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Long-term air pollution exposure and cardio- respiratory mortality

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ABSTRACT

Current day ambient air pollution has been associated with a range of adverse health effects, particularly mortality and morbidity due to cardiovascular and respiratory causes. In the current review, we review the evidence from epidemiological studies on particulate matter and nitrogen dioxide (NO_2), elemental carbon and coarse particles. We summarized the findings on potentially susceptible subgroups across studies. We added respiratory mortality findings of the cohort studies.

We identified studies though a search in the databases Medline and Scopus and previous reviews until August 2011 and performed a meta-analysis if more than five studies were available for the same exposure metric.

Our review supports previous qualitative reviews in documenting that long-term exposure to fine particulate matter air pollution is associated with higher mortality particularly from cardiovascular disease rather than non-malignant respiratory diseases. Associations with mortality from myocardial infarction were particularly consistent across studies and this association appears to be much stronger for fatal events than non-fatal events. Significant heterogeneity in cardiovascular PM effect estimates were found across studies, which cannot be easily explained. Across studies, there was little evidence that stronger association was noted for women than men. Subjects with lower education and obese subjects experienced larger mortality effect related to fine PM. We found no evidence that fine PM was associated with respiratory mortality. There was also little evidence for an association between long-term coarse particulate matter exposure and mortality, but this may be due to the small number of studies and limitations in exposure assessment. Future studies benefit from more chemically resolved exposure estimation at a fine spatial scale such as the residential address.

Keywords: air pollution, mortality, motorized traffic, cardiovascular, respiratory, particles

INTRODUCTION

Current day ambient air pollution has been associated with a range of adverse health effects, particularly mortality and morbidity due to cardiovascular and respiratory causes (1, 2). There is a large number of time series studies which have found significant associations between short-term changes in ambient air pollution and cardio-respiratory mortality and hospital admissions (1, 2). There is growing evidence of mortality effects related to long-term exposure to ambient air pollution (1, 2). Cardiovascular effects of short- and long-term exposure to particulate matter air pollution have recently been comprehensively reviewed (3, 4). In general the effect estimates from long-term exposure studies were substantially larger than from the short-term exposure studies (3,4). Experimental and epidemiological studies in the recent decade have significantly increased our knowledge of mechanisms that could plausibly explain the associations observed in epidemiological studies between ambient air pollution and mortality (3).

Most studies have reported associations linked to particulate matter, often represented by the mass concentration of particles smaller than 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$). In many urban areas, motorized traffic emissions are an important source of ambient particles and gaseous pollutants such as nitrogen dioxides (NO_2 and NO). An expert panel from the Health Effects Institute (2009) has recently reviewed health effects related to pollutants derived from motorized traffic. Exposure contrasts related to traffic emissions are usually poorly represented by the concentration of PM_{10} or $PM_{2.5}$, because of the high regional background concentration of these particle metrics from other sources. However, there are more specific markers from traffic related air pollution, which include the elemental carbon concentration or the ultrafine particle number concentration (5,7). Janssen and co-workers recently demonstrated that health impact assessments of traffic-related pollutants based upon PM2.5 seriously underestimated the health risks compared to an assessment based upon elemental carbon. There is also growing evidence of health effects related to ultrafine particles (6, 7). Finally, the effects of coarse particles (the particle fraction between 2.5 and 10 μm) have attracted renewed attention. Emission controls for road traffic have now

substantially reduced tailpipe emissions, and therefore non-tailpipe emissions including engine crankcase emissions (combusted lubricating oil), tire wear and brake wear are becoming increasingly important. A recent study in the Netherlands found similar increases of concentrations in major roads compared to urban background for metals related to break and tyre wear (Cu, Zn) as for soot and ultrafine particles which are due to tailpipe emissions (8) . In a review of the limited literature, coarse particles were associated with short-term effects on mortality and hospital admissions, but no evidence was found for long-term exposure effects (9).

In the current review, the evidence for cardiovascular mortality effects (1-3) is updated with several new studies conducted in 2009 – 2011 on particulate matter and studies on NO_2, elemental carbon, and coarse particles. We further evaluated the findings on potentially susceptible subgroups across studies. In addition, we have included the studies on more specific cardiovascular causes of death, especially fatal myocardial infarction and stroke.. Lastly, we added respiratory mortality findings of the cohort studies. Findings on associations between air pollution and lung cancer have been reviewed before (10) and will not be discussed here. We also do not discuss the emerging evidence for effects on neurodevelopment (11).

