

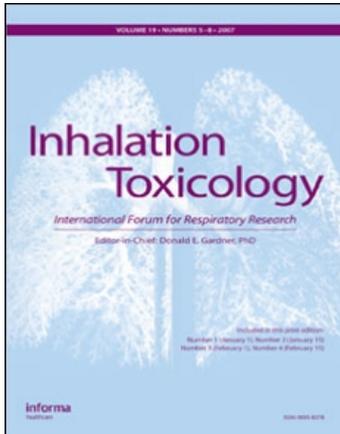
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Does improved exposure information for PM2.5 constituents explain differing results among epidemiological studies?

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RESEARCH ARTICLE

Does improved exposure information for PM_{2.5} constituents explain differing results among epidemiological studies?

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Abstract

Contrary findings are often found among epidemiological studies examining associations of different types of airborne particulates against the same health endpoints. Some studies of heart rate variability (HRV) in humans find associations with either regional particulate material 2.5 microns or smaller (PM_{2.5}) and/or with "sulfate" while some do not; some find associations with more local emissions such as black carbon (BC), while others do not. We explore if there might be a consistent methodological explanation for inconsistent findings among HRV studies. To do this, we identify studies of HRV changes in humans examining associations with ambient PM_{2.5} and sulfate, ambient PM_{2.5} and BC, or all three; we briefly review findings and methodologies, including exposure issues; then we explore why studies may come to different conclusions.

We tentatively conclude that differences in accuracy of subject exposure information for health-relevant emissions such as BC, which vary spatially over short distances in urban areas, may explain conflicting study results. HRV studies with accurate exposure information for BC or urban/industrial PM_{2.5} generally find large, significant associations with BC or urban/industrial PM_{2.5}, but rarely with secondary sulfate or regional emissions generally. However, absent accurate exposure information for BC, studies appear more likely to find associations with less spatially variable secondary sulfate or PM_{2.5}, and less likely to find strong associations with BC. However, research on this subject is limited, as are the number of studies evaluated here. Added research is necessary to confirm these findings (or otherwise), and to explore whether exposure misclassification might cause other health effects results to consistently vary.

Introduction

When examining health associations with air pollution in a given geographic area, use of more accurate subject exposure data may increase the size of the effect (Zeger et al., 2000). Although most studies of such health associations are based on ambient measures of pollution, usually from central monitors, the authors find that less measurement error and bias would be present if personal monitor pollution measurements were used. Using both daily ambient and personal exposure measurements from the Particle Total Exposure Assessment Methodology (PTEAM) study, Zeger and colleagues found a smaller coefficient when regressing

mortality on measured ambient levels than when using average personal exposure.

Van Roosbroeck et al. (2008) make similar findings. Effect estimates for soot and NO₂ were two to three times higher when personal exposure measures for schoolchildren were used, instead of measurements outside the school (which themselves would be more accurate than exposure estimates from central monitors).

These observations demonstrate the importance of better exposure information for accurately determining health effect estimates of pollution within a study. But a similar empirical issue may not have been analyzed sufficiently in

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the air pollution literature: to what extent might better estimates of exposure, versus poorer estimates, cause health effect estimates to vary among different studies of the same health endpoint?

Epidemiological studies examining or comparing health associations of different types of airborne particulates often report contrary findings. These studies often vary in how well pollutant concentration data reflects subject exposure. We explore whether differences among studies in how well pollutant data reflect actual subject exposure might cause results to vary consistently among the studies. To do this, we utilized a highly focused review of extant literature linking HRV with different types of particulate pollution.

A recent study confirms that vehicular emissions have strong local variability in a large city, while regional components of $PM_{2.5}$, (e.g., SO_4) do not. Comparing concentrations at three monitoring sites in New York City 3.2 to 9.6 km apart, Ito et al. (2004) found the highest monitor-to-monitor correlations were for a secondary aerosol factor, while correlations for a localized traffic-related factor were more variable. Secondary aerosol constituents showed consistently high ($r > 0.9$) temporal correlations across the three monitors, but correlations of elemental carbon (EC) ranged between 0.36 and 0.47. The authors state that exposure misclassification resulting from use of central monitor data for variable local emissions could mask or underestimate potential health effect associations with locally variable emissions such as EC, compared to regional PM components such as sulfate. Exposure misclassification occurs when one monitored concentration is used to reflect exposure to a pollutant of all subjects in a study, where the concentration of the pollutant may vary by two to even ten times within 150 meters (Zhu et al., 2002), in particular with distance from major roads.

Similarly, Goldberg and Burnett (2003) suggest that misclassification of important input variables could cause “transference” of causal effects “from less precisely to more precisely measured variables.”

These findings may be intuitive for epidemiologists – random misclassification resulting in underestimation of an input variable’s true relative risks is discussed in medical epidemiology texts (Hennekens & Buring, 1987). However, to the best of our knowledge, no analysis to date has attempted to review and assess the implications of exposure misclassification with regard to differential health effect associations reported in ambient air pollution literature. Our objective is to attempt this assessment, and to address these questions:

1. In epidemiological studies which compare different types or sources of PM, to what extent might reduction of exposure misclassification cause study results, regarding associations with different types of PM, to consistently change?
2. If there are consistent differences in results, among studies with or without relatively accurate exposure estimation, should researchers and regulators emphasize

studies with more accurate exposure estimation, in order to better understand which PM constituents are most harmful, or not?

Because there is a reasonably sized body of literature examining associations between various pollutants and HRV outcomes in humans, which also features differences in accuracy of exposure, we utilize the HRV literature in addressing the questions above. Changes in HRV as ambient pollution concentrations change are thought to have importance for cardiovascular outcomes, since HRV changes appear to be predictive of myocardial infarction (MI), especially for those who have had a previous MI (Tapanainen et al., 2002), or those with chronic congestive heart failure (Bilchick et al., 2002). Individuals lacking genes protective against oxidative stress also appear more vulnerable to HRV changes due to pollution exposure (Chahine et al., 2007). Rhoden et al. (2005) found that HRV changes caused by PM exposure are abolished when oxidative stress in the heart is eliminated, and Schwartz et al. (2005a) found that $PM_{2.5}$ effects on HRV measures are mediated by reactive oxidant species.

In order to focus clearly on the issue of how differences in accuracy of exposure data for different ambient $PM_{2.5}$ types might relate to HRV findings, it is important to choose studies which allow us to isolate on this variable, minimizing the number of independent variables which could complicate interpretation. We therefore examine studies with the following characteristics: 1) exposures via ambient air (to eliminate the possibility that differing results might be due to concentrated versus ambient concentrations); 2) only human subjects (so that differing results could not be due to interspecies differences, including genetically engineered animals); 3) only North American studies (so that differing results wouldn’t be due to air pollution types and amounts not typically found in North America); and 4) studies of $PM_{2.5}$ (not PM_{10}), because the sulfate and BC species which will be examined in relation to PM concentrations are generally found in the smaller fraction. Studies in particular occupational settings such as metalworking are also excluded because few people are exposed to such emissions, relative to major sources and constituents of $PM_{2.5}$ found in ambient air.

