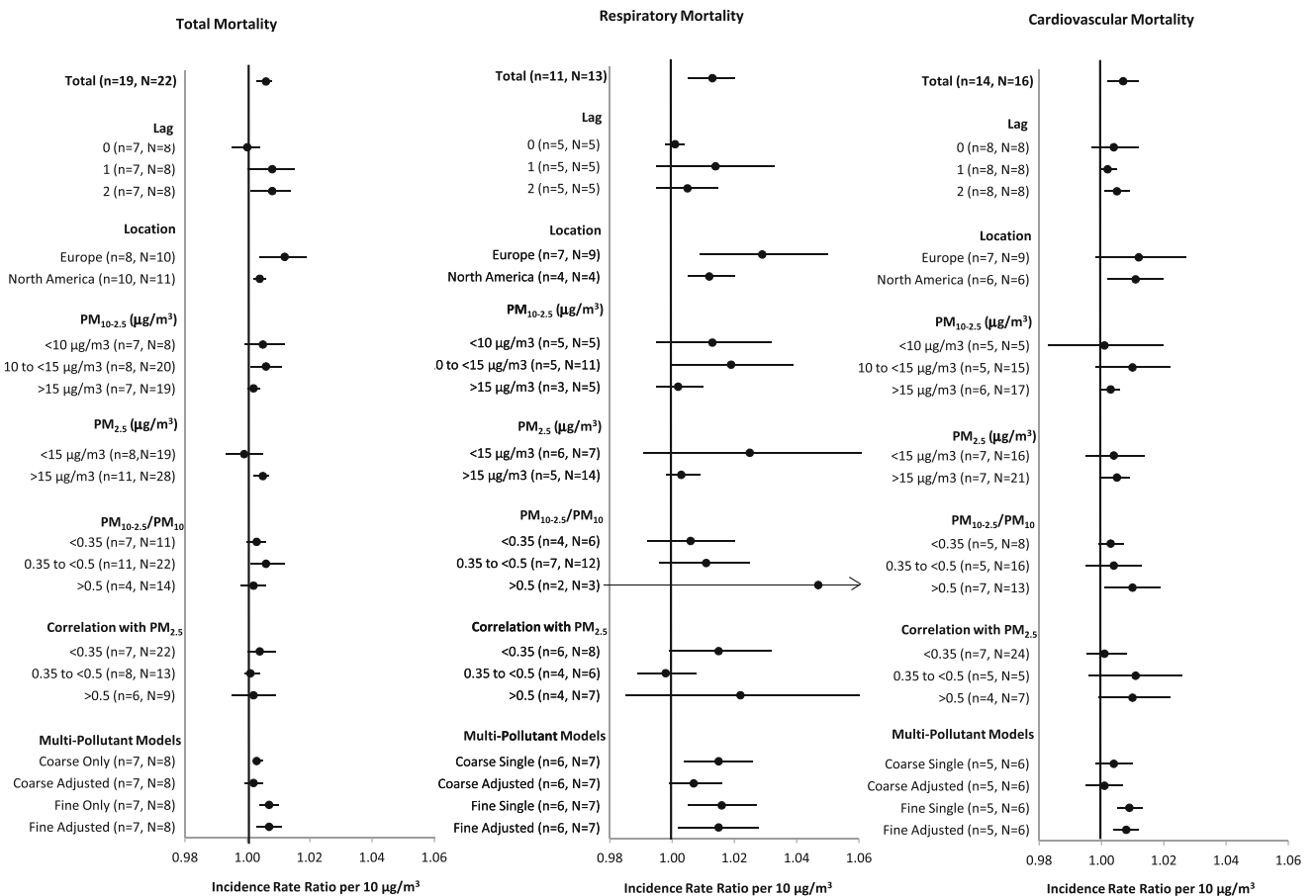


**Fig. 2** Summary incidence rate ratios for short-term exposures to $PM_{10-2.5}$ with mortality by study characteristics. Note: Estimates stratified by concentrations include city-specific data from Malig and Ostro [35] and Chock et al. [45] provided via personal correspondence. Estimates were also provided by Zanobetti and Schwartz [33••] but ultimately not included because the