MATERIALS AND METHODS

We performed a search in the databases Medline and Scopus with the search terms air pollution, cohort, and mortality through August 2011. We supplemented the search with studies included in the review by Brook et. al. (3) and by browsing the reference lists of identified papers. We focused on epidemiological studies, as experimental studies and mechanisms of effect have been discussed in detail previously (3). In case more than five studies were identified, we performed a meta-analysis for $PM_{2.5}$ (the most common exposure variable. We tested for heterogeneity of effect estimates and obtained combined effects estimates, using the methods of DerSimonian and Laird (11). From some studies multiple papers were available such as the Six Cities study (12,13). We

used only the most recent paper, that had longer follow-up. We only included studies in the quantitative meta-analysis that directly provided $PM_{2.5}$ exposure estimates.

RESULTS AND DISCUSSION

$PM_{2.5}$ AND ALL-CAUSE AND CARDIOVASCULAR MORTALITY

Table 1 summarizes the studies on long-term air pollution exposure and all-cause and cardiovascular mortality using $PM_{2.5}$ or PM_{10} as exposure metric (12 -30) . Most but not all studies report significant associations between PM2.5 and all-cause mortality. Since the publication of the authoritative American Heart Association Scientific Statement (3), eight new cohort studies were published between 2009 and 2011. These studies were often performed in more selected groups e.g. female teachers (22) or male truck drivers (31). Effect estimates differed substantially across studies, with most studies showing less than about 10% increase in mortality for an increment of 10 $\mu g/m^3$ $PM_{2.5.}$ Much larger mortality increases were reported in the Women's Health Initiative study (32). A formal test of heterogeneity was highly statistically significant for cardiovascular mortality ($p<0.001$), but not all-cause mortality ($p>0.10$). The random effects summary estimate for the percent excess risk per 10 $\mu g/m^3$ $PM_{2.5}$ for all-cause mortality was 9% 95% CI: 4 – 14%). The random effects summary estimate for cardiovascular mortality was 17% (95% CI 0, 36%). When we exclude the studies reporting only CVD estimates (23, 32) this becomes 12 (95% CI: 4 -20). Thus, the overall effect estimates were larger for cardiovascular than for all-cause mortality. This pattern was found in most of the individual studies, with the only exceptions being the Dutch cohort study (33) and the US trucking industry cohort study (31).

An important question is what the explanation is for the observed heterogeneity of effect estimates. Differences in study population, exposure assessment, pollution mixture, study period, outcome assessment, and confounder control could have contributed to these differences. Differences in the fraction of *susceptible subjects* may have contributed to the observed differences. Brook et al have suggested that women might

be more susceptible to ambient air pollution (3). The studies with higher PM effect estimates, particularly the WHI-study (32) have indeed been performed in women only. However, it is problematic to draw conclusions about susceptible subgroups based upon *between-study* comparisons as multiple factors differ between studies. A comparison of PM effect estimates between men and women *within* studies does not provide clear evidence that women respond stronger (Table 2). The findings from the AHSMOG are difficult to interpret, with higher effects in men in the larger earlier study (34) and larger effect in women in the smaller cohort with longer follow-up (35). The larger effect estimate for men in the Canadian study (23) has to be interpreted with care, because of the lack of data on a variety of important covariates, including individual smoking data, though the authors argue that smoking likely has not confounded the associations with mortality. In the French PAARC study, effect estimates for the evaluated pollutants (TSP, BS and NO_2) were similar among men and women (28). There is also only weak evidence that effect estimates are larger among never-smokers, though in all four evaluated studies a (borderline) significant association was found in never-smokers. Associations in current smokers were more variable across the studies, consistent with the larger 'noise' generated by smoking. In all four studies, $PM_{2.5}$ effect estimates were higher for those with the lowest education. In all four studies, there was actually little indication of an association in those with higher education. The absence of an association in the (highly educated) Health professionals study (21) is consistent with this observation. In contrast, in the French PAARC study, effect estimates were very similar across educational strata, with significant effect also found in those with a university degree (28). If confirmed in further studies, it is likely that multiple factors may play a role in the stronger effects observed in less-educated subjects. These may include dietary factors such as lower fruit and anti-oxidant intake (33),, higher risk of obesity or other pre-existing diseases, higher actual exposures than assumed in the studies and possibly interaction with other risk factors such as poorer housing conditions e.g. moisture.

