Air Pollution and Human Mortality: 25+ Years of Cohort Studies

C. Arden Pope III¹, Nathan Coleman¹, Zachari A. Pond¹, Richard T. Burnett²

Draft Review Copy

August 16, 2019

This paper has been prepared for the Harvard Center for Risk Analysis, “Risk Assessment, Economic Evaluation, and Decisions” workshop, September 26-27, 2019.

¹Department of Economics, Brigham Young University, Provo, UT
²Health Canada, Ottawa, Ontario, Canada

Corresponding Author:  C. Arden Pope III, PhD, 435-T Crabtree Technology Building, Brigham Young University, Provo, UT 84602. Phone: 801-422-2157; Fax: 801-422-0194; E-mail: cap3@byu.edu

Acknowledgments:  This research was supported by the Center for Air, Climate, and Energy Solutions (CACES) funded by the U.S. Environmental Protection Agency, Grant Number R835873.

Competing financial interests:  The authors declare they have no actual or potential competing financial interests.
Abstract

Much of the key epidemiological evidence that long-term exposure to air pollution contributes to increased risk of mortality comes from survival studies of cohorts of individuals. Although the first two of these studies, published in the mid-1990s, were highly controversial, much has changed in the last 25+ years. The objectives of this paper are to succinctly compile and summarize the findings of these cohort studies using meta-analytic tools and to address several of the key controversies. Independent reanalysis and substantial extended analysis of the original cohort studies have been conducted and many additional studies using a wide variety of cohorts, including cohorts constructed from public data, have been published. Meta-analytic estimates of the mean of the distribution of effects from cohort studies that are currently available, provide substantial evidence of adverse air pollution associations with all-cause, cardiopulmonary, and lung cancer mortality.

Key words: Air pollution, mortality, meta-analysis, particulate pollution, health risks

1. Introduction

Epidemiological research concerning air pollution and human health has a rich and complex history (Brimblecombe 1987; Lipfert 1994; Davis 2002; Vedal 1997; Pope and Dockery 2006; Brook et al. 2010; Rajagopalan et al 2018). Elevated pulmonary and cardiovascular morbidity and mortality accompanied historic air pollution episodes in Meuse Valley, Belgium (1930), Donora, Pennsylvania (1948), and London, England (1952) (Bell 2001). Subsequent time-series and related studies provided further evidence that episodic or short-term elevations in air pollution at even moderate levels contribute to cardiopulmonary morbidity and mortality (Pope and Dockery 2006; Brook et al. 2010; Rajagopalan et al 2018). In the 1970s and 1980s, cross-sectional studies of U.S. populations observed that long-term average concentrations of air pollution were associated with increased mortality rates (Lave and Seskin 1977; Evans et al 1984; Ozkaynak and Thurston 1987). Various quasi-experimental studies have also observed links with pollution and mortality. For example, a difference-in-differences analysis observed that differential reductions in pollution in the U.S. between 1980 and 2000 were associated with differential improvements in life expectancy (Pope et al. 2009). A regression-discontinuity
analysis of China’s Huai River policy estimated that air pollution contributed to substantive reductions in life expectancy in Norther China (Ebenstein et al. 2017).

A substantive body of evidence regarding air pollution and risk of mortality comes from survival studies of cohorts of individuals that evaluate pollution-mortality associations while controlling for individual and other risk factors. The first cohort studies of mortality and fine particulate matter air pollution were published in the mid 1990’s (Dockery et al. 1993; Pope et al. 1995). Although these studies were highly controversial, in the last 25+ years since these first studies were published, extensive independent re-analyses and extended analyses have been conducted. Pollution-mortality associations have also been explored in numerous other cohorts in the U.S. and other countries around the world. The objective of this paper is to succinctly compile and summarize the findings of these cohort studies using meta-analysis, and to briefly address several key concerns, findings, and advances of these studies.