use of shrunken Bayes estimates could have undue influence on our results
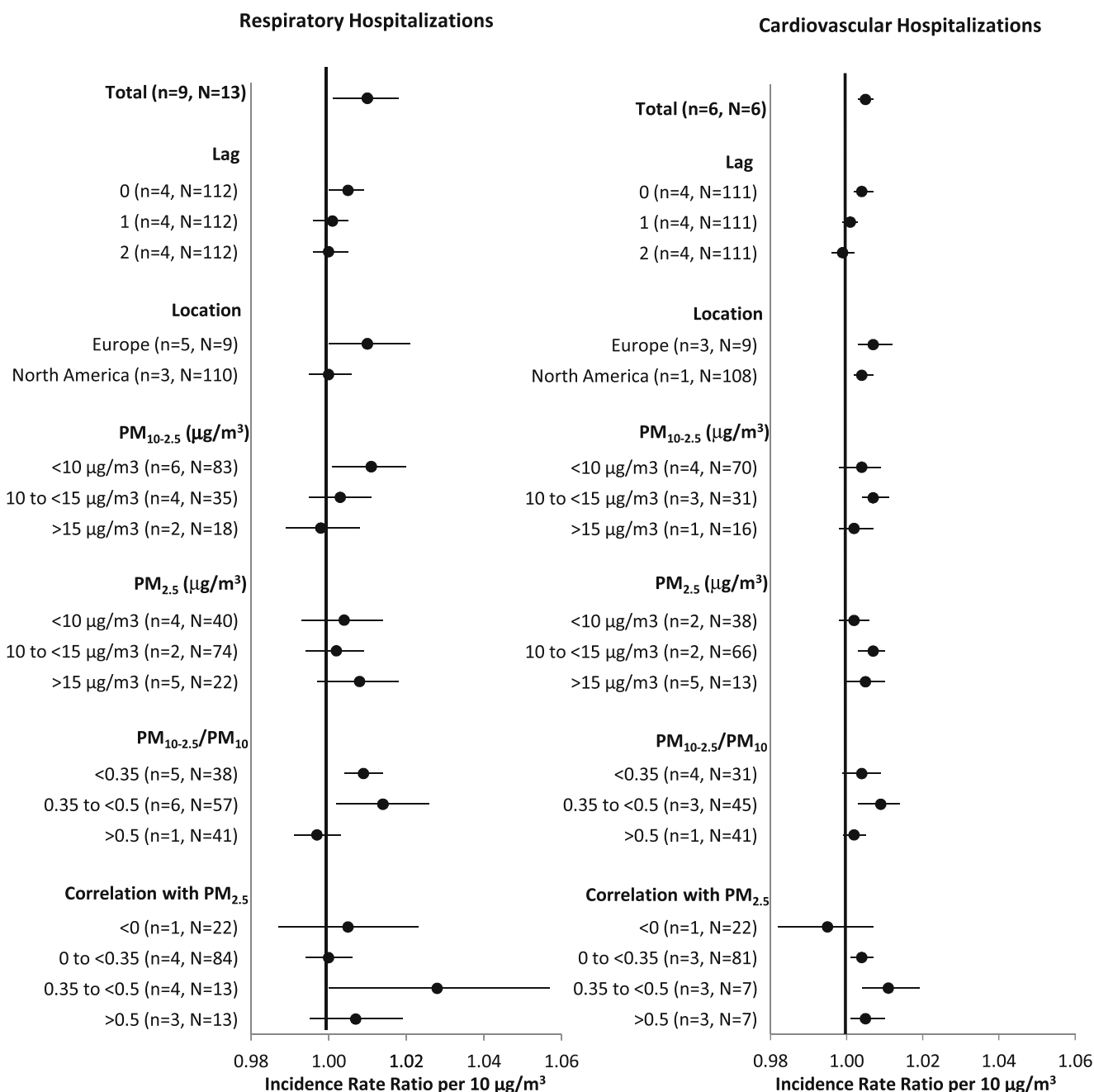
**Fig. 3** Summary incidence rate ratios for short-term exposures to $PM_{10-2.5}$ with hospital admissions by study characteristics. Note: Estimates stratified by PM concentrations and correlations include city-specific estimates provided by Peng et al. [62••] and Host et al. [61] in personal communications