In two studies, $PM_{2.5}$ effect estimates were substantially higher among subjects with high body mass index (19, 32). It is likely that subject characteristics might explain part of the variability of air pollution effect estimates across studies where subgroup analyses are limited by power to detect differences. Hence, further research is required to study the effects of air pollution on women, smokers, obese participants, and diabetes mellitus with better measurement of the exposures.. Gene-environment interactions have been shown for the (short-term) air pollution effects on inflammation markers (36, 37) Inflammation likely plays an important role in the mechanism of cardiovascular events (3). Gene-environment interactions have not yet been studied in the framework of mortality cohort studies.

One of the important sources of variability of effect estimates between studies is likely related to exposure misclassification. While the most important environmental predictor to consider is actual individual-level *exposure* to ambient particles, which presumably drives the health effects, most studies have used outdoor concentrations at sites distant to the participant's precise location. This leads to exposure misclassification. In the cohort studies, exposure has been characterized by the outdoor concentration at the city level based upon central site monitoring (e.g. 15) or the nearest monitor (e.g., 32), or modeling at the individual address (e.g. 33). These exposure estimates do not take into account time activity patterns such as time spent in the home or in traffic and factors affecting infiltration of particles indoors. There is a large literature documenting the importance of e.g. air exchange rate on infiltration of particles indoors. Importantly, these factors may differ between homes with a study area and between study areas in different climates. In a study of short-term effects, PM10 effects on hospital admissions were larger in US cities with lower % of air conditioning, related to lower particle infiltration rates (38)). This has not been investigated yet in the framework of cohort studies. In the Multiethnic study of Atherosclerosis Air study, indoor-outdoor measurements have been performed to adjust the exposure estimates (39, 40), and each participant provides time-activity information to weight exposures between time spent indoors and outdoors. Ongoing research from the MESA Air study will provide

more insights into this in the upcoming years. Evidence for the importance of time activity patterns was obtained in the US truckers study, showing higher ambient $PM_{2.5}$ effect estimates in the population excluding long-haul drivers who spend more time away from home (31). Other factors could however also explain this finding. In the WHI study, effect estimates tended to be higher for subjects spending more than 30 minutes outdoors (32). In a validation study in the Netherlands, the contrast of personal soot exposure for adults living on a major road compared to those living at a background location, was larger for those spending more time at home (41). Because of the reliance on ambient exposure estimates, it is not surprising that some heterogeneity in effect estimates across studies is found.

Differences in *particle composition* or contributing sources very likely explain some of the heterogeneity in effect estimates, as was observed for the short-term mortality and hospital admission studies of PM_{10} (42, 56, 57). This has not been systematically investigated in cohort studies. In a recent review it was shown that on a per microgram per m^3 basis, mortality effect estimates were about 10 times larger for EC than for $PM_{2.5}$ (5). Hence, in locations with higher primary combustion particles we could expect higher $PM_{2.5}$ effects.

A further important issue is for which period exposure is assigned. Air pollution exposure data may not be available for the entire follow-up period and therefore exposures at the start or end of follow-up are occasionally assigned (15). When significant (often downward) trends in pollution occur with changing (often decreasing) spatial contrasts in the study, bias may occur in the estimated association between pollution and mortality (22). The follow-up study from the Harvard Six City study (13) and two studies in potentially at-risk populations (47, 48) suggested that the relevant exposure may be the exposure in the past few years. These authors conclude that it does not take decades to bridge the gap between the short- and long-term exposure effect estimates, consistent with the effect of intervention studies showing reductions in mortality in the year after the intervention (47, 48). These studies (47, 48) have made

use of long-term temporal contrast within cities adjusting for secular trends. PM effect estimates were similar to the previously discussed studies exploiting spatial contrasts.

Finally, it is likely that the use of fairly crude health outcome data (all-cause, all cardiovascular disease) explains some of the heterogeneity, if the fraction of most affected outcomes differs across studies, see the discussion in the section specific cardiovascular causes below.