We identify (via Medline search, keywords “heart rate variability sulfate black carbon human” augmented by personal knowledge) and assess all extant studies in North America linking HRV in humans with exposure to ambient levels of $PM_{2.5}$ and to specific $PM_{2.5}$ constituents BC/EC and/or sulfate (SO_4) in the same studies. We seek to understand, utilizing this relatively small group of studies, if exposure to local emissions is well characterized in such studies, or not, and whether associations with $PM_{2.5}$ constituents vary among studies with goodness of exposure characterization.

We also examine the smaller body of literature associating pollution with ST-segment changes (another important cardiac health effect) to assess if findings might be consistent across these two cardiac endpoints. There appear to be even fewer articles examining pollution associations of $PM_{2.5}$ and either sulfate or BC with other health endpoints, which also

include studies with differing accuracy of exposure, than for these two cardiac endpoints, HRV and ST-segment changes.

Because there is no standard definition of “relatively accurate exposure” we identify a study as having such exposure to locally variable emissions in various ways. To be classified as having such exposure, a study must demonstrate that recorded concentrations of spatially variable local emissions such as BC/EC vary reasonably well with changes in actual exposure for subjects. The clearest example is when a personal exposure monitor is used. A monitor that closely follows study participants would also provide accurate exposure information. A third way to obtain reasonably accurate exposure information for vehicular emissions such as BC is if both study participants and monitor are in close proximity to the same major urban road, and the monitor isn't far from the residences, so that the type and amount of traffic and traffic emissions would be similar near both residences and monitor. A fourth way would utilize back trajectories together with composition information on different days, to characterize whether PM (and its constituents) on a given day was rural or urban/industrial in nature. In contrast, if a central monitor reading characterizes exposure to an emission, the concentration of which may vary sharply with distance from major roads, such as BC/EC, then the study wouldn't have accurate subject exposure information (unless it is in close proximity to the subjects' residences).

In reviewing study findings, we follow the methods of the authors. If a study finds significant effects with one pollutant, but not for another, we accept such findings. Methods of assessment in studies reviewed include percentage change per interquartile range; percentage change per one standard deviation; and $\Delta \log$ [HRV].

HRV studies not monitoring for BC or SO₄

Early studies of HRV found associations with measures of PM mass, usually PM_{2.5}, but tended not to examine relationships between components of PM_{2.5} and HRV. Because these studies established the connection between PM_{2.5}, or component(s) thereof, and HRV changes, we briefly review three such studies to illustrate such relationships.

Gold et al. (2000) assessed relationships between two measures of HRV (standard deviation of consecutive RR intervals (SDNN) and root-mean square of the difference of successive R-R intervals(r-MSSD)) with PM_{2.5} and several gases, among 21 volunteers in a Boston housing community. Significant negative associations with PM_{2.5} for both HRV measures were found for different time periods (1 and 4 h). Monitors located up to 7.7 km from the study site measured concentrations of different pollutants. Since ambient PM_{2.5} concentrations in a large city don't vary much over a range of 8 km, unless there is a major industrial point source of emissions such as a steel mill (Jerrett et al., 2005), subject exposure to PM_{2.5} is likely well characterized in Gold et al. (2005), since such major industrial facilities are absent in Boston.”

Liao et al. (1999) studied residents of a retirement center in metropolitan Baltimore, MD for three weeks. Several significant negative HRV associations (SDNN, high frequency

component (HF), and low frequency component (LF)) were found with the group of 26 volunteers (mean age 81 years), when days with high PM_{2.5} concentrations were compared with other days. No associations were found with a one day lag. Significant associations were found for those with previous cardiovascular-related conditions, and for all subjects combined, but not for participants without previous cardiovascular-related conditions.

A panel of 88 elderly residents in three communities in the greater Salt Lake City, Utah area (Pope et al., 2004) examined relationships between HRV changes and both PM_{2.5} and the semi-volatile component of PM_{2.5}. The study found “reasonably consistent and statistically robust” negative associations between increasing PM_{2.5} and HRV measures (SDNN, r-MSSD). Sources of PM_{2.5} noted included traffic and urban sources, an integrated steel mill, and local refineries. Ten days had “abnormally high” levels of semi-volatile material (SVM), caused by abnormally elevated ammonium nitrate concentrations. When these ten days were deleted from the analysis, negative PM_{2.5} associations with HRV strengthened to significance. Associations with PM_{2.5}, measured either by TEOM (which doesn't include SVM), or a different sampling system which does include SVM (but excluding the ten days with abnormally high semi-volatile ammonium nitrate), showed similar HRV results. The authors suggest these findings may mean that organic SVM has similar HRV effects as non-volatile PM_{2.5} in their study, and thus may point toward a need for further characterization not just of PM but also of organic gases. Results also suggest the possibility that effects of non-metallic, non-organic SVM might be smaller than those of PM_{2.5} or organic SVM.

HRV studies monitoring for BC or SO₄

Table 1 gives basic information about the eight HRV studies reviewed, in particular with regard to monitoring methodologies and pollution types monitored. Summaries of study findings in this section are found in Table 2 (US studies with accurate exposure) and Table 3 (US studies lacking such exposure); associations with gases, virtually all insignificant, are not shown.

Studies with accurate exposure information

Adar et al. (2007) examined changes in measures of HRV in elderly patients in Saint Louis during trips on diesel buses, and at other times. A portable monitor continuously measured particles (PM_{2.5} and BC mass, fine particle counts, coarse PM) during the 48 hours surrounding each bus trip, by placement in the participants' living facilities, with the participants aboard the bus, as they had lunch, or in a group activity, thus ensuring pollution concentrations reflecting subject exposure.

Strong and consistent associations per inter-quartile (IQR) change were found with the first three pollutants (which were highly correlated) for all HRV measures (negative associations for SDNN, r-MSSD, number of instances per hour in which two consecutive R-R intervals differ by more than 50 ms over 24 h (PNN50) + 1, LF, and HF, and positive

Table 1. Characterizations of US HRV studies reviewed.