more inflammatory than $PM_{2.5}$.[87–93] Controlled human exposure studies have similarly provided some evidence of acute alterations in markers of inflammation, coagulation, and autonomic tone although there was not consistent evidence of stronger associations with $PM_{2.5}$.[94–99] Epidemiological data for subclinical endpoints with $PM_{10-2.5}$ are still relatively sparse but there has been some evidence of biological activity including alterations in

cytokines and coagulation factors, pulmonary function, respiratory symptoms, and cardiac function in some [96, 100–106] but not all studies.[104, 107–110] It should be noted, however, that even results from positive studies were often only suggestive and failed to meet statistical significance.

One possible explanation for the inconclusive nature of the literature pertains to the challenges of accurate exposure
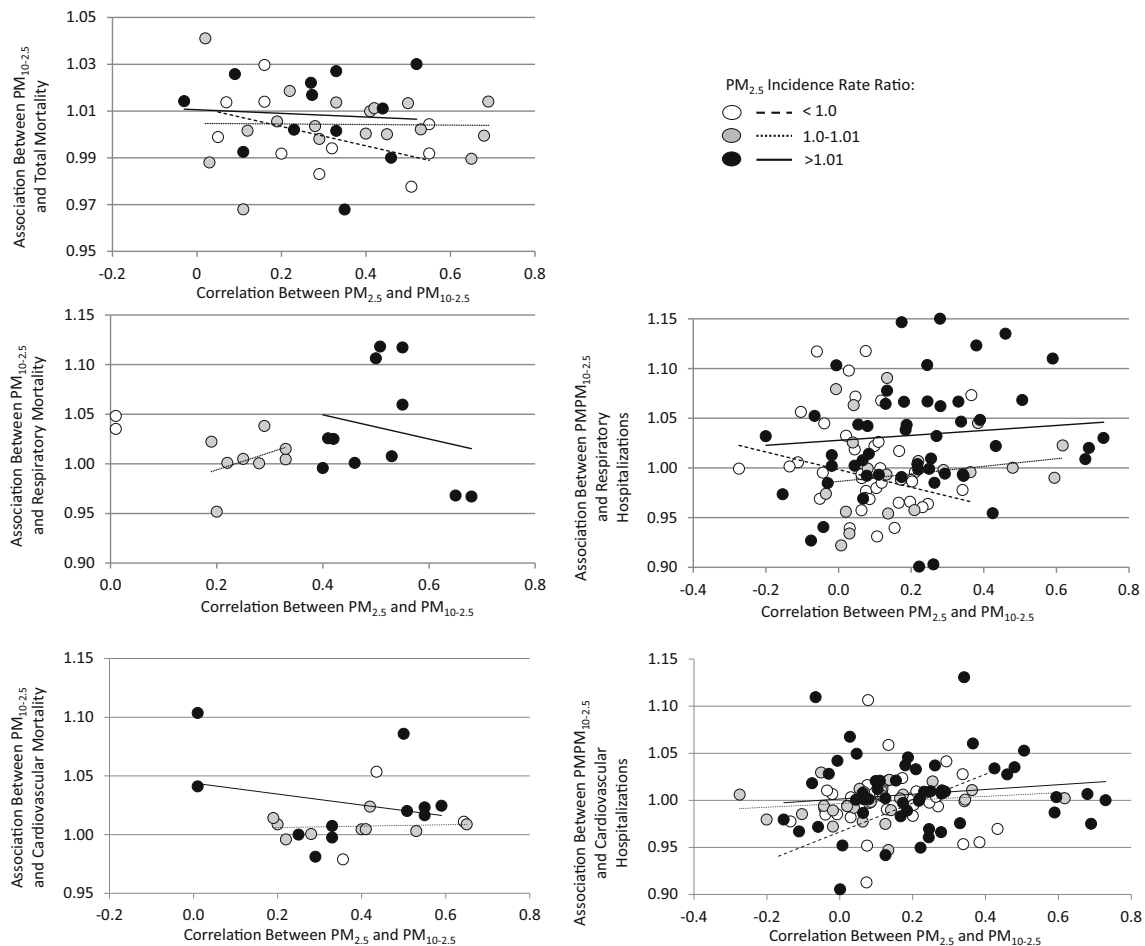
**Fig. 4** Incidence rate ratios (RR) for $PM_{10-2.5}$ as a function of the correlation between short-term $PM_{10-2.5}$ and $PM_{2.5}$ concentrations stratified by $PM_{2.5}$ associations. Note: Data include city-specific estimates provided by Peng et al. [62••] and Host et al. [61] from personal communications

