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Journal Title: Toxicology letters. (Amsterdam, Elsevier/North-Holland.)

Volume: 149 **Issue:** 1-3 **Month/Year:** 2004 **Pages:** 235-42

Article: Englert, N; Fine particles and human health--a review of epidemiological studies.

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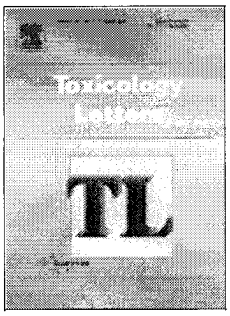

Volume 149, Issues 1-3, Pages 1-440 (1 April 2004)
Proceedings of EUROTOX 2003. The XLI European Congress of Toxicology. Science for Safety
Firenze, Italy, 28 September - 1 October 2003
Edited by Marina Marinovich, Mumtaz Iscan, Ana Ferrer Dufol, Hanna Tahti, Bert-Jan. Baars and Miguel A. Sogorb

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Fine particles and human health—a review of epidemiological studies

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Abstract

Adverse health effects of exposure to particles have been described in numerous epidemiological studies. Health endpoints thoroughly studied are all cause and cause-specific mortality, and hospital admissions. Older studies focussed on associations with PM_{10} (then named fine particles). During the last decade, $PM_{2.5}$ was increasingly emphasised, and the term "fine particles" was restricted to this size fraction. Currently, ultrafine particles (UF, $PM_{0.1}$) are discussed to be another important fraction which should be characterised by particle number instead of particle mass. However, data on UF exposure and health effects are still limited.

The mechanisms by which particles influence human health are only poorly understood. Under discussion is the role of particle size and particle composition. The risk assessment of coarse particles (i.e. the size fraction between 2.5 and 10 μm) suffers from inconsistent findings. The question of causality is not completely answered. However, it is widely accepted that PM is some kind of container including components which are toxicologically relevant and others which might be seen mainly as indicators. Thus, the local mix may influence the toxicological potency of PM, and results from studies carried out in one region may not necessarily be consistent with results gained elsewhere.

Recently, reanalyses of epidemiological studies performed by the Health Effects Institute (HEI) qualitatively confirmed the original results. New insight in the influence of socioeconomic factors extended the knowledge on health effects of particles. To some extent, the slope of the dose response relationships from time-series analyses needed downward adjustment due to some problems with statistical analysis programmes. Nevertheless, the whole body of knowledge supports the role of PM as a type of air pollution with great influence on human health.

Keywords: Health effects; Particulate matter; Cohort studies; Time-series analyses

1. Introduction

Particulate matter (PM) is a mixture of many different components with local and regional variation. PM can be characterised by origin, e.g., anthropogenic or geogenic, primary or secondary particles; by source, e.g., combustion products and traffic, or by physico-chemical properties such as solubility. For practical reasons under aspects of immission measurements, PM is characterised by particle size (aerodynamic diameter).

Several metrics have been or are still used. Total suspended particles (TSP) is the most comprehensive term including particles of any size suspended in air. However, particles larger than 30–70 μm only

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doi:10.1016/j.toxlet.2003.12.035

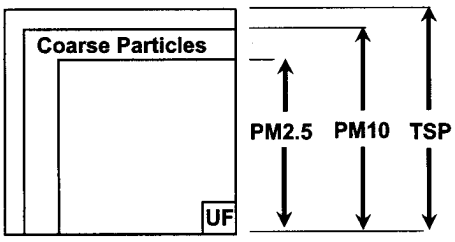

Fig. 1. Particulate matter fractions. The areas of the respective squares roughly show the relative contribution of the respective fractions to current ambient PM concentrations in European cities.

remain suspended for a very short period before deposition. PM_{10} and $PM_{2.5}$ is PM with an aerodynamic diameter of less than 10 and 2.5 μm, respectively. Ultrafine particles (UF) are those with a thermodynamic diameter of less than 0.1 μm, also called $PM_{0.1}$. The $PM_{2.5}$ fraction is also called "fine particles", and those particles between 10 and 2.5 μm are currently named "coarse particles". However, about one decade ago, the term "coarse particles" was used for particles larger than 10 μm. PM_{10} is also called "inhalable particles". As shown in Fig. 1, the larger fractions comprise the smaller ones, i.e., $PM_{2.5}$ is part of PM_{10}, UF are part of $PM_{2.5}$ and PM_{10}.

