Regional effects unlikely to explain association between ozone and cardiovascular mortality in China

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We read with interest the Article by Yue Niu and colleagues in *The Lancet Planetary Health* in which they found an association between long-term ozone exposure and increased risks of cardiovascular mortality in China.[1] The study could provide additional evidence of this association in middle-income countries; however, we have concerns regarding their subgroup analysis.

The association between exposure to ozone and the outcomes was analysed by age and sex stratified Cox proportional hazards models adjusted for several confounders. Furthermore, the authors did several subgroup analyses. The authors intended to analyse between-group differences in the subgroup analyses, but did not discuss the changes in parameter estimates from the original analysis. Although the subgroup analyses for age, sex, education, and smoking showed different hazard ratios (HRs) in each stratum, each analysis gave a point estimate of approximately 1·093, which was similar to the original point estimate in the non-stratified analysis.

The fact that the subgroup analyses gave point estimates of around 1·093 is explained from the regression model as follows. Generally, if there are no interactions among explanatory variables, the Cox hazard model is formulated as

$$h_g(t,X)=h_{0g}(t)\exp(\beta_1x_1+\beta_2x_2+\cdots+\beta_kx_k)$$

where $h_g(t, X)$ is the hazard function, $h_{0g}(t)$ is the baseline hazard function, g denotes stratum, β is a constant, x is the explanatory variable, t is survival time, X is a vector of explanatory variables, and k is the number of explanatory variables.

HRs are expressed as

$$HR_k = e^{\beta k}$$

Niu and colleagues' subgroup analysis assumed possible interactions between ozone exposure and other variables. When β_1 is the parameter estimate for mortality associated with ozone exposure (x_1) and β_2 is the parameter estimate for mortality associated with educational status ($x_{2=0}$ indicates low educational status and $x_{2=1}$ indicates high educational status), the multiple regression model is formulated as

$$h_g(t,X)=h_{0g}(t)\exp(\beta_1x_1+\beta_2x_2+\beta_{12}x_1\times x_2+\beta_3x_3+\cdots+\beta_kx_k),$$

$$h_g(t,X_{x2=0})=h_{0g}(t)\exp(\beta_1x_1+\beta_3x_3+\cdots+\beta_kx_k), \text{ or}$$

$$h_g(t,X_{x2=1})=h_{0g}(t)\exp(\beta_1x_1+\beta_2+\beta_{12}x_1+\beta_3x_3+\cdots+\beta_kx_k)$$

And the HRs of ozone exposure in subgroup analysis are expressed as

$$HR_{1[x2=0]} = e^{\beta_1} \text{ and } HR_{1[x2=1]} = e^{\beta_1+\beta_{12}}$$

Thus, if the regression model was valid (ie, there was no interaction other than the combination), average parameter estimates of HRs in subgroup analysis would be comparable to the HR in the original analysis.

However, the subgroup analyses for residence and regional statuses showed smaller HRs in each stratum than in other subgroup analyses. Especially for regional status, there was no significant effect of ozone concentration on the risk of cardiovascular mortality in both regions (north region HRs 0·974 [95% CI 0·915–1·037]; south region HR 1·054 [0·980–1·134]). This finding suggest that ozone exposure was not a risk of cardiovascular mortality, and regional status was confounded with unmeasured variables. Further discussion is needed for potential confounding in regional differences in ozone exposure and cardiovascular mortality.

We declare no competing interests.

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1 Niu Y, Zhou Y, Chen R, et al. Long-term exposure to ozone and cardiovascular mortality in China: a nationwide cohort study. *Lancet Planet Health* 2022; **6:** e496–503.