PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Contributions that epidemiological studies can make to the search for a mechanistic basis for the health effects of ultrafine and larger particles

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Contributions that epidemiological studies can make to the search for a mechanistic basis for the health effects of ultrafine and larger particles

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Epidemiology is a rather blunt tool for elucidating biological mechanisms that can account for the increased mortality and morbidity associated with population exposures to ambient air particulate matter (PM). However, it has an essential role to play. Recent studies indicate that three readily measurable ambient air PM concentration indices can be significantly associated with one or more elevations of rates of specific disease or dysfunction categories. These three indices, i.e. ultrafine particle number, fine particle mass ($PM_{2.5}$) and thoracic coarse mass ($PM_{10–2.5}$) differ not only in size range, but also in terms of their sources, deposition patterns, and chemical reactivities, factors that may account for their different associations with human health effects. Further epidemiological studies employing a wider array of air quality and health effects variables should enable us to resolve some of the outstanding questions related to causal relationships for PM components or, at the minimum, to pose some better questions.

Keywords: ultrafine particles; fine particles; thoracic coarse particles; epidemiology; air pollution; lung deposition

1. Introduction

Hypothesis-driven epidemiological studies will be needed to clarify the role(s) that ultrafine particles may play in the causation of the various health effects that have been associated with community air pollution. While it is generally acknowledged that typical ambient air pollutant mixtures in economically developed countries contribute to excess daily mortality, greater usage of clinical and medical facilities and services, reductions in school and work attendance, increased rates of cardiopulmonary symptoms and abnormal function, and reduced longevity, there is much less agreement on which pollutant components, or mixtures of components, are most influential on the health-related responses.

In terms of strength of association for one or more of the health effects, there have been positive epidemiological findings reported for each of the common pollutant gases, i.e. ozone (O_3), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and carbon monoxide (CO), as well as for various indices of particulate matter (PM) concentrations. These PM indices include black smoke (BS) and coefficient of haze (CoH), both of which are closely related to the elemental carbon content of the PM, as well as various size-selective gravimetric concentrations. These gravimetric PM indices

include: so-called total suspended particulate matter (TSP), which had an effective upper cut-size that varied from 20 to 50 μm in aerodynamic diameter, dependent on wind speed and direction; thoracic PM (PM_{10}), which approximates the PM fraction inhaled through the larynx; fine particles in the accumulation mode ($PM_{2.5}$); and thoracic coarse particles ($PM_{10–2.5}$). This Discussion Meeting has been focused on another component of PM_{10}, i.e. ultrafine particles (UPs), which are mostly smaller than 0.1 μm in diameter and which contribute very little mass to the aforementioned gravimetric concentration indices. In fact, the implicit assumption is that the health effects that can be produced by UPs are more closely influenced by their number concentration than by their mass concentration. In almost all cases, the number concentration of UPs is nearly equal to the total number concentration of particles of all sizes in ambient air, and the underlying hypothesis is that the net cardiopulmonary responses are related to the summation of the individual responses caused or initiated by each ultrafine particle that deposits on respiratory and/or conductive lung airways. In this model of response, the size of the particle is not important, since each individual particle can initiate a local cellular response that contributes to the aggregate change in function, symptoms, and/or disability.

Support for a causal role of UPs comes from the results of recent studies involving measurements of both the number concentration of UPs and gravimetric concentrations, which reported closer associations of some health-related responses for UPs than for some simultaneously measured gravimetric indices (Peters *et al*. 1997; Ostro & Lipsett 2000).

(*a*) *Identifying PM components as possible causal factors for health effects*

Recent toxicological and clinical exposure studies using concentrated accumulation mode ambient aerosols have produced health-related responses that correspond to effects indices found in epidemiological studies, demonstrating that effects of concern can be produced by $PM_{2.5}$ of ambient air origin alone. In these concentrated ambient air PM studies, the ambient $PM_{10–2.5}$ component had been removed by inertial separators, and the ambient air UPs and pollutant gas components were not concentrated. A comprehensive summary of current mechanistic knowledge for the health effects of PM was recently prepared by Schlesinger (2000) and is presented in tables 1 and 2.

