

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

MILLER *ET AL* (2007) LONG-TERM EXPOSURE TO AIR POLLUTION AND INCIDENCE OF CARDIOVASCULAR EVENTS IN WOMEN – POSSIBLE REASONS FOR LARGE COEFFICIENT

1. Members' discussed the study by Miller *et al* (2007) at the February 2007 meeting. The journal article and accompanying editorial are reattached for Members' convenience at Annex1a and Annex 1b.
2. The paper reported a strikingly large coefficient of a 75% increase in the risk of death from cardiovascular disease for a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$. An extract from the February 2007 minutes describing Members' discussion of the paper is attached at Annex 2. It was suggested that the Secretariat produce a list of possible reasons for the large coefficient ranked in terms of likelihood.
3. Since the discussion in February 2007, correspondence in response to this study has been published (see Annex 3). The Committee was informed at the last meeting of correspondence between the Chairman and the authors of the study regarding the effect of drug treatment (see below). The Secretariat has also received a letter from Professor Poole-Wilson who was not able to be present for the previous discussion. This is attached at Annex 4.
4. Taking the original discussion and the additional information received since together, the following list of possible reasons can be suggested. These are not in any particular order. The issue of ranking is discussed in paragraph 19.

Women without heart disease aged 50-79 are a particularly susceptible group

5. The editorial and Professor Poole-Wilson's letter discuss the point that there are important differences between women and men in relation to coronary heart disease. Thus, it is at least theoretically possible that the process of development of coronary heart disease in women renders them more susceptible to the effects of $\text{PM}_{2.5}$. However, there is no direct evidence to support this. [Note: no direct comparison between risks in women and men was possible in this study as only women were covered.]
6. The paper does quote examples of other studies that found increased risks in women (Chen *et al* 2005; Künzli *et al* 2005). Chen reported a 42% increase in risk of fatal coronary heart disease in women and no increase in men in a study of non-smoking Seventh Day Adventists. Künzli found a

15.7% increase in carotid intima-media thickness in women over 60 compared with 4.4% in the total sample (consisting of men and women over 40 without clinical signs of cardiovascular disease but with biomarkers (increased LDL cholesterol or homocysteine) for cardiovascular disease. It is unclear, however, whether an increased risk in women is a systematic finding across a wide range of cohort studies.

7. Professor Poole-Wilson notes that, although possible mechanisms could be suggested, confirmation of these would need much further research, and difficult research, to establish.

Untreated subjects with undiagnosed heart disease are a particularly susceptible group

8. The study excluded subjects with a history of physician-diagnosed cardiovascular disease at baseline. It is possible that subjects with undiagnosed cardiovascular disease were included in the study group. One possibility is that drug treatment for cardiovascular disease might protect subjects against air-pollution mediated effects on cardiovascular disease. As it is subjects with diagnosed cardiovascular disease that will be treated, and these subjects were excluded, the study group might be at increased risk compared with a general population sample that included both treated and untreated subjects. There is no agreed consensus on a protective effect of drug treatment as this has been examined in only a few studies. For example, Schwartz (Schwartz *et al* 2005) found that PM_{2.5} decreased the high frequency component of heart rate variability in Glutathione-S-Transferase M1 null subjects in the Normative Aging Study of male veterans but this effect was not present if the men were taking statins.
9. The authors of the Miller study had not looked at the issue of protection by drug treatment in detail but intended to do so.

Reduced measurement error

10. The allocation of exposure data from the nearest monitor to each individual subject would be expected to have reduced measurement error compared with the ACS study (Pope *et al*; 2002). (The ACS study allocated exposure to individuals on the basis of average exposure across a whole metropolitan area which might include several monitors). This is consistent with the fact that smaller spatial scale studies generally appear to find larger coefficients than were found in the ACS study.
11. On the other hand, the coefficient is still substantially larger than found in most of the smaller spatial scale studies. In addition, the study included a between cities coefficient (allocating a weighted mean exposure for each city to all women in that city) of a 63% increase per 10 µg/m³ increase in

PM_{2.5}. Thus, although the effect of reduced measurement error may be contributing, it may not be enough to explain the whole difference.