2. Harvard Six-Cities and ACS CPS-II cohorts

The Harvard Six-Cities study (Dockery et al. 1993) was a 14-16 year prospective follow-up of a cohort of over 8,000 adults living in 6 U.S. cities that were selected to be representative of the range of air pollution in the U.S. Various air pollutants were monitored and analyzed including: TSP (total suspended particulate matter), PM$_{10}$ (particles < 10 µm in aerodynamic diameter), PM$_{2.5}$ (particles < 2.5 µm in aerodynamic diameter), SO$_4$ (sulfate particles), H$^{+}$ (aerosol strong acidity), SO$_2$ (sulphur dioxide), NO$_2$ (nitrogen dioxide), and O$_3$ (ozone). Air pollution and mortality associates were analyzed using Cox proportional hazards regression models to estimate hazard ratios (HR) controlling for age, sex, cigarette smoking, body mass, education, and occupational exposures. Elevated mortality risks were most strongly associated with PM$_{2.5}$. Estimated HRs per 10 µg/m$^3$ long-term exposure to PM$_{2.5}$, were 1.13 (95% CI=1.04–1.23) for all-cause mortality and 1.18 (1.06–1.32) for cardiopulmonary mortality.

The findings of the Harvard Six-Cities study provided primary motivation to conduct a replicative analyses using an independent cohort of approximately 500,000 adults drawn from the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) who lived in up to 151 U.S. metropolitan areas and who had been followed prospectively from 1982-1989 (Pope et al. 1995). The ACS CPS-II cohort data were linked to available ambient PM$_{2.5}$ and SO$_4$ data and Cox proportional hazards regression models were used to estimate HRs controlling for age, sex,
race, cigarette smoking, pipe and cigar smoking, exposure to passive smoke, body mass, education, occupational exposure, and alcohol use. Elevated mortality risks were associated with both PM$_{2.5}$ and SO$_4$. Estimated HRs per 10 µg/m$^3$ long-term exposure to PM$_{2.5}$, were 1.07 (95% CI=1.04–1.10) for all-cause mortality and 1.12 (1.07–1.17) for cardiopulmonary mortality.

The Harvard Six-Cities and ACS CPS-II cohort studies were controversial in part because they reported remarkably robust pollution-mortality associations, especially for cardiopulmonary mortality, and because the pollution-mortality associations were much larger than expected based on the short-term associations observed in the daily time-series studies. There were also concerns about validity, analytic methods, data quality and accessibility. In 1997 the original investigators of both studies agreed to provide the cohort and related study data for an intensive reanalysis by an independent research team (Krewski et al. 2000). This effort was conducted under the oversight of the Health Effects Institute that assured confidentiality of information from study participants and it provided data quality assurance audits, replication and validation of the originally reported results, and sensitivity analyses.

Subsequently there have been multiple extended analyses of the Harvard Six-Cities cohort (Laden et al. 2006; Lepeule et al. 2012) and the ACS CPS-II cohort (Pope et al. 2002; Pope et al. 2004; Smith et al. 2009; Krewski et al. 2009; Jerrett et al. 2009; Turner et al. 2011; Pope et al. 2015; Turner et al. 2016, Thurston et al. 2016b; Jerrett et al. 2017). These extended analyses include substantially increased mortality follow-up with much larger numbers of deaths and increased statistical power; improved assessment of air pollution exposures from metro-level averages to modeled exposures at geocoded residential addresses; and improved statistical modeling that allows for control of both individual and ecological covariates. For both the Harvard Six-Cities study and the ACS CPS-II study, estimated adjusted HRs across the originally reported results, the independent reanalysis, and the various extended analyses are remarkably consistent (see Figures 1, 2, and 3).

3. Meta-analytic compilation of expanding cohort studies

There is a large and growing number of studies that have evaluated pollution-mortality associations in other cohorts from various areas around the world. The HRs (and 95% confidence intervals) from these cohorts are also illustrated in Figures 1, 2, and 3. The cohort studies illustrated in these figures have been complied based on searches of Medline and
supplemented with studies included in reviews by Pope and Dockery (2006), Brook et al. (2010), Hoek et al. (2013), Vodonos et al. (2018), and the Integrated Science Assessment for Particulate Matter (U.S. Environmental Protection Agency, External Review Draft October 2018).