Health endpoints often studied in relationship to PM are mortality (total and cause-specific) and morbidity, hospital admissions due to cardiovascular and respiratory diseases, lung function, and functional endpoints, e.g., heart rate variability (HRV).

Commonly used epidemiological approaches are time-series analyses and cohort studies, as reviewed in this paper. Other approaches are case-crossover studies, cross-sectional studies, panel studies, and case-control studies. In practice, these approaches may have some overlap, e.g., cohort studies with nested case-control studies.

Some questions are only in part answered by current knowledge with respect to health effects of PM:

- Which ones are the health-relevant size fractions of PM?
- What about the dose–response relationships (concentration–response relationships) for various endpoints?
- What about effect modifiers?
- Is PM a causative agent, an indicator, a container?

Epidemiology cannot provide definite answers to these questions but can contribute to completing the picture.

2. Methodological aspects

Particulate matter is a ubiquitous air pollutant. Health effects concern the whole population. On an individual scale, however, the magnitude of effects on health of ambient PM air pollution is relatively small compared to health effects from smoking (Fig. 2).

The relatively small effect on health of PM can only be adequately examined in epidemiological studies of sufficient size and observation time. Data needed for large time-series studies on mortality are generally easily available. In contrast, cohort studies with a sufficient number of participants require much more effort on the effects side.

A general problem is assessment of personal exposure, because the relationship between fixed-site measurements and personal exposure may vary from study to study (Lipfert and Wyzga, 1995). Measurements carried out every sixth day—as done in many US cities—also make exposure estimates more difficult. With respect to cohort studies, an additional difficulty is the choice of the adequate time frame. Exposure measurements are often not available for the whole follow-up period. For mortality and for morbidity, the

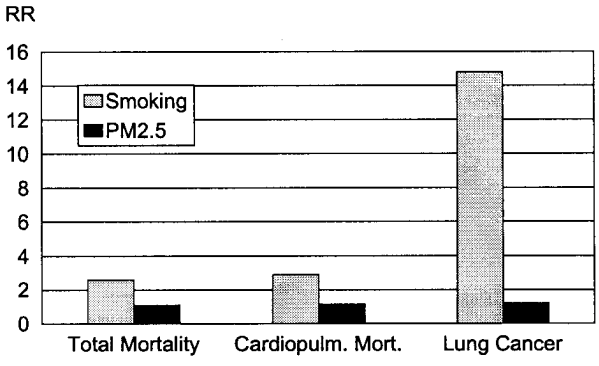

Fig. 2. Comparison of health effects (relative risk ratio, RR) associated with exposure to ambient $PM_{2.5}$ and smoking. Data from Pope et al. (2002) calculated for the difference in mean $PM_{2.5}$ concentrations between the most-polluted city and the least-polluted city in the ACS study (24.5 $\mu g/m^3$, Pope et al., 1995), and for an average current smoker (men and women combined, 22 cigarettes per day for 33.5 years, with initiation before age 18 years).

adequate latency period (i.e., the time lag between exposure and effect) is unclear.

It is commonly accepted that cohort studies cover both short-term and long-term effects of air pollution, thus providing a comprehensive picture (Künzli et al., 2001). In contrast, time-series studies often are described as covering mostly or even exclusively short-term effects and thus not adequately reflecting long-term effects (WHO, 2001). This is often proposed as an important reason why time-series mortality studies yield considerably lower numerical relative risk estimates than cohort studies. However, the difference is not so clear cut. In both cases, i.e., in time-series and in cohort studies, people are exposed to current air pollution and have been exposed to past air pollution. Health effects associated with current exposure may occur. But exposure to short-term air pollution affects people who may have accumulated residuals from many past short-term exposures. Thus, mortality observed in time-series and in cohort studies is influenced by current short-term effects as well as by residuals of short-term effects in the past—i.e., long-term effects (Englert, 1999). Not only cohort studies, but also time-series studies can provide some information on loss of life expectancy (Burnett et al., 2003). An RR of 1.05 derived from cohort studies corresponds to some 6 months of average loss of life expectancy (Brunekreef, 1997; Englert, 1999).