Traffic-related PM_{2.5}

12. This is an analogous point to that above. It is proposed that the use of smaller spatial scale analyses picks up variations in traffic-related pollution better than 'between-city' analyses. There is other evidence potentially supporting a greater effect of traffic-related pollution.
13. The points made in paragraph 11 above also apply here.
14. The letter to the Editor from Michael Jerrett and Richard Burnett (2nd page Annex 3) suggests that the exposure increment of 10 µg/m³ PM_{2.5} used to express the hazard ratio in the Miller study is an unrealistically large within-city traffic-related increment for most US cities except Los Angeles. An exposure increment of 3.3 µg/m³ PM_{2.5}, based on data for New York city, was considered more appropriate. The authors responded that the increment of 10 µg/m³ was chosen for comparison with other studies such as the ACS study and was within the range of exposures allocated to individuals across the whole study group. This debate does not explain why the coefficient is higher on a per 10 µg/m³ basis but is worth bearing in mind in terms of actual public health impact.

Better design/control of confounding

15. Cardiovascular deaths were confirmed by a review of medical records in the Miller study. This was not possible in the ACS study. Misclassification of deaths would only have underestimated the coefficient in the ACS study if (i) true cardiovascular deaths had been misclassified as other deaths at high exposures or (ii) true other deaths had been misclassified as cardiovascular deaths at low exposures. So, a better definition of cardiovascular deaths might or might not be an explanation for an increased coefficient.
16. The Miller study included more information on cardiovascular risk factors and the hazard ratio was adjusted for systolic blood pressure and for the presence or absence of diabetes, hypertension or hypercholesterolaemia. This was in addition to factors such as BMI and smoking that were included in the ACS study. This might or might not account for the increased coefficient depending on how these unmeasured risk factors were distributed across exposure categories in the ACS study.

Uncontrolled confounding

17. The possible reasons listed above all assume that the increased coefficient is 'real'. It is also possible that the design of the Miller study has, in some way, introduced an unknown confounder that was not present in the studies that gave lower coefficients. If so, the source of such unknown confounding is not obvious. It is now some time since the study was published and the Secretariat is not aware of any published articles pointing out any major flaws in the study. On the other hand, there has been debate about the plausibility of the coefficients in the smaller spatial scale studies relative to the ACS study (in terms of historical changes in pollution and in mortality rates) (COMEAP, 2007)¹ and the same issues apply to this study to a greater degree.
18. The study did not appear to control for spatial autocorrelation to such a rigorous degree as in the ACS study and this could have an effect on the size of the coefficient. How much of an effect and in what direction is unclear.

Ranking

19. The above list has not currently been ranked according to likelihood although some qualitative comments relating to likelihood have been made in some cases. It is noted that consideration could be given to both the likelihood of the possible reason operating and the likelihood of the possible reason being of sufficient quantitative importance to account for the increased size of the coefficient.
20. Members' are invited to comment on the collated list of reasons and on the feasibility of ranking them by likelihood.

**Secretariat
February 2008**

¹ The plausibility annex of the COMEAP report related to all cause mortality but similar issues would apply to cause-specific mortality.

References

Chen, L.H., Knutsen, S.F., Shavlik, D., Beeson, W.L., Petersen, F., Ghamsary, M. and Abbey, D. (2005) 'The association between fatal coronary heart disease and ambient particulate air pollution: are females at greater risk?' *Environmental Health Perspectives* 113(12): 1723-1729.

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Kunzli, N., Jerrett, M., Mack, W.J., Beckerman, B., LaBree, L., Gilliland, F., Thomas, D. Peters, J., and Hodis, H.N. (2005) 'Ambient air pollution and atherosclerosis in Los Angeles' *Environmental Health Perspectives* 113: 201-206.

Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L. and Kaufman, J.D. (2007) 'Long-term exposure to air pollution and incidence of cardiovascular events in women.' *New Eng. J. Med.* 356(5):447-458.