As is illustrated in Figures 1-3, there are now many additional cohort studies from the U.S. including a cohort of California Seventh-day Adventists (McDonnell et al. 2000; Chen et al. 2005), a cohort of Cystic Fibrosis patients (Goss et al. 2004), a cohort of postmenopausal women from the Women’s Health Initiative (WHI) (Miller et al. 2007), multiple cohorts constructed from U.S. Medicare data (Eftim et al 2008; Zeger et al. 2008; Shi et al. 2016; Kioumourtzoglou et al. 2016; Wang et al. 2017a; Di et al. 2017; Eum et al. 2018), a cohort of U.S. veterans (Lipfert et al. 2006), the Nurses’ Health Study cohort (Puett et al 2009; Puett et al. 2014; Hart et al. 2015), the California Teachers cohort (Ostro et al. 2011; Lipsett et al. 2011; Ostro et al. 2015), the Male Health Professionals cohort (Puett et al. 2011), a cohort of males in the U.S. trucking industry (Hart et al. 2011), the Agricultural Health Study cohort (Weichenthal et al. 2014), the U.S. National Institutes of Health—AARP Diet & Health cohort (Thurston et al 2016a), a California Elderly cohort (Garcia et al. 2016), a New Jersey Department of Health cohort (Wang et al. 2016), and cohorts constructed from National Health Interview Survey data (Pope et al. 2018a; Parker et al. 2018; Pope et al. 2019).

Studies from Canada include studies of cohorts based on the Canadian Census Health and Environment Cohort (Crouse et al. 20012; Crouse et al. 2015; Weichenthal et al. 2016; Crouse et al. 2016; Pinault et al. 2017; Pinault et al. 2018; Cakmak et al. 2018), a Breast Screening cohort (Villeneuve et al. 2015), a Canadian Community Health cohort (Pinault et al. 2016), and a cohort of survivors of myocardial infarction (MI) (Chen et al. 2016). Studies from Europe include cohorts from the Netherlands (Beelen et al. 2008; Fischer et al. 2015; Downward et al. 2018), France (Filleul et al. 2005; Bentayeb et al. 2015), Germany (Gehring et al. 2006), England (Carey et al. 2013; Dehbi et al. 2017), Italy (Cesaroni et al. 2013), Spain (Keijzer et al. 2017), Denmark (Hvidtfeldt et al. 2019), and a coordinated pooled analysis of up to 22 European cohorts (Beelen et al. 2014a; Beelen et al. 2014b; Raaschou-Nielsen et al. 2013; Kimakopoulou et al. 2014). Studies from Asia include studies of cohorts from Japan (Ueda et al. 2012; Katanoda et al. 2011) and Iran (Yarahmadi et al. 2018) as well as Chinese cohorts from Hong Kong (Wong et al. 2015; Wong et al. 2016), Taiwan (Tseng et al. 2015), and mainland China (Cao et al. 2011; Yin et al. 2017; Li et al. 2018).
Comparisons of the estimated HRs presented in Figures 1-3 provide evidence of adverse PM$_{2.5}$-associations with all-cause, cardiopulmonary, and lung cancer mortality. Based on studies reported in Figures 1-3, meta analytic estimates were estimated using Comprehensive Meta Analysis (Version 3.3.070; https://www.meta-analysis.com/). In an effort to be all-inclusive, the meta estimates were calculated for all reported studies. However, to avoid the use of multiple studies of the same or similar cohorts, and to exclude less representative, specialty cohorts (such as Cystic Fibrosis, MI survivors, or TB cohorts) meta estimates were also calculated for only selected studies. The specific selected studies are indicated with black diamond symbols with the size of the diamond proportional to the relative weight in the random effect estimate using selected studies. The selected studies generally included only the study with the largest and longest follow-up for each cohort or similar cohorts.

Visual comparisons of the estimated HRs presented in Figures 1-3 suggest that there is heterogeneity in estimates across different cohorts and across different analyses of the same or similar cohorts. Figure 5 provides a plot of the distribution of HRs for all-cause mortality (greater than or less than 1 and statistically significant [$p \leq 0.05$] versus not) for all studies and for selected studies. Most, but not all, of the studies observed statistically significant adverse PM$_{2.5}$-mortality associations. Fixed effect meta-analysis provided further evidence of between study heterogeneity ($I^2 > 90; P < 0.001$ for all and selected studies of all cause mortality). Given this observed heterogeneity and the likelihood of real differences in effects across cohorts, fixed-effect meta estimates would not be appropriate. Therefore, random-effects meta estimates, that estimate the mean of the distribution of effects, were calculated.

