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McIntyre Powder: Fine ($PM_{2.5}$) and ultrafine dust exposures and cardiovascular disease

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Introduction

The purpose of this report is to identify characteristics of McIntyre Powder (MP) and McIntyre Powder exposures that could increase the risk for cardiovascular disease (CVD) in exposed underground mine workers. The American Heart Association (AHA) published a scientific statement in 2004 that included a comprehensive review of the epidemiological, toxicological and mechanistic studies related to particulate air pollution and its influence on the risk of CVD. It was concluded that particulate matter (PM) makes a direct contribution to cardiovascular morbidity and mortality (Brook et al. 2004). In the following years many studies examined the physiological and molecular mechanisms involved in this relationship. The expanding rate of new scientific literature on this topic prompted a second AHA statement in 2010. Brook *et al.* discussed factors that influence the risk of CVD from airborne PM focusing on physical and molecular PM characteristics (Brook et al. 2010). Particle size was determined to be an important characteristic which influences cardiovascular effects, with exposure to particulate matter <2.5 μm in diameter ($PM_{2.5}$) being a major factor contributing to CVD morbidity and mortality (Brook et al. 2010).

It has been shown that inhalation of diesel exhaust at high concentrations overwhelms the lungs with particulates, resulting in chronic lung disease (e.g. COPD) and an increased risk for lung cancer (Hart et al. 2009; Hart et al. 2006; Mauderly 1996). Originally, the association with lung cancer was thought to be related to chemicals associated with the diesel particles and/or in the vapor phase. However, additional research has shown that inhalation of high levels of carbon black particulate matter, without any chemicals, results in the same response (Mauderly 1996). This evidence suggests that exposure to any high level particulate matter insult creates the potential for a chronic inflammatory response that may result in an increased lung cancer risk (Ballaz and Mulshine 2003; Kamp et al. 2011; Lee et al. 2009).

Characterization of MP particle size distribution has demonstrated a similarity to the particle size distribution of carbon black diesel exhaust particulate matter. The epidemiological and mechanistic literature reviewed here identifies shared mechanisms which drive the development of chronic inflammatory diseases in response to inhaled PM, including cancer and CVD (Bakand and Hayes 2016). Because these underlying mechanisms can be driven by biological interaction with inhaled particles, regardless of chemical composition, there is potential for synergistic/additive interactions between cigarette smoke, diesel exhaust, radon, mine dust and MP exposures experienced by mine workers (Puukila et al. 2017; Zarnke et al. 2019). Such a synergistic relationship would indicate a high risk among miners of developing CVD. The particle size distribution of MP particles and the manner of the MP exposures suggests that MP should be considered a potential substantial contributing factor influencing increased risk for CVD in exposed workers (Brook et al. 2004; Brook and Rajagopalan 2010; Brook et al. 2010).

McIntyre Powder characterization

Underground mine workers were purposefully exposed to MP before every work shift with the intent to prevent the harmful effects of inhaling crystalline silica dust present in the underground mine environment. The MP was described as a "lamp black" powder composed of 15% elemental aluminum (Al) and 85% Al oxide. Approximately, 70% of the Al particles are below 0.5 µm (500 nm) in diameter (Figure 1) and 30% of the particles are below 0.2 µm (200 nm) (Figure 2) eight minutes after dispersal in air (Hannon 1958; Jacob 1944). It was also observed by the McIntyre Research Foundation that there were a significant number of particles below the 0.2 µm (200 nm) analytical grain size detection limit that could not be categorized (Figure 3). The International Organization for Standardization (ISO) defines fine particulate ($PM_{2.5}$) as dust primarily composed of particles below 2.5 µm (2500 nm) in diameter and ultrafine particulate as dust primarily composed of particles ≤0.1 µm (≤100 nm) in diameter (ISO 2007). The MP particle characteristics would be categorized as a fine ($PM_{2.5}$) particulate matter with the potential for a substantial fraction of the powder to be categorized as an ultrafine particulate matter. Therefore under the American Conference of Governmental Industrial Hygienists (ACGIH) definitions MP would be considered respirable particulate matter meaning it can reach the deepest part of the lung which are the alveolar sacs.