There are many time-series studies available, among them large ones like NMMAPS (National Morbidity, Mortality, and Air Pollution Study) in the US and APHEA 2 (Air Pollution and Health, a European Approach) in Europe (WHO, 2003).

With respect to large cohort studies, the list is very short. Results are available from the Harvard Six Cities Study (Dockery et al., 1993), the American Cancer Society (ACS) Study (Pope et al., 1995, 2002), and the AHSMOG Study (Adventist Health Study of Smog) (Abbey et al., 1999).

Detailed reanalyses of the Six Cities Study and the ACS Study have been performed in the framework of the Particle Epidemiology Reanalysis Project of the Health Effects Institute (HEI) after some doubts had been raised with respect to the results of and the statistical methods used in these studies. The Reanalysis Team concluded: "Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality" (HEI, 2000).

With respect to time-series analyses, reanalyses have been performed as well. The reason was the finding that the statistical software most commonly used in recent years (the generalised additive models (GAM) part of the S-Plus statistical software) may provide inadequate effect estimates and underestimate standard errors (HEI, 2003). The reanalysed studies showed to be not affected in a uniform way. The APHEA 2 results need only small corrections, whereas the NMMAPS effect estimates experienced considerable downward revision. However, the qualitative association remained unchanged (HEI, 2003).

3. Time trend and revised studies

During the last decade, effect estimates from time-series analyses showed a downward trend. A compilation published in 1994, based on 10 time-series studies performed in the US, provides an RR estimate of 1.06 associated with a 100 $\mu g/m^3$ increase in TSP (Schwartz, 1994). Supposing a relation $PM_{10} = 0.6 \times TSP$, the indicated RR corresponds to an RR of 1.01 for a 10 $\mu g/m^3$ increase in PM_{10} concentration. The summary of relative risk estimates given in the WHO Air Quality Guidelines for Europe (WHO, 2000) reflects the knowledge of about 1997. The RR estimate for total mortality provided by WHO amounts to 1.0074. The RR found in the NMMAPS based on data from the largest 20 and 90 US cities amounts to 1.005 and 1.0041, respectively (HEI, 2003). The APHEA 2 study based on total mortality results from 21 European cities provides an RR of 1.0062. The development of RR estimates over time including the reanalyses carried out to examine the GAM programming problems is shown in Fig. 3.

The influence of the statistical model used in the time-series analyses differed between studies. This is shown in Table 1 for NMMAPS and APHEA 2. The highest effect estimate resulted from the original GAM analyses, whereas stricter convergence criteria resulted in a marginal decrease of the APHEA estimates and a substantial decrease in the NMMAPS estimates. Generalised linear models (GLM) with natural

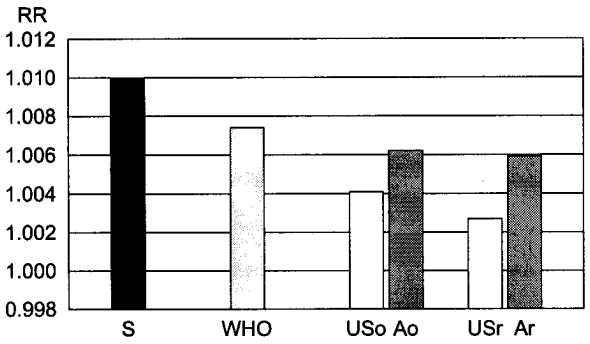

Fig. 3. Changes in total mortality RR estimates (per 10 μg/m³ PM_{10}) based on time-series analyses. S: meta analysis (Schwartz, 1994); WHO: WHO meta analysis (WHO, 2000); USo, USr: NMMAPS 90 cities, original (o) and revised (r) estimate (Dominici in HEI (2003)); Ao and Ar: APHEA 2, original (o) and revised (r) random pooled estimate (Katsouyanni in HEI (2003)).