A number of recent epidemiological studies have examined the relative roles of $PM_{10–2.5}$, $PM_{2.5}$, and pollutant gases, and have concluded that $PM_{10–2.5}$ can also have a significant influence on short-term health responses. These findings are summarized in table 3.

(*b*) *Differing characteristics of ambient air* $PM_{10–2.5}$, $PM_{2.5}$ *and UPs*

$PM_{10–2.5}$, $PM_{2.5}$ and UPs can be considered to be different pollutants in terms of their particle size ranges, compositions, and potentials for causing adverse health effects. $PM_{10–2.5}$ is largely mineral dust derived from wind-blown soil, mineral ash, and resuspended road dust. $PM_{2.5}$ is dominated by the accumulation mode in the ambient air. It is largely derived from combustion sources and its mass is composed largely of aged reaction products such as the ammonium salts of sulphuric and nitric acids, aggregates of ultrafine carbon emitted from engine exhaust, and of semi-volatile

Table 1. *Mechanistic plausibility: coherence between PM-exposure associated health effects from epidemiological and toxicological studies (Schlesinger 2000)*

(Mø, macrophage; UF, ultrafine; WBC, white blood cells; ROI, reactive oxygen intermediates; ROFA, residual oil fly ash; BALT, bronchus associated lymphoid tissue; COPD, chronic obstructive pulmonary disease; Δ, change in parameter noted.)

epidemiological health endpoints	toxicological health endpoints	
	concentrated ambient PM	specific PM components
↑ hypertension/↑ stroke	Δ PM homeostasis (e.g. peripheral blood differential cell counts)	Δ Blood coagulation factor: UF Carbon ↑ platelets, WBC; diesel exhaust (whole)
↑ ischemic heart disease/ ↑ heart attack	Δ heart-rate variability Δ EKG waveform segments	↑ arrhythmia incidence; ROFA
↑ acute respiratory infection (e.g. acute bronchitis, pneumonia)	↓ Mø ROI production ↓ BALT Δ pulmonary cytokine profile	↓ Mø ROI production; ammonium sulphate Δ pulmonary cytokines; metals
exacerbation of COPD, asthma	—	↑ airway reactivity: H^+ Δ mucociliary function: H^+
↑ respiratory symptoms Δ lung function indices	—	pulmonary inflammation: UF, metals Δ pulmonary cytokines: metals

organic droplets formed in engine and boiler exhaust streams and in complex photochemical reaction sequences. In the absence of rainfall, $PM_{2.5}$ concentrations have much less temporal variation than either $PM_{10–2.5}$ particles, which settle out fairly rapidly under low widespread conditions, or UPs, which coagulate rapidly, becoming part of the $PM_{2.5}$. It should also be noted that as the UPs age, coagulate, and react chemically with gaseous air pollutants, they tend to become less biologically and chemically reactive and/or biologically potent.

The three size ranges also differ in respiratory tract deposition efficiencies and locations. $PM_{10–2.5}$ particles have preferential deposition by impaction at branch points in the larger conductive airways, producing concentrated deposition hot-spots on a small fraction of the conducting airway surface. Particles less than 2.5 μm in aerodynamic diameter down to *ca.* 0.1 μm have very little impaction or diffusional deposition in large airways and penetrate, with the tidal convective flow, to the respiratory acinus, where some of them mix with residual lung air. The expiratory tidal flow carries most of the inhaled particles back out into the atmosphere. The remaining 10–30% of the particles left behind in the residual lung air deposit by sedimentation and/or diffusion in terminal bronchioles, respiratory bronchioles, and alveolar ducts, especially at or near small airway bifurcations, where the insoluble particles can accumulate as centrilobular deposits (Lippmann *et al.* 1994).