Study	Population studied	Exposure description	Concentrations	BC (EC) ^a	PM _{2.5} ^a	SO ₄ ^a
Adar et al. (2007)	44 non-smokers > 60 years, living in senior residences	Portable monitors which travel with subjects, inside residences at other times	median (IQR)			
			Overall	330 (337) ^b	7.7 (6.8)	NA
			On Bus	2911 (2464) ^b	17.2 (10.3)	NA
Ebelt et al. (2005)	16 non-smoking COPD patients, mean age = 74	Personal monitors	Residence	285 (270) ^b	6.8 (5.1)	NA
			mean (IQR)	NA	18.5 (10.1)	1.5 (0.9)
Schwartz et al. (2005b)	27 subjects, 61-89 years old	Monitor on same major urban street as residences, < 1 km from residences	25% (24 h, 1 h)	0.8, 0.9	7, 6	NA
			50%	1.0, 1.2	10, 10	NA
			75%	1.3, 1.6	17, 19	NA
Creason et al. (2001)	56 non-smokers, mean age 82, residents of retirement center	Central monitor, monitors in and at residences, in concert with wind back trajectories	mean (indoor at residences)		8.9 (3.9, 20.0) ^c	^d
			mean (outdoor at residences)		27.1 (13.8, 55.5) ^c	^d
			mean (community monitor)		28.5 (12.5, 54.2) ^c	^d
Luttmann-Gibson et al. (2006)	32 senior non-smokers (29 women), in 3 subsidized apartments	Central monitor, located ~ 1 mile away, several hundred feet higher than apartments	mean	1.1	19.7	6.9
			25%	0.7	11.6	3.3
			75%	1.3	25.0	8.5
Park et al. (2005)	497 male veterans, mean age 72.7 (Normative Aging Study participants)	Central monitor	mean (±SD)	0.92 ± 0.47)	11.4 (±8.0)	NA
Wheeler et al. (2005)	18 people with COPD, 12 with recent MI, mean age 65 (55-73)	Central monitors	10%	0.9	7.0	NA
			25%	1.2	11.6	NA
			50%	1.6	16.5	NA
			75%	2.9	22.2	NA
			90%	4.4	30.9	NA
Riediker et al. (2004)	9 non-smoking healthy male patrol officers	Pollutants measured inside patrol cars on four nine-hour shifts	mean (±SD)	NA	23 (±8.0)	1.7 (±0.8) ^e

IQR, interquartile range; ^a µg/m³; ^b nanograms/m³; ^c mean (minimum, maximum); ^d S measured, utilized and discussed in text, not presented in tables or figures; ^e sulfur (not sulfate).

associations for LF/HF and HR). HRV associations for PM_{2.5} and BC were both about an order of magnitude larger during the bus period – when PM_{2.5} and BC exposures were also about an order of magnitude higher – than during the non-bus periods (particle number associations not reported). BC and PM_{2.5} were both significantly associated with most HRV measures whether on the bus or not. These findings suggest the importance for HRV effects both of BC per se, and of ambient traffic-related emissions correlated with BC.

Ebelt et al. (2005) conducted a small panel study of 16 patients with COPD during summertime in urban Vancouver, BC. Subjects wore a personal PM_{2.5} sampler providing integrated personal PM_{2.5} data; all filters were analyzed for PM_{2.5} and sulfate. Non-sulfate PM_{2.5} was calculated as the difference of PM_{2.5} and sulfate. Both ambient concentrations and concentrations of exposure were analyzed. HRV measures (SDNN, r-MSSD) were among various respiratory and cardiovascular endpoints examined. For these two endpoints, there were significant or borderline significant reductions in various HRV measures with non-sulfate PM_{2.5} (with virtually identical but slightly weaker associations with PM_{2.5}), while sulfate associations were generally small and insignificant.

The 28 subjects of Schwartz et al. (2005b), aged 61-89, lived in housing adjacent to a major urban road in Boston.

The monitor for hourly measures of PM_{2.5}, BC, and CO was also adjacent to this road (1 km from the subjects' housing), suggesting that the monitor measured pollution concentrations at the residences reasonably well, assuming no major differences in traffic within the 1 km distance. The authors note that sulfate and other secondary PM have a different diurnal pattern (a broad peak from late morning to early afternoon) than BC/traffic emissions (peaks at morning and evening rush hours). Regressing PM_{2.5} against BC allowed estimation of hourly concentrations of regional PM_{2.5}, including regional secondary particles.

For each PM type (PM_{2.5}, BC, secondary PM_{2.5}), there were eight regressions (1 h and 24 h time periods, four measures of HRV). BC was significantly associated with reduced HRV in six such tests and borderline significant in a seventh. PM_{2.5} was significantly associated with reduced HRV in two tests, borderline in a third. Secondary (regional) PM_{2.5} was never significantly associated with reduced HRV.

Figure 1 (Figure 3 in Schwartz et al., 2005b) illustrates these relationships. When BC and PM_{2.5} are highly correlated, at low levels of PM_{2.5}, a monotonic decrease in SDNN with increasing levels of PM_{2.5} occurs. At higher levels of PM_{2.5}, when the correlation with BC disappears, and PM_{2.5} is more correlated with regional secondary PM_{2.5}, SDNN no longer

Table 2. Findings of US HRV studies with good subject exposure.

Study	HRV measures		Associations and significance					
			BC	PM _{2.5}	SO ₄	Non-SO ₄ PM _{2.5}	Secondary PM _{2.5}	
Adar et al. (2007) ^a	5 minute means	SDNN	Bus	-4.6*	-5.0*			
			Non-bus	-0.1	-0.5*			
	RMSSD	Bus	-2.6*	-4.8*				
		Non-bus	-0.3*	-0.7*				
	PNN50 + 1	Bus	-2.0*	-6.3*				
		Non-bus	-0.5*	-0.8*				
	LF	Bus	-6.0*	-7.0*				
		Non-bus	-0.2	-0.6				
	HF	Bus	-5.8*	-10.7*				
		Non-bus	-0.9*	-0.7				
	LF/HF	Bus	-0.8	3.9*				
		Non-bus	0.8*	1.4*				
	Ebelt et al. (2005) ^b	24 hour means	SDNN	Ambient		~ -4.2	~ -3.5	~ -4.0 [#]
				Exposed		~ -4.0	~ -0.5	~ -4.0 [#]
RMSSD		Ambient		~ -2.5	~ 0.2	~ -3.0*		
		Exposed		~ -1.0	~ 1.0	~ -1.5		
Schwartz et al. (2005b) ^c		SDNN	1 h	-4.6*	-3.4		-0.5	
			24 h	-5.1*	-2.6		-0.9	
RMSSD	1 h	-6.1 [#]	-7.4			-3.0		
	24 h	-10.1*	-10.1*			-6.4		
PNN50	1 h	-9.4*	-12.9 [#]			-6.6		
	24 h	-16.9*	-12.7*			-5.8		
LF/HF	1 h	1.8	1.4			1.4		
	24 h	7.2*	0.2			-2.4		
Creason et al. (2001) ^d	24 hour means	HF (all 24 days)	Indoor		-0.07			
			Outdoor		-0.03			
	HF (2 high PM _{2.5} rural days removed)	Indoor		-0.18*				
		Outdoor		-0.07*				
	LF (all 24 days)	Indoor		-0.07				
		Outdoor		-0.03				

Table 2 continued on next page

Table 2. continued.