McIntyre Powder exposure characterization

The MP exposure recommended by the McIntyre Research Foundation to prevent silicosis was one gram of MP per 1000 cubic feet of locker room volume for an exposure time of 10 minutes (1 g/1000 ft^3 = 1 g/28.32 m^3 = 35.3 mg/m^3) (Jacob 1944). Based on worker accounts, underground miners were required to breathe MP before every work shift for a minimum of ten minutes. At certain mines the exposure times varied substantially ranging from 10 minutes to 45 minutes. It was also reported that some mines required their workers to breathe MP immediately before travelling underground as well as immediately after returning to surface. It is also important to note that the recommended concentration for MP of 35.3 mg/m^3 would be 7 times the Ontario Occupational Health and Safety Act (OHSA) excursion criterion for Al and compounds (excursion criteria for Al: 1.0 mg/m^3 x 5 = 5.0 mg/m^3 ; 35.3 mg/m^3 ÷ 5.0 mg/m^3 = 7.12) (ACGIH 2008). The excursion criteria requirement is that if a substance does not have a STEL, the exposure shall not exceed the following excursion limits: three times the TWA TLV for any 30 minute period or five times the TWA TLV at any time (O. Reg. 833/90).

Because the MP particulate matter size distribution includes a 70% proportion of particles below 500 nm, 30% below 200 nm and a possible fraction below 100 nm, the dose required to elicit lung overload conditions would be much lower than that of an average mine dust with larger particles. Moreover, the high dose rate of the MP would have presented more opportunity for lung overload conditions to be met. During lung overload conditions, inhaled particulates accumulate with no effective clearance. In humans this type of accumulation has also been shown to be associated with increased translocation of inhaled particles to the lung interstitium and then to other organs via the circulatory system. The fact that the MP exposures occurred directly before

Table 6. Overall Summary of Epidemiological Evidence of the Cardiovascular Effects of $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure at Ambient Levels

Health Outcomes	Short-Term Exposure (Days)	Longer-Term Exposure (Months to Years)
Clinical cardiovascular end points from epidemiological studies at ambient pollution concentrations		
Cardiovascular mortality	↑ ↑ ↑	↑ ↑ ↑
Cardiovascular hospitalizations	↑ ↑ ↑	↑
Ischemic heart disease*	↑ ↑ ↑	↑ ↑ ↑
Heart failure*	↑ ↑	↑
Ischemic stroke*	↑ ↑	↑
Vascular diseases	↑	↑†
Cardiac arrhythmia/cardiac arrest	↑	↑
Subclinical cardiovascular end points and/or surrogate measures in human studies		
Surrogate markers of atherosclerosis	N/A	↑
Systemic inflammation	↑ ↑	↑
Systemic oxidative stress	↑	
Endothelial cell activation/ blood coagulation	↑ ↑	↑
Vascular/endothelial dysfunction	↑ ↑	
BP	↑ ↑	
Altered HRV	↑ ↑ ↑	↑
Cardiac ischemia	↑	
Arrhythmias	↑	

The arrows are not indicators of the relative size of the association but represent a qualitative assessment based on the consensus of the writing group of the strength of the epidemiological evidence based on the number and/or quality, as well as the consistency, of the relevant epidemiological studies.

↑ ↑ ↑ Indicates strong overall epidemiological evidence.
↑ ↑ Indicates moderate overall epidemiological evidence.
↑ Indicates some but limited or weak available epidemiological evidence.
Blank indicates lack of evidence.
N/A indicates not applicable.
*Categories include fatal and nonfatal events.
†Deep venous thrombosis only.

Figure 4 – Table taken from the AHA's 2010 statement summarizing the strength of the associations between $PM_{2.5}$ exposure and cardiovascular disease mechanisms and health outcomes found in the epidemiological literature (Brook et al. 2010).

the workers' shift would make it more likely to enhance the toxicity of the inhaled mine dust during their shift by impeding clearance of mine dust particulates. The Time-weighted average (TWA) exposures and typical exposure profiles under current Ontario exposure limits (OEL) may not be applicable to how former miners were exposed to MP. The cited scientific evidence indicates that MP exposure is distinctly different from an average mine dust exposure and supports the potential for these two exposures to act synergistically or in an additive manner to compound the risk for CVD and other related health effects (Zarnke *et al*., 2019, attached supporting document).