Pope, C.A. III, Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., and Thurston, G.D. (2002) 'Lung cancer, cardiopulmonary mortality and long-term exposure to fine particulate air pollution' *JAMA* 287(9):1132-1141.

Schwartz, J., Park, S.K., O'Neill, M.S., Vokonas, P.S., Sparrow, D., Weiss S., and Kelsey, K. (2005) 'Glutathione-S-transferase M1, obesity, statins and autonomic effects of particles' *Am. J. Resp. Crit. Care Med.* 172: 1529-1533.

Annex 1a:

Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L. and Kaufman, J.D. (2007) 'Long-term exposure to air pollution and incidence of cardiovascular events in women.' *New Eng. J. Med.* 356(5):447-458.

Annex 1b:

Dockery, D.W. and Stone, P.H. (2007) 'Cardiovascular Risks from Fine Particulate Air Pollution' *New Eng. J. Med.* 356(5): 511-513.

Annex 2: Extract from minutes of February 2007 COMEAP meeting.

ITEM 5d. LONG TERM EXPOSURE TO AIR POLLUTION AND INCIDENCE OF CARDIOVASCULAR DISEASE IN WOMEN. NEJM MILLER K ET AL, 2007; 356 (5): 447-458

60. Members' attention was drawn to this paper which reported an association between air pollution levels and the occurrence of cardiovascular disease in a cohort of 65,893 women in the USA, followed up between 1994 and 1998.

61. The paper reported a clear association between air pollution levels close to the individual's place of residence and the risk of illness. An editorial on the paper had been tabled.

62. It was noted that a statement on the paper would not be required, but that the paper was an important one to consider.

63. The Chairman drew Members' attention to a surprisingly large effect that was noted: each 10µg/m³ increase in PM_{2.5} was associated with a 76% increase in the risk of illness - an increase which was statistically significant.

64. Members discussed why the effect size might be so large and questioned the possibility of the effect size increasing further if the study focussed on an increasingly smaller group. This encouraged Members to discuss the group which had been studied and in particular, to note that this cohort were not taking drugs for cardiovascular conditions. It was questioned whether members of the cohort were taking HRT as this is believed to protect against coronary artery disease, but possibly increase thrombosis. It was agreed that the Chairman would write to the paper author to question whether a therapeutic effect might be occurring i.e. general population studies including treated patients with cardiovascular disease were giving smaller results than this study which excluded those treated for cardiovascular disease (at least at the start of the study) .
Action: Chairman

65. It was agreed that the Secretariat would contact Philip Poole-Wilson, who had sent his apologies for this meeting, to establish further information on the Euro-heart study and the proposed theory regarding increased risk for women as referred to in the tabled editorial.

Action: Secretariat

66. Other indicators of health of the cohort were questioned, such as BMI. It was noted that half of the cohort had a BMI greater than 27.3 and it was questioned whether this was considered 'healthy'.

67. It was established that there were many caveats which could explain the size of the coefficient, other than spatial scale, and in particular, the different types of confounding associated with between city studies and within city studies. The ACS study controlled for spatial autocorrelation, but this study appeared not to do this to such a rigorous degree. It was agreed that a greater degree of controlling for spatial autocorrelation would influence the size of the effect estimate. It was suggested that a list of reasons suggesting why the coefficient was so large should be produced, which would include susceptible group, measurement error, better design / control of confounding etc and that this list would be ranked in terms of likelihood.

Action: Secretariat

68. The Committee agreed that this was a most striking paper.

Annex 3:

Letters from Brook R.D. and Rajagopalan S. and from Jerrett M. and Burnett R.T. and authors reply from Kaufman J.D., Miller K.A. and Sheppard, L. (2007) 'Air Pollution and Cardiovascular Events' New Eng. J. Med. 356(20): 2104-2106.

Annex 4:

Letter from Professor Poole-Wilson 11 September 2007 (see separate document 'Annex 4 to COMEAP,2008,05').