	LF (2 high PM _{2.5} rural days removed)		
		Indoor	-0.14*
		Outdoor	-0.06*
Riediker et al. (2004) ^e	Source factors based on 9 hour exposure, cardiac effects measured 10 hours after exposures		
	SDNN	(factor)	
		road surface	~ 0%
		gasoline	~ 3%
		speed change	~ 16%*
	PNN50	(factor)	
		road surface	~ 5%
		gasoline	~ 1%
		speed change	~ 22%*

* significant; # borderline significant. ^a Percentage change per interquartile range. ^b Effect estimate (ms). ^c Percentage change per interquartile range increase. ^d $\Delta \log$ [HRV]. ^e Percentage change per standard deviation in source factor.

Table 3. Findings of US HRV studies without good subject exposure.

Study	HRV measures	Associations and significance			
		EC/BC	PM _{2.5}	SO ₄	Non-SO ₄ PM _{2.5}
Luttmann-Gibson, et al. (2006) ^a	24 hour averages for previous day				
	SDNN	1.5	-4.0*	-3.3*	-2.1 [#]
	RMSSD	-1.1	-6.5*	-5.6*	-3.8 [#]
	HF	3.1	-11.4*	-10.3*	-5.9
	LF	-4.7	-10.7*	-8.4 [#]	-7.2
Park et al. (2005) ^b (single pollutant models)	24 h moving ave.				
	Log ₁₀ SDNN		-2.2		
	Log ₁₀ HF		-13.2 [#]		
	Log ₁₀ LF		-0.6		
	Log ₁₀ LF:HF		14.5*		
	48 h moving ave.				
	Log ₁₀ SDNN	-3.4	-5.4		
	Log ₁₀ HF	-13.8	-20.8*		
	Log ₁₀ LF	-2.4	-6.0		
	Log ₁₀ LF:HF	13.2 [#]	18.6*		
Wheeler et al. (2006) ^c	Overall				
	SDNN (1 h)				
	MI only		-2.75		
	COPD only		5.07*		
	SDNN (4 h)				
	MI only	-1.06	-2.89		
	COPD only	0.51	8.29*		
	SDNN (24 h)				
	MI only		-4.38		
	COPD only		1.58		
	W/baseline FEV ₁ as effect modifier				
	SDNN (4 h)				
	FEV ₁ = 105	-3.9*	-2.5		
	FEV ₁ = 35	2.5	10.2*		

* significant; # borderline significant. ^a Percentage change per interquartile range. ^b Percentage change per one standard deviation. ^c Percentage change per interquartile range.

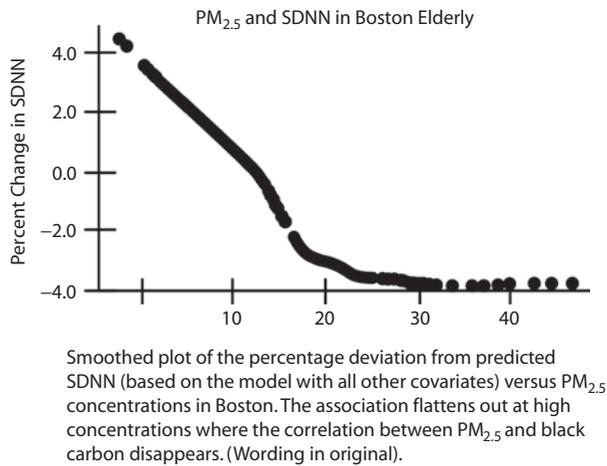


Figure 1. SDNN monotonically decreases with increased PM_{2.5} when PM_{2.5} is highly correlated with BC, but is not affected by rising levels of PM_{2.5} when PM_{2.5} is higher and correlated with regional PM, not BC. From Schwartz et al. (2005), reproduced with permission.

decreases with higher levels of PM_{2.5}. The authors conclude that at low levels, PM_{2.5} is acting as a surrogate for BC and traffic effects, and that traffic related emissions are associated with disturbances of autonomic control of the heart.

Creason et al. (2001) examined changes in HF and LF in 56 elderly non-smoking retirees living in a retirement center in Baltimore County, MD, during 24 summer days. PM_{2.5} levels were presented (minimum outside at community center = 7.8 µg/m³; maximum = 46.7 µg/m³; mean = 20.5 µg/m³) and relationships with daily PM_{2.5} levels were examined. Sulfur concentrations were not presented, but the authors stated sulfur averaged 14% of outdoor PM_{2.5} over all the days.

Using all 24 days, Creason et al. found a U-shaped relationship between HF and PM_{2.5}. HRV declined with increasing PM_{2.5} until high levels of PM_{2.5}, at which point HRV reversed direction and increased to levels found at the lowest PM_{2.5} levels. The authors found that two days – those with the highest and third highest PM_{2.5} concentrations – caused the relationship to revert upward. When these days were removed, a monotonic decrease in HRV with increasing PM_{2.5} appeared.

The two eliminated days were different from other days. Back trajectories showed that the PM_{2.5} mass on these two (non-effect) days came from rural Pennsylvania, not from urban or Midwestern industrial areas. Although the sulfate/PM_{2.5} ratio on these two days was 9% (versus 14% average), the sulfate concentrations were higher than most days because PM_{2.5} was higher. The authors suggest that PM on these two days had different sources and composition than on the other 22 days, all but one of which had lower PM_{2.5} concentrations. These findings parallel those of Schwartz et al. (2005b), where HRV measures decreased with increasing PM_{2.5} at lower PM_{2.5} concentrations, where BC was highly correlated with PM_{2.5}, with HRV effects disappearing at higher PM_{2.5} concentrations, where PM_{2.5} was mostly secondary.

Subjects in Riediker et al. (2004) were nine young male patrol officers, exposed to pollutants measured inside their vehicles while on duty. Associations were studied between 11

health endpoints (including two HRV variables, SDNN and PNN50) and three different traffic-related factors. These were 1) a soil and road surface factor, marked by Al, Si, Ti, and Fe; 2) a gasoline factor, marked by benzene and CO; and 3) a “speed changing” factor, marked by Cu, S, and aldehydes. Cu may be associated with brake wear in slowing traffic, while aldehydes and S emissions may be associated with accelerating diesels. The authors speculate, paralleling laboratory analysis by Kweon et al. (2003), that diesel combustion in accelerating trucks might contribute the higher levels of sulfur found in this factor versus other factors. All but one of the eleven health associations, including positive associations with both HRV measures, were found with the “speed changing” factor.

