COMMENTARY

Death stroked by dusty air: more mysteries to be solved

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Commentary on the paper by Yamazaki *et al* (see page 17)

After several reports in the early 1990s showing excessive mortality associated with unexpectedly low concentrations of particulate matter, substantial research efforts have been devoted to investigating particulate matter health effects and elucidating the related pathophysiological mechanism. Despite remaining knowledge gaps, epidemiological and toxicological studies have provided reasonably coherent evidence supporting the significance of particulate matter-mediated acute cardiovascular effects.¹ Among the mounting volume of literature on air pollution epidemiology, multi-city ecological studies using time-series or case-crossover analyses have reported fairly consistent associations between increased concentrations of particulate matter over short periods of one or several days and increased cardiovascular mortality and morbidity (eg, hospitalisations and emergency visits). However, scientific data linking air pollution to stroke, including ischaemic stroke and intracerebral haemorrhage (ICH), remain relatively scant and inconclusive.²

In this issue, Yamazaki *et al*³ present a case-crossover study examining the acute effect of particles on mortality from stroke among elderly people (aged ≥ 65 years) across 13 Japanese cities in 1990–1994. They found that high hourly particulate matter ($PM_{2.5} > 200 \mu g/m^3$), measured 2 h before death and independent of the 24-h particulate matter, was associated with increased mortality from ICH (ICD-9: 431). Compared with previous air pollution time-series studies or case-crossover analyses relying only on daily exposure data, although all ecological in nature, this study had two major strengths. Firstly, given data on “timing” of the presumed acute event, Yamazaki *et al* prudently applied time-stratified selection of control periods matched to the clockhours. This additional matching effectively adjusted for potential confounding by circadian variations of unmeasured physical activities, which may determine exposures to particulate matter and temporally correlate with the

onset of either cardiovascular⁴ or cerebrovascular events.⁵ Secondly, except few panel or individual-based case-crossover studies,^{6,7} the rich literature on air pollution epidemiology provides only limited corroborative insights for experimental studies attempting to delineate the short-term course of particulate matter effects.^{8,9} By contrast, the availability of data on hourly pollutants matched to time of death allowed the authors to explore temporal profile analyses of mortality from stroke associated with both daily and hourly exposures to particulate matter.

Interestingly, the illustrated time dependence of particulate matter effects on mortality from stroke seemed to be present only in warmer months (April–September), especially for ICH. Daily particulate matter was associated with statistically non-significant increases in both ICH and ischaemic stroke mortalities, and such associations disappeared with exposures lagged for >12 –35 h (fig 1). Hourly concentrations of particulate matter with various lags of up to 30 h were associated acutely with increased mortality from stroke, with many reaching statistical significance for ICH cases (fig 3). The variation of hourly particulate matter effect within the 24-h before mortality from ICH calls for a distributed lag structure¹⁰ to jointly model this dynamic temporal profile, which speaks to the probably invalid assumption of “equal weighting” (equation 1) implicated for estimating 24-h (lag0–23) particulate matter effect.

On the other hand, both the shown temporal dynamics and the magnitude of effect estimate (adjusted odds ratio of 2.4 associated with $PM_{2.5} > 200 \mu g/m^3$) are intriguing and appropriate interpretation is challenging. Clearly, the time of death recorded on death certificates as used in this study should not be equated to the onset of either ICH or ischaemic stroke. Although arguably high exposure to particulate matter may trigger abrupt changes to sympathetic tone which cause rupture of large cerebral aneurysms and consequently massive subarachnoid

haemorrhage (SAH) leading to sudden death in hours, it cannot explain the described particulate matter–ICH association because victims with SAH (ICD-9: 430) were excluded. One related hypothesis is that high exposure to particulate matter may cause rapid-accumulating infratentorial haemorrhage, with subsequent brain-stem herniation and sudden death. However, these severe forms of ICH account only for a small portion of clinical cases, hardly explaining the statistically significant and large effect size observed in this study. Therefore, the reported acute effect of hourly particulate matter on increased mortality from stroke should not be interpreted as the onset of fatal stroke triggered by short-term increases in ambient particulate matter. Although growing evidence on particulate matter toxicity may provide putative pathways (eg, vascular inflammation, endothelial dysfunction and hypercoagulation) linking particulate matter to ischaemic stroke, the biological plausibility for the alleged direct effect of particulate matter on ICH is still lacking. Alternatively, findings of Yamazaki *et al* may suggest that high exposure to particulate matter triggers other acute deadly events in subjects with existing ICH (or ischaemic stroke) but without the real causes of death being identified in their death certificate. This assumed indication of susceptibility to particulate matter-mediated excessive mortality in patients with stroke is consistent with recent findings¹¹ and is also supported by the propensity to cerebrogenic sudden death in stroke.¹²