Table 1
Influence of modelling on estimates of PM_{10} effects on total mortality (RR per 10 μg/m³ PM_{10})

	Model 1	Model 2	Model 3
NMMAPS	1.0041	1.0027	1.0021
APHEA 2, fpe	1.0068	1.0066	1.0042
APHEA 2, rpe	1.0062	1.0059	1.0041

NMMAPS, based on 90 US cities; and APHEA 2, based on daily data available for more than 5 years for 21 cities in 13 countries of the European Region (HEI, 2003). Model 1: GAM, default convergence criteria; Model 2: GAM, strict convergence criteria; Model 3: GLM, natural spline. fpe: fixed pooled estimate; rpe: random pooled estimate.

cubic splines resulted in a further substantial reduction of effect estimates in both studies. It is difficult to decide on the adequate way of analysis. The HEI statement on the revised analyses says: "... there is no gold standard for determining the appropriate degree for smoothing" (HEI, 2003).

As in the case of mortality, the APHEA 2 effect estimates for hospital admissions remained mainly unchanged when using more stringent convergence criteria in the GAM procedure (Table 2).

4. Fine or coarse particles

Recently, a WHO Working Group stated: "There is strong evidence to conclude that fine particles (<2.5 μm, $PM_{2.5}$) are more hazardous than larger

Table 2
Influence of modelling on estimates of PM_{10} effects on hospital admissions (RR per 10 μg/m³ PM_{10})

Health endpoint	Original criteria	Revised criteria
Cardiac	1.005	1.005
Cardiac >65 years	1.007	1.007
Ischemic heart disease <65 years	1.003	1.003
Ischemic heart disease >65 years	1.008	1.007
Stroke >65 years	1.000	1.000
Respiratory disease >65 years	1.009	1.010

APHEA 2 study, cardiovascular admissions in seven cities and respiratory admissions in eight cities (Le Tertre, Atkinson, HEI, 2003).

ones (coarse particles) in terms of mortality and cardiovascular and respiratory endpoints in panel studies. This does not imply that the coarse fraction of PM_{10} is innocuous". Another statement was "... the relative importance of fine and coarse PM may depend on specific sources present in some areas but not others" (WHO, 2003).

In many studies, PM measurements focus on one size fraction only. Therefore, the number of studies providing comparable effect estimates for several size fractions is limited, especially if one looks at studies with the same time lag chosen for the respective metrics. Table 3 gives an overview of effect estimates from three time-series studies on total and cardiovascular mortality and the respective particle concentrations.

As shown in Fig. 4, statistically significant associations can be found with $PM_{2.5}$, coarse particles, and PM_{10}. In the study with the largest contribution of coarse particles to the PM_{10} concentration, cardiovascular mortality was significantly associated with PM_{10} and coarse particles as well, but not with $PM_{2.5}$. In the study with the smallest contribution of coarse particles, total mortality was significantly associated with $PM_{2.5}$ and PM_{10}. In the intermediate study, coarse particles showed the relatively highest effect estimate for cardiovascular mortality and a statistically significant association.

Looking at single cities in the time-series analysis of the Harvard Six Cities Study, there are also considerable differences between the cities (Fig. 5). In three out of the six cities and in the cities combined, there is a statistically significant association between total daily mortality and $PM_{2.5}$ and PM_{10}, respectively. In one city, there is no significant association with $PM_{2.5}$,

Table 3
RR estimates for $PM_{2.5}$, coarse particles (CP), and PM_{10} in three time-series studies