Epidemiological data related to the health effects of MP, fine ($PM_{2.5}$) and ultrafine dust on CVD

Based on the AHA's comprehensive literature review it is estimated that a 10 µg/m^3 increase in mean 24 hour $PM_{2.5}$ concentrations (short term increases) elevates the relative risk (RR) for daily cardiovascular mortality by approximately 0.4% to 1.0% (Pope and Dockery 2006). Cohort studies estimate that the RR for cardiovascular mortality associated with living in areas with higher yearly average PM levels over the long term is much greater than that estimated for short term PM exposure increases. The RR for long term exposures per 10 µg/m^3 increase in ambient $PM_{2.5}$ levels is between 6% and 76% (RR = 1.06 to 1.76) (Pope and Dockery 2006). Figure 4 summarizes the strength of the epidemiological evidence of the cardiovascular effects from ambient $PM_{2.5}$ exposure (Appendix 1 summarizes the cohort studies used in this assessment). In a world health report published by the World Health Organization in 2002 it was estimated that 800,000 premature deaths per year are associated with $PM_{2.5}$ exposures, ranking it the 13th leading cause of worldwide mortality (2002). A recent study by Pozzer *et al.* (2019) using novel

hazard ratio functions calculated estimates of premature mortality due to air pollution that are double those previously reported. Their analysis reported that between 40% and 80% of the premature deaths are due to cardiovascular events. The strongest pollutant associations were found between $PM_{2.5}$ ozone (O_3) and cardiovascular disease (Pozzer et al. 2019).

A study by Bourdrel *et al.* (2017) analyzed pooled epidemiological studies and reported that a 10 $\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$ was associated with an increase of 11% in cardiovascular mortality (Bourdrel et al. 2017). Bourdrel *et al.* (2017) also reported a 13% increase in cardiovascular mortality after a 10 $\mu g/m^3$ (equivalent to 0.005 ppm) increase in annual nitrogen dioxide (NO^2) concentrations (Bourdrel et al. 2017). Underground miners are exposed to NO^2 from diesel exhaust, carbon monoxide (CO), ambient mine dust, and ultrafine particulate from diesel exhaust and MP. The health effects of these combined exposures cannot be assessed separately. Long-term exposure to all five of these agents in combination contributes to chronic inflammation through reactive oxygen species (ROS) signalling, the production of proinflammatory cytokines, immune cell activation and vascular dysfunction. Therefore CVD risk in underground miners exposed to MP is more likely than not related to the combined exposures from MP, NO^2, CO, ambient mine dust and ultrafine particulate matter.

As a 24-hour time-weighted average, MP exposure duration of ten minutes at 35 mg/m^3 would equate to 0.24 mg/m^3 (240 $\mu g/m^3$). Because in most cases MP exposures were experienced daily over the course of months and years, exposure would be considered an extremely elevated short-term exposure, coupled with long term exposure. Therefore, based on the epidemiology, we can theoretically and conservatively estimate an increased relative risk of CVD mortality for MP exposed miners using the lower limits of the RR increase for long term $PM_{2.5}$ exposure of 6% to 76% per 10 $\mu g/m^3$. This equates to an increased relative risk of CVD related mortality of 144% to 1824% (RR = 2.44 to 19.24) for a long term repeated 10 minute MP exposure. These values would drastically increase for MP exposure durations greater than ten minutes as reported by miners. Exposure durations were reported to be as long as forty-five minutes, in some cases both before and after the work shift.