UPs have greater diffusional mobility, and in the low nanometre end of the range,

Table 2. *Currently hypothesized PM physiochemical properties related to biological responses (Schlesinger 2000)*

(FP, fine particulates; CP, coarse particulate; UF, ultrafine particulate; ROFA, residual oil fly ash.)

	response	
PM characteristic	epidemiology	toxicology
mass concentration	associated with health outcomes	associated with biological responses
particle size	relative association with health outcomes often related to size mode (FP, CP, UF, etc.)	different biological responses noted with different size modes
metals	Utah Valley: effects from steel mill related to metals	ROFA: effects related to metals
acidity	some evidence for H^+ association with health outcomes	various biological responses
organics	association of PM with lung cancer possibly due to carcinogenicity of organic fraction	known mutagens/carcinogens
biogenic PM	possible association with health outcomes	generally allergenic
sulphate/nitrate salts	association with some health outcomes (markers for H^+)	generally not very toxic at low concentrations
peroxides	?	high levels may produce biological effects
elemental C (soot)	?	mutagenic/carcinogenic/irritant

where the number concentrations are highest, they can deposit by diffusion in both large conductive airways, as well as penetrate more deeply than their penetration depth by convective tidal transport into the lung acinus. They can deposit by diffusion to a greater extent in the gas exchanging alveoli of the lung than can the larger particles having more limited diffusional mobilities.

Thus, it is not unreasonable to expect that there would be different effects produced by concentrations of coarse-mode mineral particles deposited on large conductive airway bifurcations, by aged accumulation mode acidic and organic particles depositing at limited surface areas in centrilobular lung regions, and by relatively freshly formed ultrafine singlets deposited relatively uniformly on the alveolar epithelium.

Since each of the three size-specific PM indices under discussion ($PM_{10–2.5}$, $PM_{2.5}$ and UPs) have different size and compositional characteristics, they can be considered to be separate pollutants in health effects regression analyses, and as targets for control effects. Such separate and/or joint analyses in multiple regressions are aided by the generally minimal collinearity of these three PM indices in ambient air. For

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Table 3. *Recent epidemiological studies reporting short-term health-related associations with* $PM_{10-2.5}$, $PM_{2.5}$ *and/or UPs*
(+, significantly associated; (+), approaching statistical significance; nr, not reported; −, not significantly associated; *, summer only; nm, not measured.)

			pollutant associations					
study	location	effects studied	PM_{10}	$PM_{10-2.5}$	$PM_{2.5}$	O_3	CO	UPs
1. Castillejos *et al.* (2000)	Mexico City	mortality (acute)	+	+	+	nr	nr	nm
2. Cifuentes & Vega (2000)	Santiago, Chile	mortality (acute)						
		total and respiratory	nr	−	+	−	+	nm
3. Ostro & Lipsett (2000)	Coachella	mortality (acute)						
	Valley, CA	cardiovascular	+	+	−	−	−	+
		respiratory	−	−	−	−	−	−
		all causes	−	−	+	−	−	+
4. Simpson *et al.* (2000)	Melbourne,	mortality (acute)*						
	Australia	cardiovascular	−	nr	−	−	nr	nm
		respiratory	+	nr	+	+	nr	nm
		all causes	+	−	−	+	nr	nm
5. McDonnell *et al.* (2000)	California	mortality						
	(non-smoking)	(reduced longevity)						
		all causes (male)	+	−	+	nr	nr	nm
		all causes (female)	−	+	−	nr	nr	nm
6. Van Den Eeeden *et al.* (1999)	Los Angeles, CA	hospital admissions						
		cardiovascular	+	+	+	+	nr	nm
		chronic respiratory	−	−	−	−	nr	nm
		acute respiratory	−	−	−	−	nr	nm
7. Burnett *et al.* (1997)	Toronto, ON	hospital admissions*						
		cardiac	+	+ (+)	+	+	nm	
		respiratory	+	+	+	+	−	nm
8. Sheppard *et al.* (1999)	Seattle, WA	hospital admissions						
		asthma	+	+	+	+	+	nm
9. Neas *et al.* (1999)	Philadelphia, PA	peak expiratory flow	+	(+)	(+)	(+)	nm	nm
		(in children)						
10. Creason *et al.* (2000);	Baltimore, MD	heart rate variability	−	−	+	−	−	nm
Liao *et al.* (1999)								