	$PM_{2.5}$	CP	PM_{10}	Reference
IQR ($\mu g/m^3$)	9.0	19.6	24.6	Ostro et al. (2000) (a)
Mean ($\mu g/m^3$)	16.8	30.5	47.4	Ostro et al. (2000) (a)
TM, RR per IQR	0.9911	0.9937	0.9932	Ostro et al. (2000) (a)
CV, RR per IQR	0.9879	1.0174*	1.0179*	Ostro et al. (2000) (a)
5–95% ($\mu g/m^3$)	36	24	51	Lippmann et al. (2000) (b)
Mean ($\mu g/m^3$)	18	13	31	Lippmann et al. (2000) (b)
CV, per 5–95%	1.046	1.075*	1.070	Ito in HEI (2003) (c)
Median ($\mu g/m^3$)	14.7	9.0	25.0	Schwartz et al. (1996) (d)
TM, per 10 $\mu g/m^3$	1.015*	1.004	1.008*	Schwartz et al. (1996) (d)

TM: total mortality, CV: cardiovascular mortality, IQR: interquartile range, 5–95%: difference between 5th and 95th percentile of PM concentration. Lag 1 in (a)–(c), 2-day means in (d). RR estimates for TM and CV (a) taken from Fig. 1 in (a).
* $P \leq 0.05$.

but with coarse particles and with PM_{10} (Schwartz et al., 1996).

Besides possibly different composition of airborne particles, the absolute and relative concentrations and the relative size of measurement errors in the respective PM fractions may influence the strength of the statistical association (Lipfert and Wyzga, 1995). With decreasing contribution of coarse particles to PM_{10}, the probability to find significant associations between health effects and coarse particles may be expected to decrease. This may support the impression of a stronger correlation between health effects and fine particles than with PM_{10}. Episodes of high coarse particle concentrations from windblown dust, however, were not associated with increased mortality (Schwartz et al., 1999).

Unfortunately, the available cohort studies cannot clarify the situation because the ACS study has looked at $PM_{2.5}$ effects in more detail than at coarse particles and PM_{10} (Pope et al., 2002).

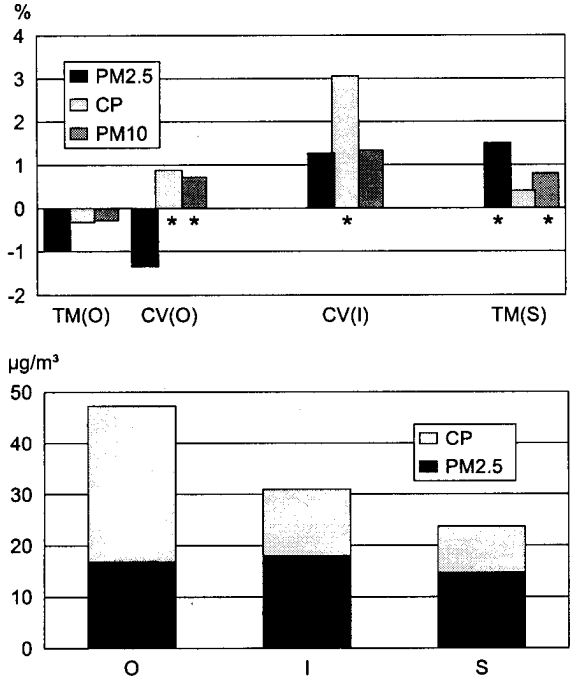

Fig. 4. Size fractions of PM and mortality in time-series analyses. CP: coarse particles. Upper part: % increase in total (TM) and cardiovascular (CV) mortality per 10 $\mu g/m^3$ difference in PM concentration. *$P \leq 0.05$. Lower part: concentration of fine and coarse particles in the three studies. O: from Ostro et al. (2000); I: from Ito (HEI, 2003) and Lippmann et al. (2000); S: from Schwartz et al. (1996).

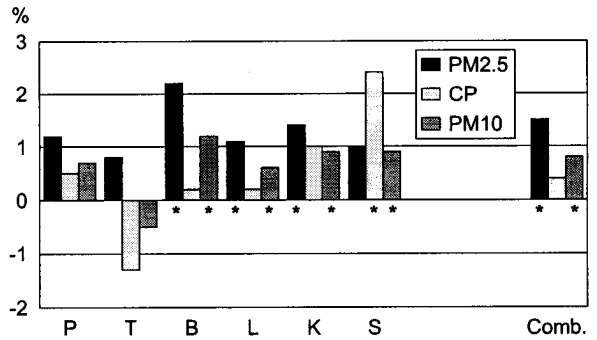

Fig. 5. Associations between total mortality and PM fractions in the Harvard Six Cities time-series analysis (% increase in RR per 10 $\mu g/m^3$). CP: coarse particles. *$P \leq 0.05$. P, T, B, L, K, S: Portage, Topeka, Boston, St. Louis, Knoxville, Steubenville; Comb.: combined (Schwartz et al., 1996).