assessment for $PM_{10-2.5}$. $PM_{10-2.5}$ concentrations are often highly spatially and temporally variable as a consequence of higher deposition velocities as well as the intermittent nature of many $PM_{10-2.5}$ sources.[2] For temporal trends, this has resulted in correlation coefficients between different sites that are generally lower than those reported for $PM_{2.5}$ or $PM_{10}$.[111] Concentrations have also been shown to vary across space based on proximity to different sources [112, 113], making long-term exposure assignment especially difficult given the limited numbers of monitoring stations with data to estimate $PM_{10-2.5}$. In addition, most measurements of $PM_{10-2.5}$ are indirect, estimated through subtraction of $PM_{2.5}$ from $PM_{10}$ concentrations measured at the same location. While past research has deemed this a reliable approach to estimating $PM_{10-2.5}$ in urban areas [114], there are inherently errors due to the uncertainty of both filters. Even dichotomous samples for $PM_{10-2.5}$, which are generally thought to have less error due to the use of a virtual impactor, may also have additional uncertainty due the small deposition of $PM_{2.5}$ in the $PM_{10-2.5}$ channel [115]. Similarly, continuous monitors such as the TEOM have been shown to be subject to

measurement error if the losses of semi-volatile material are not properly accounted for [13]. Finally, infiltration rates for $PM_{10-2.5}$ are quite low in comparison to $PM_{2.5}$ and the presence of indoor sources are high, suggesting that ambient exposure may not accurately estimate personal exposure [116].

Although we only had limited data to investigate the impacts of measurement error on associations with health, we found some evidence of its importance with stronger associations among short-term concentrations measured using dichotomous samplers as compared to difference metrics, and weaker associations in studies using TEOMs as compared to other techniques. The three investigations using spatial prediction models to assess small-scale variability of long-term $PM_{10-2.5}$ concentrations, however, did not consistently have stronger associations with mortality than other investigations relying only on central monitoring stations. Given these challenges for the measurement of $PM_{10-2.5}$, we encourage researchers to be mindful of the methods used to assess exposure and report on the potential implications for their analyses. Epidemiological research is underway as part of the Colorado

| Study | Population | Period | ES (95% CI) | % Weight |
|---|---|---|---|---|
| Beelen 2013 | ESCAPE | 1992-2007 | 1.08 (0.96, 1.21) | 8.20 |
| Lipfert 2006 | Veterans | 1989-1996 | 1.06 (1.01, 1.11) | 26.72 |
| McDonnel 2000 | AHSMOG | 1977-1992 | 1.05 (0.92, 1.20) | 6.46 |
| Pope 2002 | ACS | 1982-1998 | 1.01 (0.97, 1.05) | 30.75 |
| Puett 2009 | Nurses Health | 1992-2002 | 1.03 (0.89, 1.19) | 5.81 |
| Puett 2011 | Physicians Health | 1989-2003 | 0.96 (0.91, 1.02) | 22.06 |
| Overall (I-squared = 37.9%, p = 0.154) | | | 1.02 (0.98, 1.06) | 100.00 |