Ischemic cardiac disease

When the AHA's analysis focused on specific cardiovascular health outcomes, ischemic cardiac events accounted for the largest relative and absolute risk (RR 1.18, 95% CI 1.14 to 1.23) for mortality per 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ concentration (Pope et al. 2004; Pope et al. 2006). Interestingly a US Medicare study showed a reduction of $PM_{2.5}$ by 10 $\mu g/m^3$ was estimated to reduce ischemic heart disease hospital admissions in 204 countries by 1523 (95% CI 69 to 2976) cases per year (Dominici et al. 2006; Pope III et al. 2002). In general the epidemiological literature consistently shows acute increases in risk for ischemic cardiac events associated with elevated $PM_{2.5}$ levels (Al Rashida et al. 2019; Bakand and Hayes 2016; Costello et al. 2018; Costello et al. 2014; Costello et al. 2016). This effect has been shown to occur as rapidly as one to two hours after exposure to elevated levels of $PM_{2.5}$, in case-cross-over analyses (Murakami and Ono 2006; Peters et al. 2001; Peters et al. 2004).

Cerebrovascular disease

A cohort study conducted in conjunction with the Women's Health Initiative found significant increases in both nonfatal stroke (hazard ratio (HR) 1.28, 95% CI 1.02 to 1.61) and fatal cerebrovascular disease (HR 1.83, 95% CI 1.11 to 3.00) per 10 $\mu g/m^3$ with prolonged exposure to $PM_{2.5}$ (Miller et al. 2007). Several other studies have shown small but statistically significant links between short term PM exposure and cerebrovascular disease. Daily time-series studies in Seoul, Korea have observed that increased air pollution (PM, NO_2, CO and O_3) was associated with increased stroke mortality (Hong et al. 2002a; Hong et al. 2002b). When stroke type was analyzed separately, the pollution association was associated with ischemic stroke but not hemorrhagic stroke (Hong et al. 2002b). Several studies have also observed increased stroke or cerebrovascular hospital admissions associated with increased exposure to PM and other related air pollutants (Chan et al. 2006; Dominici et al. 2003; Franklin et al. 2007; Le Tertre et al. 2002; Tsai et al. 2003; Wellenius et al. 2005). Another daily time series study conducted in Helsinki, Finland found that $PM_{2.5}$ and carbon monoxide (CO) were associated with stroke mortality in the warm season but not the cold season (Kettunen et al. 2007). These findings could have strong implications with respect to mining occupations because CO concentrations underground fluctuate regularly, and the underground mining environment can be substantially warmer than the surface environment regardless of the season.

Mechanisms associated with the biologic effects of MP, fine ($PM_{2.5}$) and ultrafine dust on CVD

In the last 20 years there have been substantial advances in our understanding of PM mediated biological mechanisms responsible for adverse cardiovascular effects. Recently, a number of experiments have demonstrated rapid responses to air pollution, such as vascular dysfunction. This response suggests there are signalling pathways conveyed systemically within hours of PM inhalation (Brook et al. 2010). In addition, evidence for chronic biological effects, such as the promotion of atherosclerosis, has been reported (Brook and Rajagopalan 2010; Brook et al. 2010). The AHA's findings strongly support the integral role of reactive oxygen species (ROS) dependent pathways at multiple stages of the PM mediated biological response at the molecular level, such as instigation of pulmonary oxidative stress, systemic proinflammatory responses, vascular dysfunction and atherosclerosis (Brook et al. 2010). Three main pathways are identified that influence extra-pulmonary effects on the cardiovascular system in response to inhalation of PM (Brook et al. 2010). The first pathway involves the release of proinflammatory mediators or vascular-active molecules from pulmonary based immune cells (Kreyling et al. 2006; Moller et al. 2010; Moller and Loft 2010; Simkhovich et al. 2008). The second pathway involves the perturbation of the systemic autonomic nervous (ANS) system balance by particle interactions with lung receptors or nerves (Brook et al. 2010; Rhoden et al. 2005). The third pathway involves the translocation of PM (ultrafine particulate) or particle constituents (organic compounds or metals) into the systemic circulation (Maher et al. 2016; Nel et al. 2006). The characteristics of MP particles will implicate MP exposures in many of the pathways and mechanisms described in the literature related to PM mediated biological responses responsible for CVD. As previously discussed, the particle size distribution of MP ($PM_{2.5}$ and potentially ultrafine) and the exposure

profile (high concentration, repeated chronic exposure) substantially increase the probability of MP particles being translocated via the lymphatic and circulatory systems to other tissues in the body.