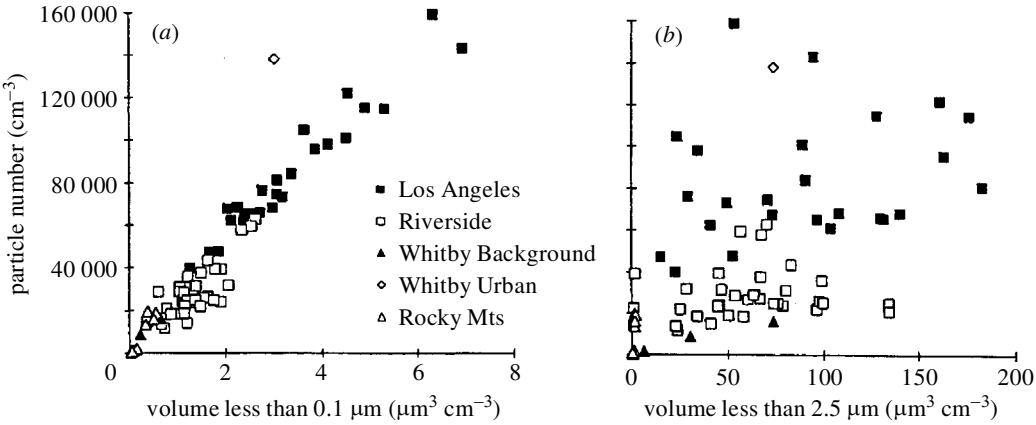

Figure 1. Relationship between particle number and particle volume (volume at diameters of less than (*a*) 0.1 and (*b*) 2.5 μm). From *Air quality criteria for particulate matter*, vol. 1. EPA/600/P-95/001aF. US Environmental Protection Agency, Washington, DC, April 1996.

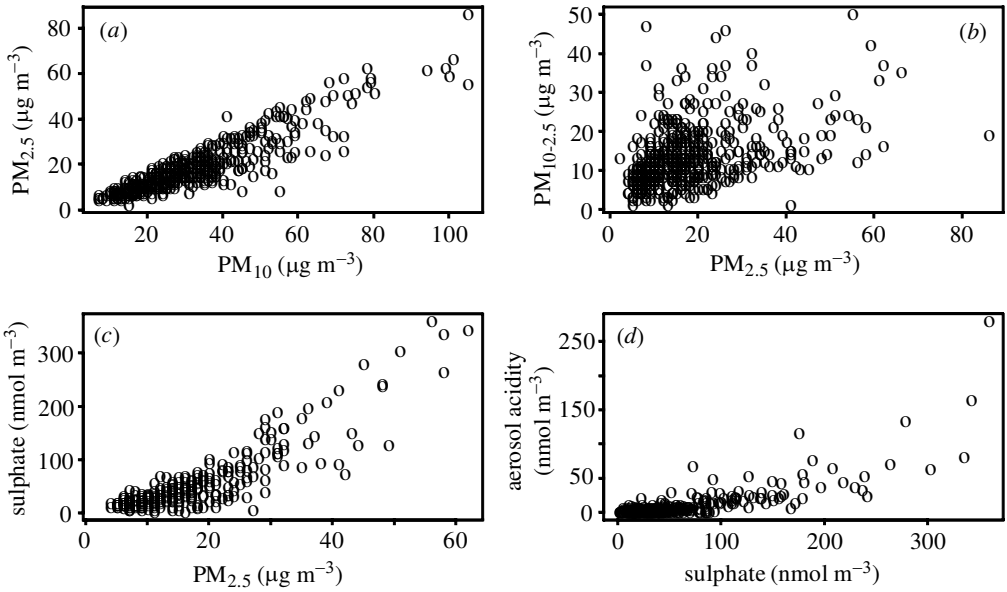

Figure 2. Scatter plots among key PM components in Detroit for summer days in 1992–1994. (*a*) $PM_{2.5}$ versus PM_{10}; (*b*) $PM_{2.5}$ versus $PM_{10-2.5}$; (*c*) $PM_{2.5}$ versus sulphate; (*d*) sulphate versus acidity.