Coarse particles, black carbon and nitrogen dioxide

Table 3 presents studies that have used elemental carbon, NO_2 or coarse PM as the exposure metric. Table 3 illustrates that there is no evidence that long-term exposure to coarse PM is related to mortality. In three of the four cohort studies that reported no significant association with coarse PM, significant associations with $PM_{2.5}$ were found (15,20,49). However, exposure assessment for coarse PM is more challenging than for PM2.5 because of the influence of local sources—hence central site monitors less well represent residential concentrations. It is therefore possible that with more spatially resolved exposure assessment methods such as land use regression models or dispersion models, potential effects will be detected. The California Teacher's study did not evaluate coarse PM and did not find significant associations between all-cause mortality and elemental concentrations of Si, Fe and Zn, elements abundant in coarse particles (22). All constituents including these coarse PM markers were significantly associated with ischemic heart disease mortality, but no two-pollutant models were reported in the revised report (22).

There is fairly consistent evidence of associations of mortality with nitrogen dioxide and elemental or black carbon, suggesting that some of the effects reported for particulate matter may be due to motorized traffic emissions, the main source of these pollutants in urban areas. As traffic-related air pollution varies on a small spatial scale, it is even more critical to assess exposure on a fine spatial scale such as the residential address than for $PM_{2.5}$.The two US studies assessing EC exposure at the city-scale (22, 26) are likely too crude to obtain a valid estimate of the association of EC with mortality. Many

studies have documented significant intra-urban contrasts, related to especially major roads (5). Most likely EC and NO_2 should be considered as indicators of the complex mixture of traffic-related air pollution, rather than as the components causally associated with mortality. The associations are consistent with studies documenting associations between indicators of motorized traffic pollution, such as distance to a major road or traffic intensity of nearby streets.

Specific cardiovascular causes of death

Table 4 shows associations between ambient air pollution and mortality from ischemic heart disease or myocardial infarction (MI). This includes studies based upon death certificates, more detailed studies using registry data, or ideally cohort studies with epidemiological review of medical records, allowing more precise identification of disease incidence. Several studies based upon M.I. registries or epidemiological studies with clinical review have found associations between NO_2 and fatal M.I. but not non-fatal M.I. (19, 43, 44, 45, 50). Thus far, this was interpreted as evidence that air pollution particularly affects the frail. On the other hand, it is also possible that the outcomes of ischemic heart diseases are misclassified and combined as composite outcomes, where fatal outcomes are captured more precisely (51). Although there is increasing evidence that air pollution is associated with markers of early atherosclerosis, it is possible that the air pollution will affect the underlying biological processes that predispose to atherothrombosis (which leads to MI and stroke) compared to atherosclerosis (52,53). Another explanation is that the type of outcomes affected by pollution are those that have higher case-fatality rates (e.g., arrhythmic sudden death has higher case-fatality rate than overall MI.

Fewer studies have evaluated cerebrovascular mortality. In the Dutch cohort study and in the Women's Health Initiative Study, a strong association was found (32, 33). In contrast, in the ACS study, the Norwegian cohort, and the Swiss national cohort study no association was found. (16,30,24. It is possible that poorer recording of cerebrovascular mortality on death certificates has contributed to these inconsistencies.

There is also some evidence from ecological studies that air pollution may contribute to stroke mortality (54, 55).

Two studies have reported significant associations between particulate matter air pollution and dysrhythmia, heart failure and cardiac arrest combined (16,46) . These results are based upon smaller numbers of events, and require a large cohort studies for further verification. The results are consistent with several studies documenting significant associations between short-term PM or NO_2 exposure and mortality due to heart failure and dysrhythmia; defibrillator discharges (3).

Air pollution and respiratory mortality

Table 5 shows the effect estimates for respiratory diseases. In the two original US cohort studies, no association between $PM_{2.5}$ and respiratory mortality was found (16,13). In contrast to this, strong associations were found in the Dutch cohort study (33), a Norwegian study (30) and a Chinese study (25)). The heterogeneity across studies was not statistically significant ($p>0.10$). The random effect pooled estimate was 2% (95CI -7, 12, highly non-significant. Associations for PM were weaker in the Dutch and Chinese cohort study than with NO_2 or NO_x. Respiratory mortality may be more related to primary traffic-related pollutants than with long-range transported particles, though further work is needed to test this hypothesis. The smaller number of deaths due to respiratory disease compared to cardiovascular diseases, contributed to larger confidence intervals within individual studies and larger variability of the main effect estimates across studies. In time series studies including several large multi-city studies in the USA and Europe, significant associations between daily variations in PM and respiratory mortality were found (1-3). Expressed per 10 $\mu g/m^3$ PM excess risks of about 1% are typically reported for short-term exposures, larger than for all-cause mortality (1-3). In contrast to cardiovascular disease, current evidence therefore does not suggest an additional risk from long-term exposure, but more studies are needed to evaluate this more thoroughly. There is a large literature documenting effects of short- and long-term air pollution exposure on respiratory diseases and lung function (1,2).