Main Points:

- McIntyre Powder should be considered 100% $PM_{2.5}$ or smaller and under the ACGIH definitions would be entirely respirable and $PM_{2.5}$ poses the greatest health risk for cardiovascular disease.

- McIntyre Powder has a similar particle size distribution as carbon black in diesel exhaust particulate matter.

- Evidence suggests a dose response relationship between $PM_{2.5}$ and cardiac/pulmonary disease.

- The small particle sizes and high dose rate of the MP favour conditions for lung overload. These conditions provide an opportunity for MP particles to translocate from the lung into the circulatory system.

- The 24 hour time weighted average for McIntyre Powder exposures (240 $\mu g/m^3$) was 24 times higher than the standard increment increase in PM2.5 used in epidemiological studies (10 $\mu g/m^3$).

- The association between $PM_{2.5}$ exposure and CVD morbidity and mortality in the epidemiological literature suggests that MP exposed miners are at high risk of developing CVD.

- Associations between $PM_{2.5}$ exposure and cerebrovascular disease implicate MP in neurological health outcomes such as ischemic stroke and cognitive dysfunction.

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TABLE 1.—PERCENTAGE OF PARTICLES IN VARIOUS SIZE GROUPS

SIZE IN MICRONS	8 MINUTES AFTER DISPERSAL	60 MINUTES AFTER DISPERSAL
0.5 or less	71.7	69.1
0.5 to 1.0	21.9	21.1
1.0 to 2.0	4.1	8.8
2.0 to 3.0	1.1	0.5
3.0 to 4.0	0.7	0.4
4.0 to 5.0	0.3	..
5.0 to 6.25	..	..
6.25 to 7.50	0.2	0.2
TOTAL	100.0	100.1

Figure 1 – Image of data taken from an engineering report which describes the application of McIntyre Powder for the prevention of silicosis*: 8 ten gram cans of McIntyre Powder were dispersed in a 80,000 square foot mine change house as recommended. Samples of the airborne particles were collected with a thermal precipitator and particle counts and particle size distributions were measured. It was observed that there was a sizable fraction below 0.5µm (500nm) which could not be characterized sufficiently with this method (Jacob, 1944).

* Jacob, A. W. (1944). "The Engineering Aspects of Aluminum Prophylaxis." Canadian Institute of Mining and Metallurgy **XLVII**: 185-202.

Table 2.—Size distribution of HM–38 and D–R powders 8 minutes after dispersal

Size Group Mean Diameter (M.)	Percentage Occurrence		Percentage up to Max. Size of Group	
	HM–38[1]	D–R[2]	HM–38	D–R
Up to 0.2	24.60	2.69	24.60	2.69
0.2 to 0.4	30.85	5.83	55.45	8.52
0.4 to 0.8	32.58	20.18	88.03	28.70
0.8 to 1.2	8.64	19.73	96.67	48.43
1.2 to 1.6	1.72	17.04	98.39	65.47
1.6 to 2.0	0.79	16.14	99.18	81.61
Above 2.0	0.82			
2.0 to 2.5		4.48		86.09
2.5 to 3.0		2.24		88.33
3.0 to 4.0		3.58		91.91
4.0 to 5.0		2.69		94.60
Above 5.0		5.40		

[1] HM–38 represents the atmosphere produced by the specified aluminum powder in accordance with the present invention.
[2] D–R represents the optimum atmosphere produced under same conditions as HM–38 but using optimum powder available prior to the present invention.

Figure 2 – Image of data taken from a patent held by the McIntyre Research Foundation describing a method of producing an atmosphere that protects against silicosis: HM-38 was characterized as the most current version of Al powder using the invention described (large commercial ball-mill). D-R is Al powder characterized as the best powder produced prior to the previously described invention (small ball-mill which produced unfiltered powder) (Hannon, 1958).

*Hannon, J. W. G. (1958). Method of Producing an Atmosphere Protective Against Silicosis. U. S. P. Office, McIntyre Research Foundation.