Studies lacking accurate exposure information

Luttmann-Gibson et al. (2006) studied elderly participants living mostly in three subsidized apartment buildings in Steubenville, Ohio, during summer and fall 2000. PM_{2.5}, sulfate, and EC were monitored. Nonsulfate PM_{2.5} was calculated by subtracting sulfate from PM_{2.5}. EC was well correlated with PM_{2.5} (0.59), nonsulfate PM_{2.5} (0.62), and sulfate (0.47). The monitor is located at the Franciscan University of Steubenville, over one hundred meters up a hillside from both Ohio Route 7 and from the elevation of the subjects' apartments (not on Route 7), 0.8 to 1.6 km distant. This vertical elevation precludes accurate exposure characterization for the subjects for vehicular emissions. Restrepo et al. (2004) found concentrations of vehicular emissions (NO₂, CO) at street level were up to twice as high, compared to measurements at a monitor about 15 meters above street level, while PM_{2.5} mass was equivalent.

In Luttmann-Gibson et al., an interquartile increase of 5.1 µg/m³ in previous day sulfate was associated with a decrease of -3.3% SDNN, -5.6% r-MSSD and -10.3% HF, with similar associations with PM_{2.5}. HRV changes were not associated with EC.

Park et al. (2005) examined HRV associations with air pollution among elderly veterans in the greater Boston area. Concentrations of PM_{2.5}, particle number, BC (but not sulfate), and several gases were obtained. After controlling for confounders, several associations were found with 48 h, 24 h, and 4 h average PM_{2.5}. One weak association was found with 48 h BC. Comparison of BC and PM_{2.5} associations for the same endpoints found BC effects to be consistently weaker, with significant associations only for PM_{2.5}.

Wheeler et al. (2006) examined effects of various air pollutants on 18 people with COPD and 12 people with recent myocardial infarctions (MIs) across the Atlanta, GA area. PM_{2.5} was measured at three locations (urban, rural, and suburban/commercial).

BC was measured at the urban site. CO, SO₂, and NO₂ levels were measured at the suburban/commercial site, and at an additional suburban site.

Several significant and positive associations for SDNN were found with PM_{2.5} for those with COPD (1 h and 4 h time periods, but not 24 h). For 4 h NO₂ concentrations, positive and significant associations were found for overall

SDNN for those with COPD, whereas negative and significant associations were found for those having had a heart attack (the only significant MI finding). When FEV1 was included as an effect modifier, a negative and significant association was found with BC for those without compromised FEV1.

The authors note that the results might be skewed because of exposure misclassification due to greater spatial variability for NO₂ and BC versus PM_{2.5}: “For both NO₂ and BC, this greater exposure error may explain the lower and insignificant effect estimates found for these pollutants.”

Park et al. (2007) Study Using Clusters of Wind Trajectories

We learned of a recent study (Park et al., 2007) relevant to this review which was not picked up by our Medline search, perhaps because “sulfate” and “black carbon” weren’t among the study’s keywords for search. Because of its complexity and interesting results, we discuss this study here, after discussing other HRV studies.

Park et al. (2007), a follow-up to Park et al. (2005) using the same subjects, uses back trajectory analysis to explore whether individual pollutants within clusters of air masses from six different directions (S, SW, W, NW, N, plus a slower air mass called “local”) are differentially associated with four HRV measures (SDNN, HF, LF, and LF/HF). Averaged levels of PM_{2.5}, BC, sulfate, and several gases are presented for each trajectory cluster. The PM measures plus ozone are fitted for each pollutant separately, for each trajectory, in determining associations (sulfate concentrations were not available in Park et al. (2005), preventing some comparisons between the two studies). Ninety-six possible associations are tested (four pollutants (ozone plus PM_{2.5}, BC, and sulphate), times four measures of HRV, times six trajectory clusters – see Figure 4 in original), using 48 h average pollutant concentrations for PM types. Concentrations of PM types in the NW and N trajectories are considerably lower than for the other four trajectories (including “local”), with only small differences among the other four (Table 4). Pollution monitoring for Park et al. (2007) used central monitor data.

Results of Park et al. (2007)

Significant PM associations include the following (single pollutant models only):

- SW cluster trajectories: decreases in SDNN, LF, and HF for 1 interquartile range (IQR) increase in black carbon.

Table 4. Concentrations of different particle types (µg/m³) and ozone (ppb) in wind trajectory clusters in Park et al. (2007).

PM type	Identified cluster by wind trajectory					
	S (South)	SW	W	L (Local)	NW	N
PM _{2.5}	14.4	14.1	13.7	15.1	8.5	8.5
BC	1.1	0.99	0.99	1.1	0.63	0.79
SO ₄	4.2	4.0	3.8	4.0	2.7	2.3
Ozone	29.1	25.4	17.0	22.8	22.9	21.3

- L (“local”) cluster: increases in LF/HF for IQR increase in black carbon, PM_{2.5}, and sulfate.
- NW cluster: increase in LF/HF for IQR increase of sulfate.

In models using 1 day lags, “effect modification and the independent effect of the clusters were less prominent compared to the results of the clusters with no lag (data not shown).” An association with ozone was found for the W trajectory, which was interesting because ozone levels were lower in this trajectory than in all the others.

Before discussing the results, two issues should be noted. First, as with Creason et al. (2001) and Lippmann et al. (2006), the use of trajectories can provide added insights not otherwise available. Secondly, use of central monitors may bring exposure misclassification.

Discussion of Park et al. (2007)

Four trajectories (S, SW, W, and local) have relatively high levels of the three PM types, with very little variability among them (PM_{2.5} between 13.7 and 15.1 µg/m³; sulfate between 3.8 and 4.2 µg/m³; BC virtually identical, between 0.99 and 1.1 µg/m³). Yet the only associations are found with the two most urban trajectories (SW and local), suggesting that urban emissions are more important for HRV associations, paralleling the findings of Schwartz et al. (2005b) and of Creason et al. (2001).

The SW trajectory travels through the Washington DC – Philadelphia – New York City corridor before reaching Boston, and shows three HRV associations, all with BC. Other urban emissions, including (unmeasured) V and Ni from shipping, electricity generation, and commercial residual oil sources, might also be present, especially in New York City (Peltier et al., 2008). The local (L) trajectory by definition is slow moving and therefore would contain a greater proportion of local Boston air and a smaller proportion from transported air masses. There were significant associations between all three PM types and a HRV measures in the L trajectory. (Of the less urban trajectories, the S trajectory reaches Boston from the south, from over the ocean after having been over land. The W trajectory passes over rural New York State north of Pennsylvania and New York City.)