example, for data collected in the western US, figure 1 shows that while UPs number concentration varies directly with the cumulative volume concentration of UPs, there is very little, if any, correlation with the volume concentration of $PM_{2.5}$, whose volume is generally dominated by aged aerosol.

In terms of the collinearity among gravimetric PM concentrations, figure 2, showing data from multiple monitoring stations in Detroit, shows that there was a reasonably high degree of correlation between sulphate, a major component of $PM_{2.5}$, and $PM_{2.5}$ overall. Likewise, there was fairly good correlation of $PM_{2.5}$, a major

component of PM_{10}, and PM_{10} overall. However, there was very little correlation between the two separate size-fractions of PM_{10}, i.e. $PM_{2.5}$ and $PM_{10-2.5}$.

A key assumption underlying hypothesized causal connections between daily variations in PM exposures, as measured either by non-chemically specific number concentrations, or by size-range based gravimetric concentrations on the one hand, and temporally varying rates of health effects on the other, is that the chemical compositions of the particles are of little or no importance. An alternative explanation for the frequently reported associations between PM concentration indices and health indices is that the concentrations of the active agent(s), be they components of PM, or pollutant gases, co-vary with one or more of the non-specific concentration indices used in the studies.

If we are to disentangle the separate influences of number and mass concentrations of PM and its size and compositional components from each other and from gaseous air pollutants, we will need (1) a better mechanistic understanding of the physiologic and toxic responses to the inhaled agents, and (2) an increased number of more comprehensive, short-term, exposure–response studies in human populations that incorporate daily measurements of more of the components of the air pollution mixtures. Such studies would facilitate multipollutant regression analyses that could better define active components.

These more definitive epidemiological studies will need to account for the measurement errors associated with each of the exposure indices used in the regression analyses. Measurement errors have several major components in time-series studies. One is the error resulting from the concentration differences between those at the measurement sites and the average concentration in the community. Many studies have relied on air quality measurements made at only one central monitoring site in a city or region. As shown in figure 2, there can be great concentration differences between different sites in an urban area, especially for larger particles. A second measurement error is related to the concentration differences between outdoor air and the air in the micro-environments occupied by members of the population being studied. Third, there are other sources of measurement error that vary from pollutant to pollutant, e.g. (a) loss of semi-volatile aerosol components from sampling filters, (b) artefactual collection of vapours and their reaction products on the PM filters, and (c) analytical laboratory errors. Such errors can lead to weaker correlations for causal factors than for more precisely measured exposure indices that are merely temporally associated with causal factors. Analysts should recognize and, to the extent possible, account for such errors when engaged in exposure and risk assessments.

(*c*) *A more comprehensive approach for associating multiple pollution indices with a variety of health effects*

Future epidemiological time-series studies should, to the extent feasible, consider as many different health-related measures as possible, since the different effects measures may be related to different components of the pollution mixture. This issue is illustrated by some of the results obtained from an analysis of time-series data in a study of mortality and hospital admissions in the Detroit, MI, metropolitan area (Lippmann *et al*. 2000). Figure 3 shows the strengths of association between each of seven components of the air pollution mixture and hospital admissions for