Based on the random-effects meta estimates using the selected studies, the estimated HRs per 10 µg/m$^3$ long-term exposure to PM$_{2.5}$, is 1.08 (95% CI=1.06–1.10) for all-cause mortality, 1.11 (1.08–1.14) for cardiopulmonary mortality, and 1.13 (1.07–1.20) for lung cancer mortality. Similar HR estimates were obtained using all studies. For all-cause and lung cancer mortality the meta estimates are similar for North American, European, and Asian studies. For cardiopulmonary mortality, the meta estimated HR is larger for North America. These results are comparable to previously reported estimates (Hoek et al. 2013; Vodonos et al. 2018). To explore for publication or selection bias, funnel plots of standard errors plotted over log hazard ratios for all-cause mortality are presented in Figure 4. The funnel plot on the left includes all studies except the China TB study (which is clearly a unique outlier cohort and falls outside of
the scale of Figure 4). The funnel plot on the right includes all selected studies (as indicated with black diamonds in Figure 1). Although funnel plots are not definitive, the plots presented in Figure 4 do not provide substantive evidence of publication or selection bias.

4. Key Controversies

There have been various controversies regarding the results and use of cohort studies of long-term exposure to PM$_{2.5}$ and mortality risk. Some of these controversies and concerns have been at least partially resolved. The initial controversies regarding the need for independent reanalyzes and replication of early studies has been reasonably well addressed. With regards to the original Six-Cities and ACS CPS-II cohort studies, intensive independent reanalysis as well as substantial extended analyses have been conducted. Furthermore, although it is not generally possible to fully replicate original epidemiological studies, PM$_{2.5}$-mortality associations have been observed in many different cohorts and by many different research teams. Although there are limitations to using meta-analytic approaches to summarize this large and growing literature, random-effects meta estimates of the mean of the distribution of effects indicate highly statistically significant adverse PM$_{2.5}$-mortality associations for all-cause mortality, cardiopulmonary mortality, and lung-cancer mortality.

Another controversy regarding cohort studies of mortality and air pollution is the assertion that they are “Secret Science” because they use private and confidential health and personal data with ethical and legal restrictions on the release of these data. Data collected for cohort studies often involve confidentiality agreements with research participants. Proposed legislation (Michaels and Burke 2017) and a proposed U.S. Environmental Protection Agency rule (Cornwall 2018) would disallow the EPA from using scientific research that is not public data. It is unclear how this controversy can be fully resolved, because of continued counter demands to protect private health and personal data. However, recently there have been cohort studies of air pollution and mortality that have used public data. Di et al (2017) constructed a massive open cohort of over 60 million persons with nearly 0.5 billion person-years of follow-up using the U.S. Medicare data from the Centers for Medicare and Medicaid Services. The estimated HR per 10 µg/m$^3$ long-term exposure to PM$_{2.5}$, from this study was 1.073 (95% CI=1.071–1.075) for all-cause mortality—similar to the meta-estimate from the combined studies (see Figure 1). Parker et al (2018) and Pope et al (2019) estimated PM$_{2.5}$-mortality HRs
from constructed cohorts using public data from National Health Interview Surveys, linked to the National Death Index. The estimated HRs per 10 µg/m³ long-term exposure to PM$_{2.5}$, from these studies for all-cause mortality were 1.08 (95% CI=1.01–1.16) and 1.12 (95% CI=1.09–1.15) respectively—again comparable to the meta-estimate from the combined studies (See Figures 1-2). Similarly, the studies of the Canadian Census Health and Environment Cohort (Crouse et al. 2012; Crouse et al. 2015; Weichenthal et al. 2016; Crouse et al. 2016; Pinault et al. 2017; Pinault et al. 2018; Cakmak et al. 2018) and the Canadian Community Health Cohort (Pinault et al. 2016) use public data. There is little evidence of substantially different estimated PM$_{2.5}$-mortality HRs using cohorts constructed from public data. The random-effects meta estimate using only selected studies using these public cohorts (Di et al. 2017; Pope et al. 2019; Crouse et al. 2015; Pinault et al. 2016), resulted in a somewhat larger HR per 10 µg/m³ long-term exposure to PM$_{2.5}$, of 1.10 (95% CI=1.08–1.13) for all-cause mortality. Even with public data sets, however, there is typically limited and controlled access to underlying data such as sex, race, age, birth and death dates, linked with specific geographic information regarding place of residence (which is required for linkage with air pollution data), and that may allow for personal identification.