NOTE: Weights are from random effects analysis

**Fig. 5** Summary of rate ratios between long-term exposure to $PM_{10-2.5}$ and death per 10 $\mu g/m^3$

Course Rural Urban Sources and Health Study [117] for short-term exposures and the Multi-Ethnic Study of Atherosclerosis and Coarse Particulate Matter (MESA Coarse) [112] for long-term exposures that incorporates more accurate estimates of exposure, and thus should be subject to less measurement error.

Larger measurement error relative to $PM_{2.5}$ may be a plausible explanation for the weakened associations for $PM_{10-2.5}$ in two-pollutant models. First, the presence of greater classical measurement error is likely to result in a reduction of the point estimate towards the null. In addition, it has been hypothesized that a transfer of association from a variable with more measurement error to another with less error may occur in situations where there are substantial differences in the measurement error [118]. Another explanation is that confounding is present, although $PM_{2.5}$ and $PM_{10-2.5}$ concentrations only exhibited modest correlations in the incorporated studies (range: 0.0–0.7, median~0.3). Furthermore, there was no consistent evidence of increasing associations for $PM_{10-2.5}$ with increasing correlations between $PM_{2.5}$ and $PM_{10-2.5}$ concentrations when $PM_{2.5}$ was associated with a worsening of health. Nor did we find consistent evidence of decreasing $PM_{10-2.5}$ associations with increasing correlations between $PM_{10-2.5}$ and $PM_{2.5}$ concentrations when $PM_{2.5}$ was found to be protective of health. Thus, while it may be compelling to assume that any observed associations with $PM_{10-2.5}$ are due to $PM_{2.5}$, our results do not support this as the sole explanation. Nevertheless, we encourage future investigations to continue exploring multi-pollutant models and reporting correlations between pollutants to better understand these complex relationships.

While it does not appear as though associations with $PM_{10-2.5}$ are simply due to confounding by $PM_{2.5}$, it remains possible that both $PM_{2.5}$ and $PM_{10-2.5}$ are acting as surrogates of a broader mixture of pollution. Thus, it may be that another unmeasured component or several components are the true causal factors. For example, in rural areas, gram-negative bacteria (as represented by bacterial-derived lipopolysaccharide or endotoxin) $PM_{10-2.5}$ may be of special interest, especially for inflammatory mechanisms [87, 88, 97]. In urban areas, metals associated with roadway dust may be similarly important [89, 91, 119, 120]. The general lack of investigation of endotoxin levels, components of $PM_{10-2.5}$, and multi-pollutant mixtures remains a weakness of the existing literature and an area for future development.

Along similar lines, it has been hypothesized that the toxicity of $PM_{10-2.5}$ may be greater for particles originating in urban environments as compared to rural environments. Some evidence of such a relationship has been reported in 108 US counties [62••] and at least one toxicology study [88]. In this meta-analysis, we found evidence that $PM_{10-2.5}$ associations with health were often weaker in regions with higher levels of $PM_{10-2.5}$. This may suggest a non-linear dose response, as was reported in China [63••], or a difference in toxicity for more rural or arid regions. Weaker associations between $PM_{10-2.5}$ and hospital admissions in regions with higher $PM_{10-2.5}/PM_{10}$ ratios may also support different toxicity by region, but the same pattern was not robust for morality. Interestingly, several investigators have attempted to distinguish toxicity of particulate matter from dust storms, but uncertainty remains around this question. Among those studies included in this meta-analysis, larger associations between short-term $PM_{10-2.5}$ and health were reported on Saharan dust days in Rome [41, 59], whereas results with mortality in Madrid and Barcelona stratified by dust days were more mixed [31, 46]. While additional research may be needed from rural locations to inform this question, challenges will always remain unless speciated data is used, since anthropogenic and biological particles likely adhere to dust particles as they are transported through other airsheds.