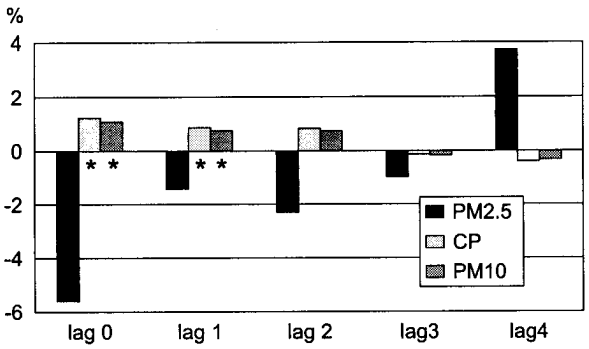

Fig. 6. Influence of lag structure on estimates of PM effects (% increase per 10 μg/m^3) on cardiovascular mortality. CP: coarse particles. * $P \leq 0.05$. GAM using original convergence defaults, data from Ostro (HEI, 2003).

The lag structure may also influence time-series results. The effect estimates for cardiovascular mortality change considerably from lag 0 to lag 4 (Fig. 6). The influence of the choice of lag clearly exceeds the importance of taking old or new GAM convergence criteria.

5. Health endpoints and effect modifiers

In time-series studies, cardiovascular and—as far as studied—respiratory effects seem to be relatively greater than effects on other endpoints (cf. Table 2, hospital admissions). Total mortality is less prone to misclassification than cause-specific mortality. In the Six Cities Study and the ACS cohort, respiratory deaths were not associated with $PM_{2.5}$ (HEI, 2000). However, respiratory deaths are a relatively small fraction, and the separation from cardiovascular deaths may be incomplete. Therefore, one possibility to avoid misclassification is to combine these causes to cardiopulmonary deaths.

The HEI reanalysis of the Harvard Six Cities Study and the ACS Study showed considerable effect modification from socioeconomic status and education in both studies (HEI, 2000). In the ACS study, there is a clear gradation with highest effects linked with lowest education ("less than high school") and vice versa. In the (smaller) Six Cities Study, there is the same tendency in total mortality (Fig. 7). Especially the effect on lung cancer is most distinct in the low education group. The reason for this effect modification may be

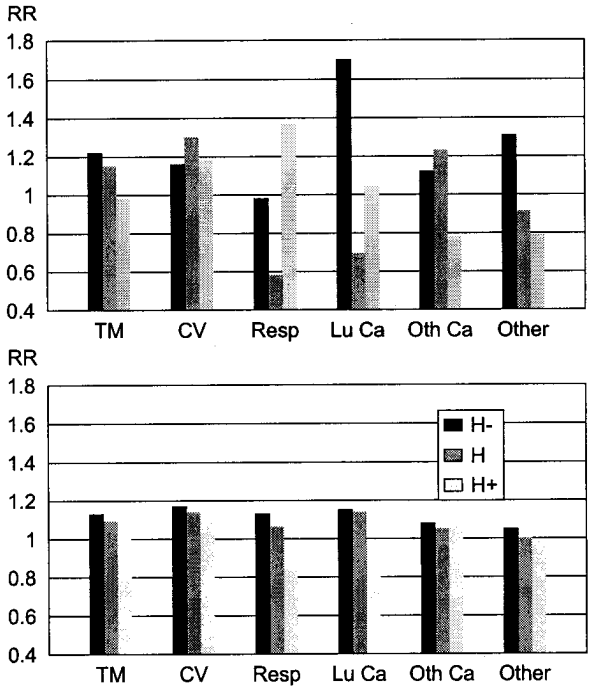

Fig. 7. Influence of education on RR (per 10 μg/m^3 $PM_{2.5}$) for several health endpoints in cohort studies. Upper part: Harvard Six cities Study, lower part: American Cancer Society Study. Education—H−: less than high school, H: high school, H+: more than high school (HEI, 2000).

an influence of socioeconomic status on exposure to air pollutants, lifestyle, and health care use.