Another controversial basic limitation of these cohort studies is their inability to definitively establish causal effects or provide specific biological mechanisms or even plausibility. These studies, however, provide evidence of consistency and coherency of PM$_{2.5}$-mortality associations and they can suggest epidemiological evidence of general pathophysiological pathways of disease (Pope et al. 2004). The cohort studies of long-term air pollution exposures and mortality are an important part of a broader and growing literature that includes explorations into biological mechanisms regarding exposure to air pollution and cardiopulmonary disease (Brook et al. 2010; Rajagopalan et al. 2018) and lung cancer (IARC: International Agency for Research on Cancer 2016). Additionally, there is a growing literature that applies causal analysis methods using observational data. Examples include a difference-in-differences analysis life expectancy in the U.S. (Pope et al. 2009); another difference-in-differences analysis of PM$_{2.5}$ and mortality in 207 U.S. cities (Kioumourtzoglou et al. 2016); a regression-discontinuity analysis of China’s Huai River policy (Ebenstein et al. 2017); and various studies of PM$_{2.5}$ exposure using instrumental variable and propensity score analysis (Wang et al. 2017b; Schwartz et al. 2016; Schwartz et al. 2018a; Schwartz et al. 2018b).
Additional controversy regarding the PM$_{2.5}$-mortality cohort studies relates to their use in developing risk functions to estimate burden of disease attributable to air pollution. A key controversy pertains to the shape of the PM$_{2.5}$-mortality exposure-response relationships. Estimators that integrate risk estimates from air pollution, second-hand cigarette smoke (SHS) and active smoking have been developed. For example, Figure 6 presents a stylized illustration of an integrated exposure-response (IER) relationship between cardiopulmonary disease mortality and long-term exposure to PM$_{2.5}$ from multiple sources. The estimates presented using gray scale symbols are estimates from exposures to cigarette smoke from active smoking and from second-hand smoke as documented elsewhere (Pope et al. 2011, 2018b). The colored symbols are estimates from exposures to air pollution from selected studies from Canada (yellow, Crouse et al. 2015; Pinault et al. 2016), the U.S. (blue, Lepeule et al. 2012; Pope et al. 2015, 2019), and China (green, Yin et al. 2017; Li et al. 2018 [estimate for all-cause mortality]), and the random effects meta estimate from the selected studies from the present meta-analysis (red, Figure 2). The adjusted relative risks are scaled and presented per approximate average PM$_{2.5}$ concentrations in each of the studies. The maroon curve illustrates an IER function with the mathematical form used in the global burden of disease estimates (Burnett et al. 2014; Cohen et al. 2017).

As is illustrated in Figure 6, the integrated response function across the full range of exposures, including active smoking is not linear but levels off at high levels of exposures. However, the IER function does not allow for differential toxicity across different sources of PM$_{2.5}$ and does not fit the studies of air pollution well. The elevated mortality risks from studies with very low average exposures (Canadian studies) tend to be lower than the IER estimates and the elevated mortality risks from studies with high exposures (China) tend to be higher than the IER estimates. In fact, recent estimates of the shape of the PM$_{2.5}$-mortality exposure-response relationship, using only estimates from cohort studies of ambient PM$_{2.5}$, suggest an exposure-response relationship that does not flatten out as much at high exposures—resulting in much higher global estimates of pollution-related mortality (Burnett et al. 2018; Vodonos et al. 2018). Although the HRs per 10 µg/m$^3$ long-term exposure to PM$_{2.5}$, are similar in both Canadian and Chinese cohorts (see Figures 1 and 2), Figure 6 illustrates that the HRs per average exposure are much higher in China than in Canada.
5. Conclusions

Much has changed in the last 25+ years regarding evidence of long-term pollution exposure contributing to mortality risk. Certainly not all of the controversies and uncertainties have been fully resolved. However, independent reanalysis and substantial extended analysis of the original cohort studies have been conducted. There are now many additional studies using a wide variety of cohorts, including cohorts constructed from public data, that have been reported. Unsurprisingly, there is considerable heterogeneity in the PM$_{2.5}$-mortality associations that are estimated across, and even within, different cohorts. This heterogeneity needs to be explored and better understood. There also remains a need for studies from understudied and often highly polluted areas of the world. However, meta-analytic estimates of the mean of the distribution of PM$_{2.5}$-mortality associations that are currently available, provide evidence of highly statistically significant adverse PM$_{2.5}$ associations with all-cause, cardiopulmonary, and lung cancer mortality.