SUMMARY

Our review supports previous qualitative reviews in documenting that long-term exposure to fine particulate matter air pollution is associated with higher mortality particularly from cardiovascular disease rather than non-malignant respiratory diseases. Associations with mortality from myocardial infarction were particularly consistent across studies and this association appears to be much stronger for fatal events than non-fatal events. Significant heterogeneity in PM effect estimates were found across studies, which cannot be easily explained. Across studies, there was little evidence that stronger association was noted for women than men. Subjects with lower education and obese subjects experienced larger mortality effect related to fine PM. We found no evidence that fine PM was associated with respiratory mortality.,. There was little evidence for an association between long-term coarse particulate matter exposure and mortality, but this may be due to the small number of studies and limitations in exposure assessment.

Our review suggests several specific research questions. Research into the reasons for the heterogeneity of effect estimates would be extremely useful for health impact assessment. Better exposure assessment including spatially resolved outdoor exposures and more chemically speciated PM might in part be able to resolve the observed heterogeneity. Chemical speciation would allow assessing particles from different sources e.g. particles from combustion sources and non-tailpipe emissions separately, a question clearly relevant for air pollution control policy. Specific attention to motorized traffic emissions is important because (road) traffic is an important source of ambient air pollution. An important question to address for the traffic pollution studies is potential confounding by road traffic noise, which has been shown to be related to cardiovascular disease including MI as well. A few studies have attempted to disentangle traffic-related air pollution and noise (45,46), but more work is needed. More work on coarse particles and at the other side of the particle size spectrum, ultrafine

particles is needed. Ongoing new research in the USA (MESA-AIR) and Europe (ESCAPE) that use large cohorts and state-of the art spatially-resolved exposure methods will likely contribute significant new answers in the near future to these questions.

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Author disclosure statement

No conflict of interest exist

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Table 1: Summary of cohort studies on particulate matter (PM_{10} or $PM_{2.5}$). and mortality from all causes and cardiovascular diseases

Study Name	**Study Design**	**Follow-up period**	**Pollutant**	**% change in risk (95% CI) in mortality associated with a 10 µg/m^3 increase PM**		**References**
				All cause	*Cardiovascular*	
Harvard six cities (original)	8111 adults in six US cities	1976 - 1989	$PM_{2.5}$	13(4, 23)	18 (6, 32)	Dockery, 1993
Harvard six cities (extended)	8096 adults in six US cities	1979 -1998	$PM_{2.5}$	16 (7, 26)	28 (13,44)	Laden, 2006
American Cancer Society (ACS) study (original)	552, 800 adults from 51 US cities	1982 - 1989	$PM_{2.5}$	26 (8, 47)	NA	Pope, 1995
ACS study (extended)	500,000 adults from 51 US cities	1982 -1998	$PM_{2.5}$	6 (2, 11)	9 (3, 16)*	Pope, 2002
ACS sub-cohort study	22,905 subjects in Los Angeles area	1982 - 2000	$PM_{2.5}$	17 (5, 30)	26 (1, 60)*	Jerrett, 2005
German cohort	4752 women in Ruhr area		PM	12 (-9, 37)	52 (8, 114)	Gehring, 2006

		2003				
Women's Health Initiative Observational Study	65,893 postmenopausal women from 36 US metropolitan areas	1994-1998	$PM_{2.5}$	NA	76 (25,147)	Miller, 2007
Netherlands Cohort Study	120, 852 subjects from Netherlands	1987 -1996	$PM_{2.5}$	6 (-3, 16)	4 (-10, 21)	Beelen, 2008
Nurses' Health Study	66,250 women from the US north eastern metropolitan areas	1992-2002	PM_{10}	11 (1,23)	35 (3, 77)	Puett, 2008
Nurses' Health Study	66,250 women from the US north eastern metropolitan areas	1992-2002	$PM_{2.5}$	26 (2, 54)	NA	Puett, 2009
California teachers study	45,000 female teachers	2002 -2007	$PM_{2.5}$	6 (-4, 16)	19 (5, 36)*	Ostro, 2011
Swiss national cohort	National census data linked with mortality	2000 - 2005	PM_{10}	NA	-1 (-3, 0)	Huss, 2010
Health professionals follow-up study	17,545 highly educated men in the midwestern and northeastern US	1989 – 2003	$PM_{2.5}$	-14 (-28,2)	3 (-17, 27)	Puett, 2011
Vancouver cohort	452,735 Vancouver residents aged	1999 –	$PM_{2.5}$	NA	1 (-2, 5)	Gan, 2011