**Table 3** Descriptive information for long-term exposure studies included in the meta-analysis

| Study | Location | Time Period | Study Design | Restrictions | Reported or Estimated # of Events (Short-Term) or # of Participants (Long-Term) | Estimated Incidence Rate Ratios (95 % CI) per 10 µg/m³ of $PM_{10-2.5}$ | Estimated Incidence Rate Ratios (95 % CI) per 10 µg/m³ of $PM_{2.5}$ | Median or Mean† $PM_{10-2.5}$ | Median or Mean† $PM_{2.5}$ | Correlation of $PM_{10-2.5}$ and $PM_{2.5}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Long-Term Associations With Non-Accidental Mortality | | | | | | | | | | |
| Beelen et al. 2013 | 19 Cohorts from 12 European Countries | 1985–2007 | Cohort Studies | | 327,780 | 1.08 (0.96, 1.21) | 1.14 (1.04, 1.28) | 4.0-20.7† | 6.6-31.0† | 0.11-0.90 |
| Lipfert et al. 2006 | 32 Veterans Hospitals, United States | 1989–1996 | Cohort Study | All-Cause | 24,642 | 1.06 (1.01, 1.11) | 1.15 (1.05, 1.26) | 16† | 14.3† | |
| McDonnell et al. 2000 | California, United States | 1977–1992 | Cohort Study | | 1,266 | 1.05 (0.92, 1.20) | 1.22 (0.95, 1.58) | 27.3† | 31.9† | 0.5 |
| Pope et al. 2002 | 50 States, United States | 1982–1998 | Cohort Study | | 359,000 | 1.01 (0.97, 1.05) | 1.06 (1.02, 1.11) | 19.2†~ | 17.7† | |
| Puett et al. 2009 | 13 Northeast and Midwest States, United States | 1992–2002 | Cohort Study | | 66,250 | 1.03 (0.89, 1.18) | 1.26 (1.02, 1.54) | 7.7† | 13.9† | |
| Puett et al. 2011 | 13 Northeast and Midwest States, United States | 1989–2003 | Cohort Study | | 17,545 | 0.96 (0.91, 1.02) | 0.94 (0.87, 1.00) | 10.1† | 17.8† | |

~ $PM_{15}$ reported instead of $PM_{10}$

Overall, this work adds to the literature by presenting the first meta-analysis results for $PM_{10-2.5}$. With numerous new investigations in the literature, we also conducted stratified analyses to explore differences in associations with hospital admissions and mortality by various characteristics of the locations studied. As substantial heterogeneity was present among the associations presented, this represents an important area that requires further exploration in future investigations. In fact, it should be noted that the summary estimates reported in this analysis should be viewed with caution due to the presence of heterogeneity. Likewise, the observed heterogeneity suggests that the trim and fill method used to account for potential publication bias may be an overly conservative approach. While it may be challenging to fully characterize different personal characteristics that confer susceptibility, or components of the air pollution mixture that may lead to greater risk of morbidity and mortality in time-series studies, other designs not included in this investigation such as panel studies and controlled clinical studies have important contributions to make.

## Conclusions

Suggestive evidence was observed for increased hospital admissions and mortality with higher levels of short-, but not long-term, $PM_{10-2.5}$ concentrations. Relationships were generally stronger for respiratory endpoints, though associations with cardiovascular endpoints could not be excluded. Similarly, in spite of some sensitivity of the associations to control for $PM_{2.5,}$ our analysis suggests that associations with short-term exposures to $PM_{10-2.5}$ cannot be fully explained by confounding by $PM_{2.5}$. Additional research is still required to better understand sources of heterogeneity in associations, including co-exposure with other pollutants, sources, spatial variability, and composition of $PM_{10-2.5}$, as well as individual susceptibilities.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Sara D. Adar, Paola A. Filigrana, Nicholas Clements, and Jennifer L. Peel declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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