Acknowledgments

This paper was developed as part of the Center for Air, Climate, and Energy Solutions (CACES), which was supported under Assistance Agreement No. R835873 awarded by the U.S. Environmental Protection Agency. It has not been formally reviewed by EPA. The views expressed in this document are solely those of authors and do not necessarily reflect those of the Agency. EPA does not endorse any products or commercial services mentioned in this publication.
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Figure legends:

Figure 1. Estimated adjusted HRs (and 95% CIs) for all-cause mortality per 10 µg/m³ elevation in PM$_{2.5}$ from multiple cohort studies. Black diamonds represent selected studies with the size of the diamond proportional to the relative weight in the random effect estimate using selected studies. The red squares represent random effects meta-estimates. The black line is a reference line at RR = 1. The red line is a reference line at RR equals the random effects meta-estimate using the selected studies.

Figure 2. Estimated adjusted HRs (and 95% CIs) for cardiopulmonary/cardiovascular mortality per 10 µg/m³ elevation in PM$_{2.5}$ from multiple cohort studies. Black diamonds represent selected studies with the size of the diamond proportional to the relative weight in the random effect estimate using selected studies. The red squares represent random effects meta-estimates. The black line is a reference line at RR = 1. The red line is a reference line at RR equals the random effects meta-estimate using the selected studies.

Figure 3. Estimated adjusted HRs (and 95% CIs) for lung cancer mortality per 10 µg/m³ elevation in PM$_{2.5}$ from multiple cohort studies. Black diamonds represent selected studies with the size of the diamond proportional to the relative weight in the random effect estimate using selected studies. The red squares represent random effects meta-estimates. The black line is a reference line at RR = 1. The red line is a reference line at RR equals the random effects meta-estimate using the selected studies.

Figure 4. Funnel plots of standard errors plotted over log hazard ratio for all cause mortality using all studies except the outlier China TB study (left) and selected studies (right).

Figure 5. Plot of the distribution of HRs for all-cause mortality (greater than or less than 1 and statistically significant [$p \leq 0.05$] versus not) for all studies and for selected studies.

Figure 6. Stylized illustration of the integrated exposure-response (IER) relationship between cardiopulmonary disease mortality and long-term exposure to PM$_{2.5}$. Estimates of adjusted
relative risk of cardiopulmonary mortality are plotted over estimates of average daily exposure using linear (left panel) and log (right panel) scales. Estimated daily exposure from cigarette smoking assumes a dose of 12 mg PM$_{2.5}$ per cigarette; estimated daily exposure from air pollution and SHS applies average air pollution concentrations and assumes an inhalation rate of 18 m$^3$/day. The estimates presented using gray scale symbols are estimates from exposures to cigarette smoke from active smoking and from second-hand smoke as documented in more detail elsewhere (Pope et al. 2011, 2018b). The colored symbols are estimates from exposures to air pollution from selected studies from Canada (yellow, Crouse et al. 2015; Pinault et al. 2016), the U.S. (blue, Lepeule et al. 2012; Pope et al. 2015, 2019), China (green, Yin et al. 2017; Li et al. 2018 [estimate for all-cause mortality]), and the random effects meta estimate for the selected studies from Figure 2 (red). The adjusted relative risks are scaled and presented per approximate average PM$_{2.5}$ concentrations in each of the studies. The maroon curve illustrates an IER function with the mathematical form used in the global burden of disease estimates, specifically: 

$$RR_{IER}(PM_{2.5}) = 1 + 3.1619\{1-\exp[-0.0976(PM_{2.5})^{0.2854}]\}.$$
All-Cause Mortality

U.S., Harvard Six-Cities
Dockery et al 1990
Laden et al 2000
Luepky et al 2012

U.S., ACS CPS-II, National
Pope et al 1995
Krewski et al 2000
Pope et al 2002
Smith et al 2009
Krewski et al 2009
Jerrett et al 2009
Pope et al 2015
Turner et al 2016