	45- 85 yr	2002				
China nat. hypertension survey	70,497 men and women	1991 - 2000	TSP	2 (0, 2)	2 (1, 4)	Cao, 2011
US trucking industry cohort	53,814 men in the US trucking industry	1985 -2000	$PM_{2.5}$	10 (1, 20)	5 (-12, 26)	Hart, 2011

* Cardio-pulmonary mortality reported if cardiovascular mortality not available

Table 2 Effect modification of the effect of PM2.5 on cardiovascular mortality

Subgroup	ACS (Pope, 2002)*	NLCS (Beelen, 2008)	Harvard Six city (Krewski, 2005)	Nurses Health (Puett, 2008)	Vancouver cohort Gan, 2011*	WHI (Miller, 2007)	AHSMOG (Abbey, 1999)	AHSMOG (Chen, 2005)
Sex								
Men	5 (0, 11)	3 (-5, 12)** **	33 (8, 63)*	NA	8 (4,12)	NA	4 (-3,11)	-6 (-18, 8)
Women	6 (0, 12)	7 (0, 14)	20 (-6, 53)		2 (-3, 7)		-3 (-9, 2)	22 (1, 47)
Smoking status								
Never	6 (1, 12)	13 (-4, 32)	36 (2, 82)	83 (20, 179)	NA	18 (-1, 40)	NA	NA
Former	5 (0, 11)	-4 (-17, 13)	29 (-3, 72)	22 (-18, 83)		21 (1, 52)		
Current	4 (-2, 11)	3 (-10, 19)	35 94, 74)	-12 (-48, 48)		68 (6, 166)		
Education								
Low	11 (6, 18)	20 (-10, 70)* *	45 (13, 85)		NA	40 (11, 75)	NA	NA

Medium	6 (1, 13)	2 (-16, 24)	30 (-2,73)			33 (14, 55)		
High	1 (-3, 6)	-10 (-35, 20)	-3 (-29, 34)			11 (-6, 31)		
Body mass index								
Non-Obese	NA	NA	NA	8 (-24, 52)	NA	-1 (-10, 29)***	NA	NA
Obese				99 (23, 222)		35 (12, 64)***		

* Read from graph

** natural-cause mortality

*** for BMI< 22.5, continuous trend observed

Table 3: Summary of the cohort studies on coarse particulate matter, elemental carbon or NO_2 and mortality from all causes and cardiovascular diseases

Study Name	**Study Design**	**Follow-up period**	**Pollutant**	**% change in risk (95% CI) in mortality**		**References**
				All causes	*Cardiovascular*	
Coarse PM *(per* 10 μg/m^3)						
ACS study	500,000 adults 51 US cities	1982 -1998	$PM_{2.5-15}$	1 (-4, 6)	3 (-3, 9)*	Pope, 2002
AHSMOG study	3769 California seventh-day Adventists	1977 – 1992	$PM_{2.5-15}$	5 (-8, 20)	NA	McDonnell, 2000
Nurses' Health Study	66,250 women from US north eastern metropolitan areas	1992-2002	$PM_{2.5-10}$	3 (-11, 18)	NA	Puett, 2009
Health professionals	17,545 highly educated	1989 – 2003	$PM_{2.5-10}$	-10 (-22, 4)	8 (-10, 29)	Puett, 2011

follow-up study	men in the midwestern and northeastern US					
EC (per 1 μg/m^3**)**						
Netherlands Cohort Study	120, 852 subjects from Netherlands	1987 -1996	BS***	5 (0, 11)	4 (-5, 13)	Beelen, 2008
ACS study (extended)	500,000 adults 51 US cities	1982 to 1998	EC	6 (1, 11)	11 (3, 19)	Smith, 2009
Worcester MI survivors	3,895 MI patients	1995 -2005	EC	2 (-7, 11)** 15 (3, 29)	NA	Von Klot, 2009
Vancouver cohort	452,735 Vancouver residents aged 45- 85 yr	1999 – 2002	BC	NA	6 (3, 9)	Gan, 2011
PAARC	14,284 adults in 24 French areas	1974 – 1998	BS	7 (3, 10)	5 (-2, 12)	Filleul, 2005
Veteran's study	70,000 male US veterans	1997 – 2001	EC	18 (5, 33)	NA	Lipfert, 2006
California teachers study	45,000 female teachers	2002 -2007	$PM_{2.5}$	3 (-11,19)	11 (-9, 36)	Ostro, 2011
NO_2 (per 10 μg/m^3)						