In these four “high PM” trajectories, sulfate was significantly associated with an HRV measure only in the local (L) trajectory, but not in any of the three trajectories which would have a greater proportion of long range transported PM versus locally generated PM. This may suggest that a local sulfate source, e.g., diesel emissions, is a more likely cause of the association (Grahame & Hidy, 2007; Kweon et al., 2003; Riediker et al., 2004).

It is curious that the BC levels are virtually the same in the four trajectories not from N or NW, given that about 2/3 more BC is measured in urban Boston (~1.0 µg/m³) than in Stow, Massachusetts (~0.3 µg/m³), about 40 km W of Boston (Allen & Johnson, 2003). Thus the location of the monitor on a busy urban road at the Harvard School of Public Health

perhaps may skew BC readings upward regardless of wind trajectory. Perhaps less BC is transported regionally than some may suppose.

In this study, trajectories appear to have more predictive value for health endpoints than do specific centrally monitored local emissions such as BC. This may suggest, again, how exposure misclassification may skew results, in that the studies reviewed herein which have reasonably accurate subject exposure information for BC show significant associations with BC. In contrast, BC is associated with HRV changes in Park et al. (2007) in only two of the four "high PM" trajectories (the two most urban ones), despite BC levels being nearly identical in all four of them.

For the two northern trajectories (N, NW), levels of all PM types are about 1/3 lower than for the four other trajectories, but there is a HRV association nonetheless, with sulfate (NW). The authors speculate, based upon other work, that perhaps Ni and V emissions (not monitored for this study) could be responsible for the sulfate association. Daily back trajectories in Lippmann et al. (2006) suggest that Ni levels can be quite high when back trajectories pass over major Ni smelter sources in Ontario, for example.

Other studies

A recent study from Taiwan (Chuang et al., 2007) failed to find associations with BC/EC, despite BC levels two to four times higher than in major US cities such as New York City, and also found associations with sulfate. A discussion of recent Taiwanese studies can be found in the Supplementary Material.

Studies of ST-segment depression

We identified four studies assessing associations of ST-segment depression with $PM_{2.5}$, two of which monitor BC as well as other PM components. We discuss these to see if similar results to the HRV studies may occur.

In Pekkanen et al. (2002), mild exercise tests were conducted biweekly for six months among 45 subjects with existing coronary heart disease in three European cities. $PM_{2.5}$, $PM_{1.0}$, $PM_{2.5-10}$, and number count (NC) of particles 10 to 100 nanometers in size ($NC_{0.01-0.1}$) and accumulation mode particles ($NC_{0.1-1.0}$) were monitored at central sites, as were NO_2 and CO. Significant associations with increased risk of ST-segment depression were found for all PM sizes except coarse PM, and for both gases, 2 days before exercise tests. Because central monitors were used and speciation of PM constituents not attempted, we conclude only that high levels of urban pollution are associated with ST-segment depression (lagged effect) among those with coronary heart disease.

Mills et al. (2007) is a double-blind, randomized crossover study. Subjects with coronary heart disease were exposed for one hour to diluted diesel exhaust ($\sim 300 \mu g/m^3$) or filtered air (alternating 15 minutes of mild exercise with 15 minutes of rest). ST-segment depression occurred in both sets of subjects, but the average change in ST-segment depression was twice as great in subjects exposed to diluted diesel exhaust.

In Gold et al. (2005) as in Schwartz et al. (2005b), subjects live in close proximity to the same major Boston road, using the same central monitor (for $PM_{2.5}$, BC, and CO concentrations) in close proximity to the road, not far from the subjects' residences. Thus monitor measures of these emissions are likely to reflect reasonably well concentrations to which subjects are exposed. The study utilized 269 observations of 24 active Boston residents 61 to 88 years of age.

Several BC and CO associations were found in single pollutant models. In multi-pollutant models, BC maintained significance, while CO associations became small and insignificant. Neither other gases nor $PM_{2.5}$ (which includes regional emissions) were ever significant.

In Lanki et al. (2006), 45 elderly, non-smoking Finnish subjects with stable coronary artery disease lived within 5 km of the central monitor, which measured 13 ions plus $PM_{2.5}$ mass, absorbance coefficient (ABS, similar to BC), and ultrafine PM number counts. Using these inputs, five factors were initially found: crustal PM, long range transport (LRT, high in sulfate), oil combustion, salt, and local traffic (high in ABS). Significant associations were found only with local traffic and LRT (both 2-day lag), for two criteria for ST-segment depression. For the stricter criteria, the oil combustion factor became borderline significant (2-day lag).

In a second set of analyses using only the single PM component most highly correlated with each factor as an indicator element for that factor, only ABS, "a marker for local traffic," was associated with ST-segment depression. LRT, marked by sulfate, became insignificant, suggesting that ABS (0.45 correlation with sulfate in LRT factor) may have caused the association between the long range transport factor and ST-segment depression in the initial analysis. As with Schwartz et al. (2005b) for HRV, it was necessary to tease out differential effects of regional PM and local BC. When this was accomplished, associations were found only with the local BC (or ABS), not the regional PM (Schwartz et al.) or the regional sulfate (Lanki et al.).

Discussion of HRV findings

Although there are different methods of obtaining good exposure measurements or proxies for subject exposure, one apparently consistent result in US studies is that BC appears to be highly and significantly correlated with HRV reductions when subject exposures to BC are reasonably well characterized (Table 2). Whether monitors which travel with and are in close proximity to subjects are used (Adar et al., 2007) or whether the monitor and the subjects' residences are both in close proximity to the same major road, nearby each other (Schwartz et al., 2005b), BC associations with HRV measures are numerous, strong and significant. The fact that both HRV effects, and exposure to diesel emissions marked by BC, are about an order of magnitude larger when the subjects are riding a bus suggests the importance of exposure to diesel emissions for autonomic cardiac control (Adar et al., 2007).

BC may itself cause harm (perhaps due to adsorption of ultrafine PM such as PAHs), and/or may be a proxy for other pollutants, such as organic gases and/or ultrafine or

submicrometer PM, co-emitted with BC. Although Chuang et al. (2005) is a Taiwanese study, with differing types and amounts of pollution, it is notable that only the submicron-sized PM caused HRV reductions, in a study with personal monitors (however, submicron PM was quite high in this study). Additional research in the US with personal monitors for different size fractions as well as submicron PM constituents is thus recommended.