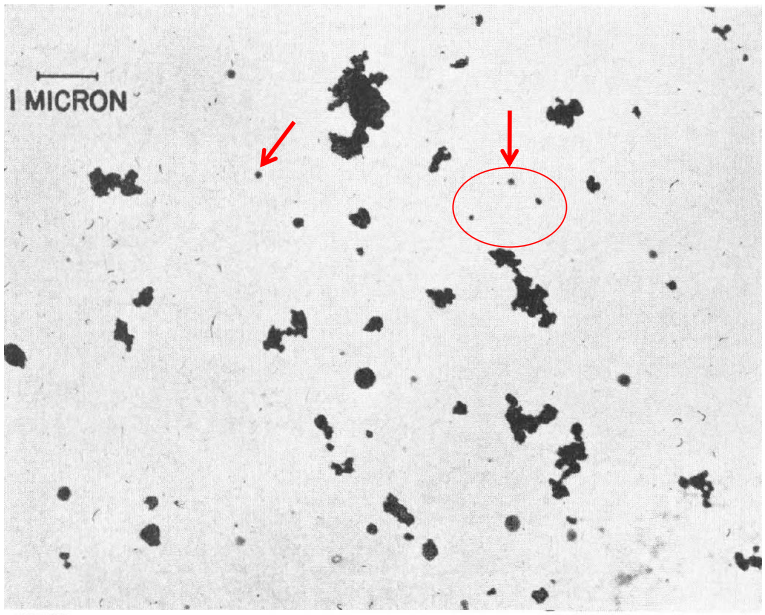

Figure 9.—Aluminium dust sample No. 6. 100 c.c. Collected 66-82 minutes after blow.

Figure 3 – Electron micrograph of McIntyre Powder particles collected after dispersal in air. Arrows are pointing at examples of particles ~200nm or below which couldn't be sufficiently categorized (Jacob, 1944). Jacob, A. W. (1944). "The Engineering Aspects of Aluminum Prophylaxis." Canadian Institute of Mining and Metallurgy **XLVII**: 185-202.

Appendix 1 – Table taken from Brook et al. 2010: Summary of Cohort Studies. The 24-hour time weighted average of McIntyre Powder exposures was 240 µg/m^3 which is 24 times higher than the increment increase of 10 µg/m^3 described in the following studies.