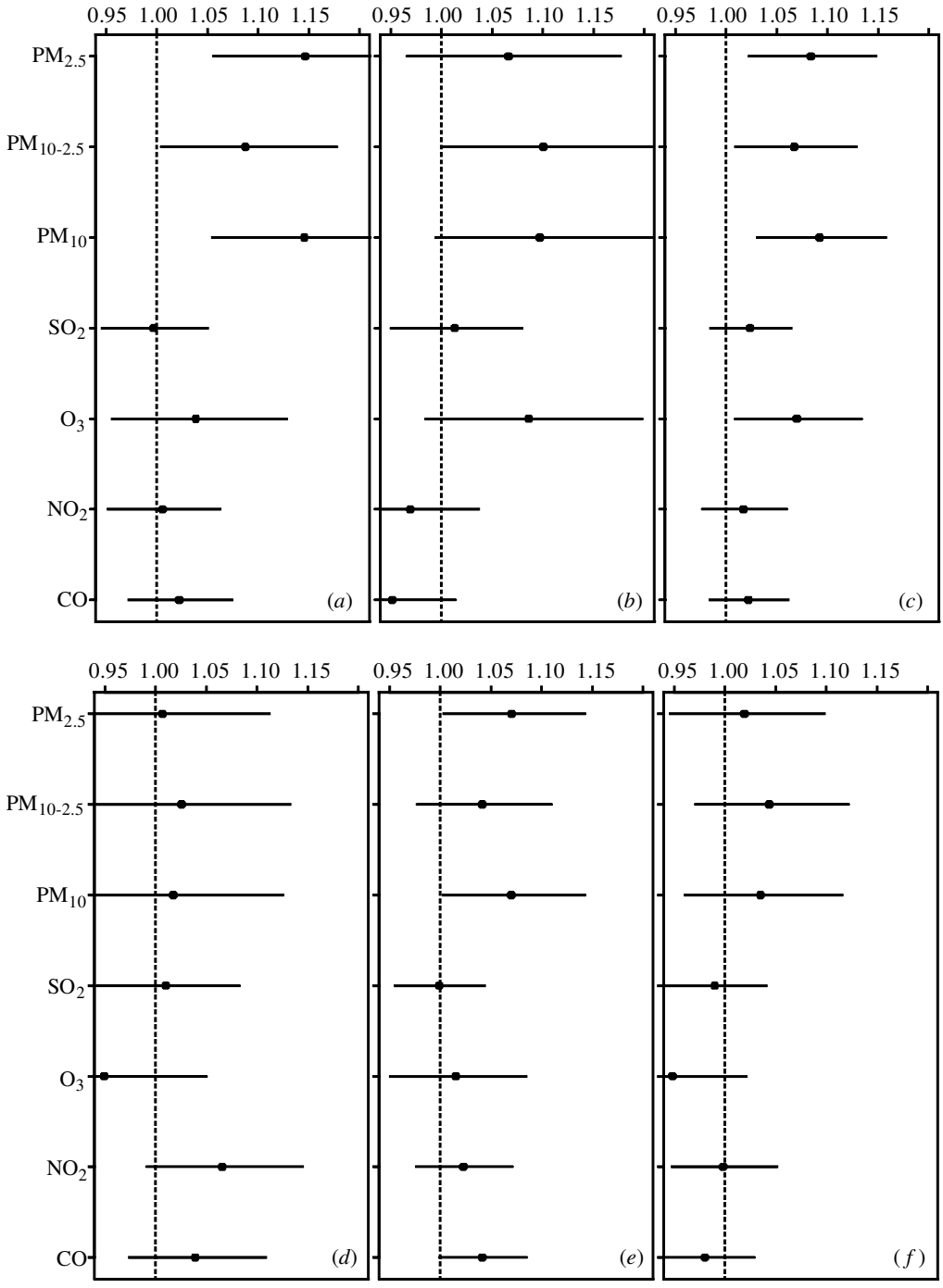

Figure 3. Relative risks per 5–95th percentile of pollution levels for hospital admissions for Medicare patients in Detroit by disease diagnosis for 490 warm weather days in 1992, 1993 and 1994. (*a*) Pneumonia; (*b*) COPD; (*c*) ischemic heart disease; (*d*) dysrythmia; (*e*) heart failure; (*f*) stroke.