The report by Yamazaki *et al* also left us other scientific uncertainties and unanswered questions: spatial heterogeneity, the roles of gaseous pollutants and the interaction with temperature for the air pollution-mediated effect on cerebrovascular diseases, to only name a few. Interested readers shall wish to see more uncertainties regarding air pollution and stroke demystified in the years to come.

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Epidemiology

Non-Hodgkin lymphoma and occupational exposures: multiple exposures $\neq$ multiple papers

H Kromhout, R Vermeulen

Commentary on the paper by Karipidis *et al* (see page 25)

In this issue, Karipidis and colleagues report the interesting finding of a possible association between non-Hodgkin lymphoma and occupational exposure to power-frequency magnetic fields.¹ Their results are important given that existing studies on this topic are few, with conflicting results.^{2–3} As in any other community-based case-control study their subjects have been exposed to a variety of chemical and physical agents. The authors, like many others, have published associations between various occupational exposures and non-Hodgkin lymphoma in separate papers.^{4–6} Every researcher ever involved in large and expensive community-based case-control studies focusing on an adverse outcome and occupational exposures will be aware of the factors increasing the likelihood of publication of the results of positive and negative exposure-response relations in multiple papers. These include a general trend towards shorter papers in journals, but an expectation that assessment methods are specifically tailored to the exposure in question and that other aspects of methodology are described in sufficient detail.

This example, however, highlights an increasingly important issue in occupational epidemiology—how to assess a series of related publications. With the use of job exposure matrices (JEMs) or experts to assign occupational exposure to cases and controls, it is possible to relate many occupational exposures to the studied health effect in the absence of

clear a priori hypotheses. The risk of finding several positive associations simply by chance may thus be substantial. Where such findings are spread across several publications, there may not be full recognition of the problem of multiple comparisons or the often complex relationship between different occupational exposures included in different papers.

Moreover, later analyses may raise questions about confounding by factors that were less completely considered in papers of earlier and different focus.

The paper by Karipidis *et al* follows two previous publications concerning the association of lymphoma with chemical exposures like solvents, metals, organic dust and PCBs and exposure to pesticides.^{5–6} A third paper was published on the protective effects of sun exposure in the same population.⁴ In the earlier papers, not all of the estimated exposures included in later analyses could be described and so adjusted for. However, when we look at the exposures considered: sunlight, pesticides, solvents, metals, organic dust and PCBs, one can safely assume that exposures to these agents did not occur independently. For instance, utility personnel clearing the undergrowth of power lines will be exposed to power-frequency magnetic fields, pesticides (herbicides) and sunlight at the same time. Also, a subset of metal workers may have been exposed to solvents and metals simultaneously. From the four papers one can derive a picture of overlapping (occupational)

exposures in this population of cases and controls (see table 1).

Analyses of occupational exposures often start with looking for increased risks in certain jobs. Most case-control studies, however, are too small to come up with conclusive results when analysing at job level. The consequent use of JEMs and case-by-case expert assessment enables more powerful analyses since exposures to single (groups of) agents are combined across industries and jobs. At the same time the intrinsic and complex underlying exposure profiles are often not fully considered. With prevalence of exposure as high as those shown above and a considerable potential of strong correlations between agents in subsets of the study population, a more elaborate statistical analysis is warranted (see for instance De Roos *et al*⁷). Simple statistical adjustment for other exposures might often not be sufficient, given different type 1 error structures for the different exposures and possible complex correlation structures.

An analogy can be made with the field of genetics where enormous amounts of data on genetic variants are being assembled that have to be correlated with outcome parameters. The huge number of comparisons (up to thousands or even hundreds of thousands) in the genetic studies gives rise to a substantial chance that an initial “statistically significant” finding will turn out to be a false-positive finding. Therefore, several techniques have been developed to account for multiple comparisons, including false

Table 1 Overlapping (occupational) exposures among cases and controls

Exposure	Cases	Controls
Sunlight	100%	100%
ELF-EMF	100%	100%
Pesticides	11%	11%
Solvents	33%	29%
Metals	13%	14%
Organic dust	20%	17%
PCB	2%	2%