Oslo cohort	16,209 men in Oslo, Norway	1972 – 1998	NO_x	8 (6,11)		Nafstad, 2004,
Netherlands Cohort Study	120, 852 subjects from Netherlands	1987 -1996	NO_2	8 (0, 16)	7 (-6, 21)	Beelen, 2008
German cohort	4752 women in Ruhr and surrounding area	1985 – 2003	NO_2	11 (1,21)	36 (14, 63)	Gehring, 2006
PAARC	14,284 adults in 24 French areas	1974 – 1998	NO_2	14 (3, 25)	27 (4, 56)	Filleul, 2005
China nat. hypertension survey	70,497 men and women	1991 - 2000	NOx	2 (0, 3)	3 (1, 5)	Cao, 2011
Vancouver cohort	452,735 Vancouver residents aged 45- 85 yr	1999 – 2002	NO_2	NA	5 (1, 9)	Gan, 2011

* Cardio-pulmonary if cardiovascular not reported

** HRs for first two years after MI and after the first two years of survival

*** BC (Black Carbon), BS (Black Smoke) and EC (Elemental carbon) are different markers used to assess soot. Increases consistent with a 1 $\mu g/m^3$ increase in EC were used (5)

Table 4: Summary of the studies on particulate matter and mortality from specific cardiovascular diseases

Study Name	**Pollutant**	**% change in risk (95% CI) in mortality associated with a 10 µg/m^3 increase**			**References**
		IHD mortality	*M.I mortality*	*Stroke mortality*	
ACS study (extended)	$PM_{2.5}$	18 (14, 23)	NA	2 (-5, 10)	Pope, 2004
Oslo cohort	NO_x	8 (3, 12)	NA	4 (-16, 15)	Nafstad, 2004
Women's Health Initiative l Study	$PM_{2.5}$	76 (25,147)	NA	NA	Miller, 2007
Netherlands Cohort Study	BS	1 (-17, 22)	NA	39 (-1, 94)	Beelen, 2008
Nurses' Health Study	PM_{10}	35 (3, 77)	NA	NA	Puett, 2008
Nurses' Health Study	$PM_{2.5}$	NA	102 (7, 278)	NA	

					Puett, 2009
California teachers study	$PM_{2.5}$	55 (24, 93)	NA	NA	Ostro, 2010
Swiss national cohort	PM_{10}	-1 (-3, 0)	NA	-1 (-2, 0)	Huss, 2010
Health professionals follow-up study	$PM_{2.5}$	-2 (-30, 35)	NA	NA	Puett, 2011
M.I. registry studies					
Stockholm	NO_2	NA	15 (-1, 35)	NA	Rosenlund, 2006
Rome residents	NO_2	NA	7 (2, 12)	NA	Rosenlund, 2008
Stockholm residents	NO_2	NA	8 (5, 11)	NA	Rosenlund, 2009

BS = Black Smoke.

Table 5: Summary of the studies on air pollution and mortality from all respiratory disease

Study Name	**Pollutant**	**% change in risk (95% CI) in mortality associated with a 10 µg/m^3 increase**	**References**
AHSMOG	PM_{10}	6 (-1, 15)	Abbey, 1999
ACS study	$PM_{2.5}$	-8 (-14, -2)	Pope, 2004
Oslo cohort	NO_x	16 (6 , 26)	Nafstad, 2004
Harvard six cities	$PM_{2.5}$	8 (-21, 49)	Laden, 2006
Netherlands Cohort Study	$PM_{2.5}$	7 (-25, 52)	Beelen, 2008
	NO_2	12 (0, 26)	
California Teachers study	$PM_{2.5}$	3 (-20, 34)	Ostro, 2011
China national. hypertension survey	NO_x	3 (0, 6)	Cao, 2011

	TSP	1 (-2,4)	
US truckers study	$PM_{2.5}$	20 (-9, 60)	Hart, 2011
	NO_2	15 (1,31)	