In contrast (Table 3), when subject exposure to BC is not well characterized (e.g., monitor located over one hundred meters above subject residences and nearby roads, 0.8 km or more distant from residences (Luttmann-Gibson et al., 2006)), or when central monitor readings characterize exposure to variable BC in studies where the subjects live across a large area (Park et al., 2005; Wheeler et al., 2006), then BC associations are fewer and/or weaker than for $PM_{2.5}$ (opposite of Schwartz et al., 2005b) or non-existent.

Spatial variability of BC may explain these patterns of associations. Ito et al. (2004) found vehicular emissions were poorly correlated among three locations in New York City (regional pollutants were highly correlated). The authors state that associations of such local emissions with health effects could be understated in comparison to regional PM, if central monitor concentrations for vehicular emissions are used.

For sulfate, the opposite pattern to that of BC/EC appears to be the case. Where BC exposure or exposure to urban air masses is well characterized (Table 2), the measure of PM which includes secondary sulfate but not urban or industrial aerosols appears not to be associated with HRV effects.

In Schwartz et al. (2005b), there were no associations with secondary $PM_{2.5}$. As the authors state, the limited number of associations with $PM_{2.5}$ mass as a whole, fewer than with BC, appear to reflect that $PM_{2.5}$ acts as a surrogate for BC when there are HRV associations with $PM_{2.5}$. No further $PM_{2.5}$ effects occur in when $PM_{2.5}$ levels are high, and correlated more with regional PM than with BC (Figure 1).

In Creason et al. (2001), the two day air mass which contains the highest levels of fine PM, including high levels of sulfate, but which comes from a rural (non-urban, non-industrial) area, is the only air mass not associated with HRV reductions as $PM_{2.5}$ levels increase; these findings parallel the lack of $PM_{2.5}$ associations in Schwartz et al. (2005b) only at high levels of PM, when the air mass is correlated with regional emissions. Ebel et al. (2005), a study using personal monitors, found sulfate was not associated with reduced HRV measures, but non-sulfate urban aerosols were so associated.

In contrast (Table 3), when exposure to BC is poorly characterized, associations with sulfate become significant, while BC/EC associations disappear (Luttmann-Gibson et al., 2006). These results may reflect that on high pollution days, regional emissions are usually elevated; if health effects occur, they would likely be associated with regional emissions in a statistical model, in the absence of good subject exposure measurements for locally variable pollutants. Thus this study may illustrate not just that associations with

local emissions are less likely when central monitors are used (Ito et al., 2004), but also the finding of Goldberg and Burnett (2003) that health associations can be "transferred" from poorly to well measured variables.

Other explanations for the findings of Luttmann-Gibson et al. (2006) exist. Steubenville in 2000 had far fewer steel and coke facilities than two decades prior, when the Six Cities study (Dockery et al. 1993) found greater mortality rates there than elsewhere. But in 2000 two blast furnaces still operated within Steubenville, with several hundred acres of coke ovens 5 km down-river, and similar facilities 6.5 km up-river in Weirton, WV. Since these facilities co-emit sulfates with metals and carbonaceous materials, sulfate associations with reduced HRV in Steubenville might reflect effects of harmful materials correlated with sulfate. PM emissions from contemporary steel/coking facilities have very high RRs for all-cause and cardiorespiratory endpoints (Jerrett et al., 2005).

HRV associations in Riediker et al. (2004) were positive, not negative. Does this reflect younger ages of subjects, a longer exposure period, and /or a different mix of (fresher) pollutants? Also, this is the only US study we found with good exposure information which finds associations reflecting sulfate. The "speed change" factor, but not other factors to which patrol officers were exposed, is marked by sulfate, copper, and aldehydes. An explanation suggested by the authors, that sulfate is emitted from accelerating diesels, appears reasonable, since sulfate levels in the gasoline and road dust factors are considerably lower. Kweon et al. (2003) found increasing levels of sulfates emitted by accelerating diesels in laboratory work. If this explanation is accurate, then the findings of Riediker et al. (2004) also reflect diesel/vehicular emissions, as in the other studies with good exposure information.

In Park et al. (2007), six different air trajectory clusters are examined, four having very similar levels of PM types. Some potentially important pollutants are not measured (V, Ni). In general, it would appear that urban air masses - those which have travelled over several major urban areas (SW cluster), or which stagnate over a large urban area (L cluster) - contain pollutants which are associated with HRV changes. Air masses with equally high levels of BC, $PM_{2.5}$, and sulfate but which are not stagnant, or do not pass over larger metropolitan East coast conurbations, appear not to cause changes in HRV. These findings are consistent with Schwartz et al. (2005b), and also with Creason et al. (2001), the other HRV study using trajectory analysis, which found that rural air masses with high $PM_{2.5}$ and sulfate were not associated with HRV changes.

Discussion of ST-segment depression findings

With regard to $PM_{2.5}$ associations with ST-segment depression, the findings of Gold et al. (2005) and Lanki et al. (2006) appear similar to those of HRV studies with good exposure: vehicular emissions (BC or ABS), but not regional PM or (regional) secondary sulfate, are associated with this endpoint. The study by Mills et al. (2007), showing that exposure to diesel exhaust exacerbates ST-segment depression,

augments these findings, since diesel emissions are the major source of BC and associated emissions in most large US and European cities. A priori, the exposure methodology of Gold et al. is likely to better reflect subject exposure to variable local emissions well, since the subjects live in close proximity to the same major road where the central monitor is located nearby. In contrast, Lanki et al. used a central monitor to express exposure of people living up to 5 km distant. Therefore, in this second study, there likely was more exposure misclassification, especially for ultrafine PM, largely from traffic within large cities, thus perhaps explaining lack of association with ultrafines. Given the smaller number of studies of ST-segment depression (versus HRV changes) which might enable differential assessment of BC and secondary sulfate, the assessment of this group of work must be considered very preliminary.

Comparison with other recent work

Earlier work assessing health associations with PM often didn't monitor for health-relevant types of PM, e.g., BC or emissions from major industrial sources; if they did, central monitor readings were often used. More recent studies have begun to address these issues, examining relative risks of vehicular emissions versus secondary regional emissions (some making direct comparisons in the same study), or reviewing recent research advances and findings. Space limitations preclude a comprehensive review of such studies; five recent ones are discussed here.

The review by Brook (2007) suggests that:

- PM_{2.5} triggers many cardiovascular (CV) events within hours (e.g., acute events);
- oxidative stress may play a central role, including for effects mediated via autonomic pathways (paralleling the HRV findings of Rhoden et al. (2005) and Schwartz et al. (2005a), e.g. oxidative stress in the heart is necessary for HRV changes);
- chemistry of pollutants can determine such toxicity;
- pro-oxidative compounds are more likely to trigger such events than inhalation of inert substances; and
- personal monitoring of air pollution exposure may enhance associations between types of PM and various CV disease risks.