U.S., ACS, Other
Jerrett et al 2005 (CPS-II, LA)
Krewski et al 2009 (CPS-II, LA)
Krewski et al 2009 (CPS-II, NY)
Jerrett et al 2013 (CPS-II, CA)
Enstrom 2005 (CPS-I, CA)
Enstrom 2005 (CPS-I, CA)
Enstrom 2017 (CPS-II, 6 yrs)

U.S., Adventists (ASHMOG)
McDonnell et al 2000

U.S., Cystic Fibrosis
Goss et al 2004

U.S., Medicare
Efim et al 2008 (ACS)
Efim et al 2008 (HSC)
Zeger et al 2008 (Central)
Zeger et al 2008 (East)
Zeger et al 2008 (West)
Shi et al 2016 (North East)
Koziourzogou et al 2016
Wang et al 2017a (South)
Di et al 2017
Eum et al 2018

U.S., Hypertensive Veterans

U.S., Nurses’ Health
Puett et al 2009
Hart et al 2015

U.S., California Teachers
Ostro et al 2011
Liptet et al 2011
Ostro et al 2015

U.S., Male Health Pros
Puett et al 2011

U.S., Truckers
Hart et al 2011

U.S., Agricultural Health
Weichenthal et al 2014

U.S., NIS-AARP
Thornton et al 2016

U.S., CA Elderly
Garcia et al 2016

U.S., NJ Department of Health
Wang et al 2016

U.S., National Health, NHIS
Pope et al 2015a
Parker et al 2018
Pope et al 2019

U.S., USP, National
Lepeule et al 2012

Canada, Canadian
Crouse et al 2012
Crouse et al 2015
Weichenthal et al 2016
Crouse et al 2016
Pinault et al 2017
Cakmak et al 2018

Canada, Breast Screening
Villesseve et al 2015

Canada, Com. Health
Pinault et al 2016

Canada, MI Survivors
Chen et al 2016

France, PAARC
Filleul et al 2005

Germany, Urban Women
Gehring et al 2000

Netherlands, NLC-AIR
Beelen et al 2008

England, Clinical Practice
Carey et al 2013

Italy, Rome Register
Cesaroni et al 2013

Europe, ESCAPE
Beelen et al 2014a

Netherlands, DUELS
Fischer et al 2015

France, Electric & Gas
Bentayeb et al 2015

Spain, Small Area
Keizer et al 2017

Denmark, DCH
Hvidtfedt et al 2019

China, Hypertension
Cao et al 2011

Japan, NIPPON
Ueda et al 2012

Hong Kong, Elderly
Wong et al 2015
Wong et al 2016

Taiwan, Taipei
Tseng et al 2015

China, TB
Peng et al 2016

China, Men
Yin et al 2017

China, CLHLS
Li et al 2018

Iran, Tehran
Yarahmadi et al 2018

Random Effects
Meta Estimates

All studies
1.09 (1.07-1.10)

Selected studies
1.08 (1.06-1.10)

North America, selected

Europe, selected

Asia, selected

Random Effects
Meta Estimates

All studies
1.09 (1.07-1.10)

Selected studies
1.08 (1.06-1.10)

North America, selected

Europe, selected

Asia, selected

Random Effects
Meta Estimates

All studies
1.09 (1.07-1.10)

Selected studies
1.08 (1.06-1.10)

North America, selected

Europe, selected

Asia, selected

Random Effects
Meta Estimates

All studies
1.09 (1.07-1.10)

Selected studies
1.08 (1.06-1.10)

North America, selected

Europe, selected

Asia, selected

Random Effects
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North America, selected

Europe, selected

Asia, selected

Random Effects
Meta Estimates

All studies
1.09 (1.07-1.10)

Selected studies
1.08 (1.06-1.10)

North America, selected

Europe, selected

Asia, selected
Adjusted Relative Risk

0 0.5 1.0 1.00 1.25 1.50 1.75

Estimated daily exposure, mg of PM$_{2.5}$ (and increments of cigs/day)

Air pollution/Second-hand cigarette smoke

Moderate/Heavy Smokers

Very light Smokers

Estimated daily exposure, mg of PM$_{2.5}$, log scale (and approximate equivalent average ambient concentration of PM$_{2.5}$, $\mu$g/m$^3$)