Study	Size of Cohort (000s)	Follow-Up Period	Covariates Controlled for	Percent Increases in Mortality (95% CI) Associated With 10 $\mu g/m^3$ $PM_{2.5}$ (or Other When Indicated)			
				All-Cause	Cardiopulmonary	Cardiovascular	Ischemic Heart Disease
Harvard Six Cities, original (Dockery et al[62] 1993)	≈8	1974–1991	Individual (smoking+others)	13 (4.2–23)	18 (6.0–32)	…	…
Harvard Six-Cities, HEI reanalysis, Krewski et al[63] 2004	≈8	1974–1991	Individual (smoking+others)	14 (5.4–23)	19 (6.5–33)	…	…
Harvard Six-Cities, extended, Laden et al[64] 2006	≈8	1974–1998	Individual (smoking+others)	16 (7–26)	…	28 (13–44)	…
Six-Cities Medicare cohort, Eftim et al[65] 2008	≈340	2000–2002	Individual (age, sex)	21 (15–27)	…	…	…
ACS, Original, Pope et al[66] 1995	≈500	1982–1989	Individual (smoking+others)	6.6 (3.5–9.8)	12 (6.7–17)	…	…
ACS, HEI reanalysis, Krewski et al[63] 2004	≈500	1982–1989	Individual (smoking+others) +ecological	7.0 (3.9 10)	12 (7.4–17)	13 (8.1–18)	…
ACS, extended I, Pope et al[67,68] 2002, 2004	≈500	1982–1998	Individual (smoking+others)	6.2 (1.6–11)	9.3 (3.3–16)	12 (8–15)	18 (14–23)
ACS, intrametro Los Angeles, Jerrett et al[69] 2005	≈23	1982–2000	Individual (smoking+others) +ecological	17 (5–30)	12 (−3–30)	…	39 (12–73)
ACS, extended II, Krewski et al[70] 2009	≈500	1982–2000	Individual (smoking+others) +ecological	5.6 (3.5–7.8)	13 (9.5–16)	…	24 (20–29)
ACS, Medicare cohort, Eftim et al[65] 2008	7333	2000–2002	Individual (age, sex)+ecological +COPD	11 (9–13)	…	…	…
US Medicare cohort, east/central/west, Zeger et al[71] 2008	13 200	2000–2005	Individual (age, sex)+ecological +COPD	6.8 (4.9–8.7),* 13 (9.5–17) −1.1 (−3 to 0.8)	…	…	…
Women's Health Initiative, Miller et al[72] 2007	≈66	1994–2002	Individual (smoking+others)	…	…	76 (25–147), 24 (9–41)†	…
Nurses' Health Study, Puett et al[73] 2008	≈66	1992–2002	Individual (smoking+others) ecological	7.0 (−3.0 to 18)‡	…	30 (0–71)‡	…
AHSMOG, males only, McDonnell et al[74] 2000	≈4	1977–1992	Individual (smoking+others)	8.5 (−2.3 to 21)	23 (−3 to 55)	…	…
AHSMOG, females only, Chen et al[75] 2005	≈4	1977–2000	Individual (smoking+others)	…	…	42 (6–90)	…
VA hypertensive male I study, Lipfert et al[76] 2006	≈42	1989–1996	Individual (smoking+others) +ecological	15 (5–26)§	…	…	…
VA hypertensive male II study, Lipfert et al[77] 2006	≈30	1997–2001	Individual (smoking+others) +ecological	6 (−6 to 22)	…	…	…
11 CA county, elderly, Enstrom[78] 2005	≈36	1973–2002	Individual (smoking+others) +ecological	4 (1–7)‖, 1 (−0.6 to 2.6)	…	…	…
French PAARC, Filleul et al[79] 2005	≈14	1974–2000	Individual (smoking+others)	7 (3–10)‡	5 (−2 to 12)‡	…	…
German women, Gehring et al[80] 2006	≈5	1980s, 1990s–2003	Individual smoking and socioeconomic status	12 (−8 to 38)	52 (9–115)	…	…

(*Continued*)

Study	Size of Cohort (000s)	Follow-Up Period	Covariates Controlled for	Percent Increases in Mortality (95% CI) Associated With 10 $\mu g/m^3$ $PM_{2.5}$ (or Other When Indicated)			
				All-Cause	Cardiopulmonary	Cardiovascular	Ischemic Heart Disease
Oslo, Norway, intrametro, Naess et al[81] 2007	≈144	1992–1998	Individual age, occupational class, education	…	…	10 (5–16),¶ 14 (6–21), 5 (1–8), 3 (0–5)	…
Dutch cohort, Beelen et al[82] 2008	≈121	1987–1996	Individual (smoking+others) +ecological	6 (−3 to 16)	…	4 (−10 to 21)	…
Great Britain, Elliott et al[83] 2007	≈660	1966–1998	Socioeconomic status	1.3 (1.0–1.6)‡#	1.7 (1.3–2.2)‡#	1.2 (0.7–1.7)‡#	

HEI indicates Health Effects Institute; VA, Veterans Affairs; COPD, chronic obstructive pulmonary disease; and CA, California.

*Three estimates are for the East, Central, and West regions of the United States, respectively.

†Any cardiovascular event.

‡Associated with 10 $\mu g/m^3$ British Smoke (BS) or PM_{10}.

§Estimates from the single-pollutant model. Effect estimates were smaller and statistically insignificant in analyses restricted to counties with nitrogen dioxide data. County-level traffic density was a strong predictor of survival, and stronger than $PM_{2.5}$ when included with $PM_{2.5}$ in joint regressions.

||Two estimates are for the follow-up period 1973–1982 and the follow-up period 1983–2002, respectively.

¶Four estimates are for men 51–70 y old, women 51–70 y old, men 71–90 y old, and women 71–90 y old, respectively.

#Using last 0- to 4-year exposure window.