In the ACS study, there was no association between PM and lung cancer after 7 years of follow-up. The extension of the follow-up period to 16 years yielded a qualitative change in the lung cancer estimate. With extended follow-up, there is a significant overall effect, as has been described before in the Six Cities Study and in the AHSMOG study, both studies with a follow-up period of about 15 years. A comparison between the lung cancer results in the three cohort studies (Six Cities, AHSMOG, ACS) is shown in Table 4. Especially in AHSMOG, the difference in lung cancer estimates for males and females is considerable (Abbey et al., 1999). However, in this study the correlation between lung cancer and ozone was stronger than that with PM.

Gender-related differences in PM health effects have also been seen in other endpoints in the AHSMOG study, generally with higher effect estimates in males (Abbey et al., 1999).

Table 4
Gender differences in lung cancer RR (calculated per 10 $\mu g/m^3$ $PM_{2.5}$) in three cohorts

Cohort	Male	Female	Combined
AHSMOG	2.14*	1.20	
Six cities			1.18
ACS	1.05	0.98	1.00
ACS 2002	1.13*	0.99	1.08*

AHSMOG (Abbey et al., 1999), Harvard Six cities study (Dockery et al., 1993), ACS, ACS 2002 (Pope et al., 1995, 2002). For comparison, the AHSMOG interquartile range of 24.08 $\mu g/m^3$ PM_{10} is set equal to 15.9 $\mu g/m^3$ $PM_{2.5}$ using $PM_{2.5} = 0.66 \times PM_{10}$.
* $P \leq 0.05$.

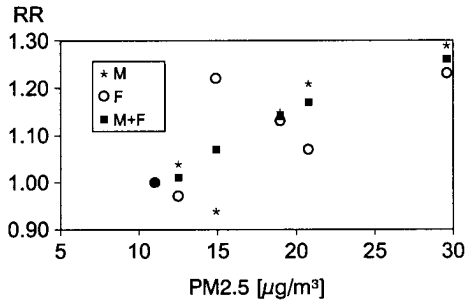

Fig. 8. City- and gender-specific total mortality in the Harvard Six cities Study (Dockery et al., 1993).

Gender-specific information on total mortality is provided from the Six Cities Study, too (Fig. 8). The concentration–response curve looks quite linear for men and women combined. However, a linear concentration–response is less probable when looking at men and women separately.

6. Concluding remarks

The body of epidemiological literature on PM health effects is impressive. A review necessarily has to focus on a limited choice of aspects. The role of particle size is an important issue. For air pollution control, it would be helpful to know exactly which part of PM is the fraction most relevant to health. Epidemiology can demonstrate associations between all PM fractions and health endpoints. No single study alone can prove or refute a relationship with one or another fraction. It seems to be prudent not to neglect any fraction of inhalable particles. At present, the available data do not allow to absolve coarse particles. The role of ultrafine particles is only beginning to be assessed.

Concentration–response relationships based on time-series studies seem to be influenced by the analytic approach applied. During the last decade, the effect estimates have been revised downwards. The number of large cohort studies is currently very low. The effect estimates based on cohort study results seem to be modified by socioeconomic status. Gender differences are not fully understood.

Causality cannot be proven in epidemiological studies. The Hill Criteria (Hill, 1965) for causality are a valuable set of criteria. However, if there is a strong association between several air pollutants, epidemiology cannot fully disentangle the contribution of individual pollutants.

PM is some kind of container comprising components which are closely related to health effects. There are good reasons to suppose that not all particles are equal with respect to health effects. The mixture varies from region to region, but in all, PM seems to be a health-relevant kind of air pollution, and a threshold below which no more effects may be expected cannot be described.

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