The potential relevance to sudden death of changes in HRV caused by exposure to vehicular emissions is suggested by Peters et al. (2004), who find that among survivors of a first MI, the strongest predictor of the MI is being in traffic an hour before (many potential causal pathways, including reduced HRV, are noted as plausible).

Adar and Kaufman (2007) review epidemiological literature implicating traffic exposure and cardiovascular disease. The authors point out, as do we, that substantial measurement error for traffic related pollutants, caused by using a single measure of exposure for a metropolitan area, can skew results away from such emissions. Despite these limitations,

inventive ways occasionally can be found to use such data. For example, between-city differences in a European study in the ratio of PM to NO₂ (considered a marker of traffic emissions in Europe) were used to show differential mortality risks for PM exposure. Such risks were four times higher per 10 µg/m³ increase in PM₁₀ in cities with high levels of NO₂ than in cities with low NO₂ concentrations. This finding "supports the hypothesis that adverse health effects are related to traffic." This study also points out another issue with central monitors: "It may not...be wise to use only government monitoring station data to build a land-use regression for traffic related exposures since often these monitors are sited away from roadways."

Jerrett et al. (2007) uses American Cancer Society (ACS) data, as do other studies (Pope et al., 1995, 2002). However, the authors break this data into five different time periods from 1982 and 2000 to analyze effects of sulfate and of PM_{2.5} mass for each period. This method of examining the data enables the authors to make inferences about the health effects of different emissions. The authors state: "We estimated the RRs of mortality associated with air pollution separately for five time periods (1982–1986, 1987–1990, 1991–1994, 1995–1998, and 1999–2000)....Sulfate RRs exhibit a large decline from the 1980s to the 1990s. In contrast, PM_{2.5} RRs follow the opposite pattern....The reduction in sulfate RR may have resulted from air quality improvements that occurred through the 1980s and 1990s....PM_{2.5} concentrations also declined in many places, but toxic mobile sources are now the largest contributors to PM in urban areas. This may account for the heightened RR of mortality associated with PM_{2.5} in the 1990s."

Cooke et al. (2007) reports on an expert elicitation of six of the identified top ten European air pollution experts. One of the major questions was: What types of PM_{2.5} are the most or least toxic with regard to mortality? All six experts identified diesel emissions, traffic emissions, or elemental and organic carbonaceous combustion products as the most toxic types of PM. Two of the six experts selected secondary sulfates as the least toxic, one selected ammonium nitrate, one selected both ammonium sulfate and nitrate (tie), and two selected crustal PM as least toxic. There were no instances where one expert identified a PM constituent as least toxic, with another expert viewing that constituent as being more toxic than the ambient mixture.

Conclusions and research recommendations

This review has a number of limitations. The number of studies meeting the selection criteria for inclusion in the core part of the review is not large. These studies used different measures of HRV and different metrics of variation, so they are not always directly comparable. There isn't yet a standard definition of accurate exposure, although studies using central monitor data for variable local emissions do not meet that definition (barring exceptional circumstances, as in Schwartz et al., 2005b). We have explained our criteria for accurate exposure, but if all studies examined herein had

used personal monitors, or monitors which followed subjects in their daily activities, and if all monitors measured several important pollutants which could be used in multi-pollution models, the results of a review of this type would be stronger.

Nevertheless, the results herein appear to be generally consistent. We tentatively conclude that studies of HRV with accurate exposure information for health-relevant variable local emissions appear to find consistently different health associations, with regard to PM constituents BC and sulfate, than do such studies without good exposure information. To explore this question, we have examined the health effect in humans (changes in measures of HRV) for which there appears to be the largest number of studies which enable comparisons of the effects on humans of different types of ambient PM_{2.5} in the same study, and which enable a judgement about whether exposure information for variable local emissions was reasonably accurate, or otherwise.

HRV studies with good exposure information for BC show consistent associations between BC and changed HRV measures. The strength of effect increases approximately monotonically with increased exposure to BC (Adar et al., 2007; Schwartz et al., 2005b). Only the HRV studies without good exposure data fail to show consistently strong and significant associations with BC. Wheeler et al. (2006) point to this exposure error as a likely reason for the paucity of significant associations with vehicular emissions in their study. Adar and Kaufman (2007) point to such exposure error as a general reason for finding minimized traffic associations in studies with such error. Similarly, studies with good exposure information for urban and/or BC emissions, which also monitor for sulfate or regional emissions, generally fail to find significant associations with sulfate (Ebelt et al., 2005) or with rural/regional emissions containing secondary sulfate (Creason et al., 2001; Schwartz et al., 2005b). The apparent consistency of these findings thus suggests the crucial nature of good exposure information for subjects of epidemiology studies of this nature.

Zeger et al. (2000) discuss several types of measurement error which can occur with exposure misclassification, including Berkson and classical type errors (the latter of which can introduce bias in risk estimates), in the context of a single study. In future research it would be useful to explore how differences in the degree and types of measurement error across different studies could influence size and significance of health effects estimates for different pollution variables.

There are even fewer comparable studies examining ST-segment depression associations, capable of separating BC from regional PM or secondary sulfate in determining significant associations. Results of these studies, which seem to parallel those of HRV studies, may suggest that findings herein with regard to harm of PM constituents might be generalized to other health endpoints, perhaps via a common biological mechanism of oxidative stress. However, considerable further research is needed to confirm these findings

(or otherwise) with regard to both HRV and ST-segment depression.

These tentative findings also suggest the importance of applying methodologies reviewed herein to other health endpoints. Studies which only look at size fractions of PM, not monitoring for PM constituents such as BC and sulfate as well as metals such as V and Ni (if residual oil is used relatively nearby), by definition will not permit clear examination of which types or sources of PM may be associated with a given health endpoint. Accurate exposure information appears necessary as well. Specifically, more studies are needed which:

1. Compare effects of different PM_{2.5} constituents against the same health endpoints in the same study;
2. Have accurate exposure data for locally variable emissions, such as BC and/or other markers of vehicular emissions; and
3. Are capable of separating the different sources of a common PM constituent (e.g., sulfate) in any such analysis (Grahame & Hidy, 2007).

Since relatively few studies meet these methodological criteria, it is recommended that other researchers examine these issues using these criteria, against additional health endpoints, in order both to confirm these results (or otherwise), and to identify which types of emissions should be reduced in order to avoid the considerable cardiovascular morbidity and mortality impacts suffered by those who live in urban areas.

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