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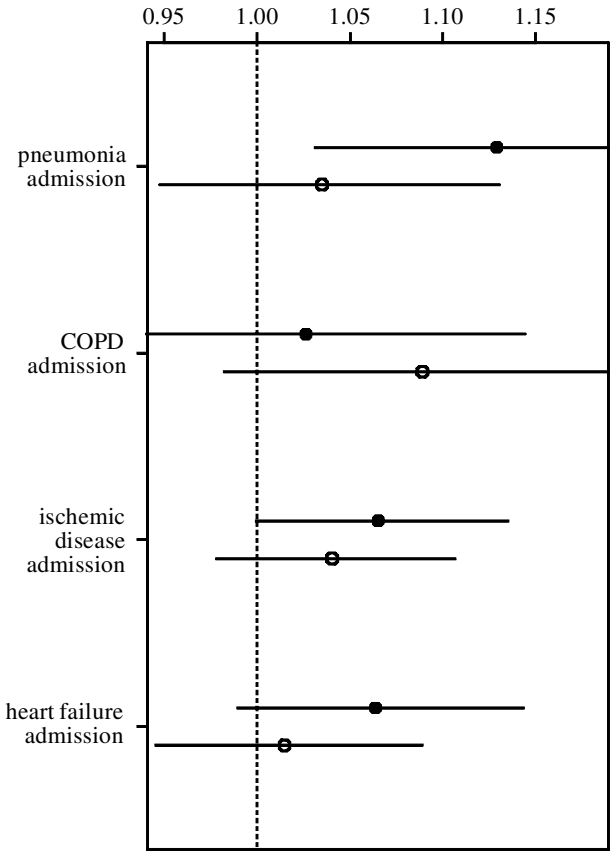

Figure 4. Relative risks per 5–95th% increment of $PM_{2.5}$ (•) and $PM_{10-2.5}$ (○) simultaneously included in Poisson regressions, adjusting for seasonal cycles, temperature (locally estimated smoothing splines (LOESS) of same day and LOESS of average of 1–3 lags, and hot-and-humid indicator), and day-of-week, for 490 warm weather days in the Detroit metropolitan area in 1992, 1993 and 1994.

15 summer months over three years for four cardiac and two respiratory diagnoses. Statistically significant associations were seen for certain pollutants and certain diagnoses, suggesting that different components within the mixture may have influenced the different health outcomes. For these Detroit data, combining all of the cardiovascular effects would have the effect of burying effects that may be both interesting and statistically significant. There is some biological plausibility for the results depicted in figure 3. For example, the indication that O_3 has its greatest apparent influence on ischemic disease is consistent with Seaton's alveolar inflammation hypothesis (Seaton *et al.* 1995), while the indication of CO having its greatest apparent influence on heart failure is consistent with CO's known effects on oxygen transport (Morris & Naumova 1998).

The Detroit study, lacking measurement data on UPs, cannot be used to help identify the role of ambient UPs concentrations on health-related population responses. However, the results do indicate that other PM components can have differing influences on the various health endpoints. One or more of the gravimetric

PM indices were significantly associated with hospital admissions for pneumonia, chronic obstructive pulmonary disease (COPD), heart failure, and ischemic disease, but none of them were significantly associated with dysrhythmia or stroke. Figure 4 shows the results of the simultaneous Poisson regressions of $PM_{2/5}$ and $PM_{10-2.5}$ on four hospital admission categories. The $PM_{2.5}$ appears to have had more influence on admissions for pneumonia, ischemic disease, and heart failure, while $PM_{10-2.5}$ appeared to have more influence on COPD. Thus, both of the mass fractions of PM_{10} appeared to have at least some positive influence.

These various findings suggest that the utility of PM_{10} as an index of cardiopulmonary health risks in many communities has not been merely as a useful surrogate measure for $PM_{2.5}$, but because both of its major gravimetric components ($PM_{2.5}$ and $PM_{10-2.5}$) contribute to the elevation of some of the cardiopulmonary effects.

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