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Effects of Prenatal Exposure to Pollutants on Children's Development: Additional Issues

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Tang et al. (2008) made a significant contribution to understanding the effects of prenatal exposure to coal-burning pollutants:

> Decrements in DQs [developmental quotients, measured by the Gesell Developmental Schedules] were significantly associated with cord blood levels of PAH–DNA adducts and lead, but not mercury.

Recent developments compel us to consider Hg sources and attenuating factors in neurodevelopment related to early human exposure. My comments are specifically directed to breast-feeding (neurodevelopment modulator) and uncontrolled sources of Hg: ethylmercury (EtHg) in thimerosal-containing vaccines (TCV), and methylmercury (MeHg) consumed in rice—not fish. Breast-feeding is essential to promote or prime neonatal neurodevelopment, and China is among the countries that use TCV; therefore, controlling for these variables is important in neurodevelopmental studies (Dórea 2007a).

Tang et al. (2008) discussed the literature showing that prenatal Hg exposure is related to adverse neurodevelopmental outcomes at 2 years of age. During the postnatal period, the central nervous system is still vulnerable to Hg exposure; therefore, additional early exposure to Hg may be difficult to disentangle from prenatal events. Newborns in China are immunized with TCVs carrying concentrations of Hg ranging from 12.5 to 17.5 g Hg/dose (Dórea 2008). Furthermore, TCVs, such as the hepatitis B vaccine, are given immediately after birth. Also, some mothers could use products containing thimerosal during pregnancy (e.g., Rh-negative mothers taking anti-RhoD immune globulins). Considering that Tang et al. (2008) reported a 70-day range in gestational age for their cohort, it is reasonable to speculate that if TCV could be taken during the first 10 weeks postnally, EtHg exposure should be normalized. We were not informed of the immunization schedule (or maternal exposure to thimerosal products) of this cohort, but it is possible that in the time interval of gestational-age variation (10 weeks), there would be opportunity for five shots of TCV (Dorea 2007a). Considering the reported 70-day interval of gestational age, we should expect an even wider range of Hg exposure (on a body mass basis) due to variation in birth weight and respective rate of weight gain.

The effects of TCV-EtHg exposure on neurodevelopment are controversial. The most recent epidemiologic studies (Thompson et al. 2007; Young et al. 2008) exemplify current uncertainties related to the U.S. Federal Court compensation claimed on adverse effects triggered by TCVs (Offit et al. 2008). Although the statistical analysis of Tang et al. (2008) was well designed for prenatal events, perinatal TCV-EtHg exposure not evaluated by cord blood measurements could not account for effects (albeit transient) on neurodevelopment at 2 years of age.

Studies that measured neurodevelopmental outcomes as a result of prenatal exposure to neurotoxic substances have shown that breast-feeding, in most cases, can counteract some of the adverse effects (Dórea 2007b); compared with formula feeding, children had better neurobehavioral scores due to prenatal exposure to several classes of environmental pollutants. Because breast-feeding is an important modifier of neurodevelopmental outcome, not controlling for its duration could be a limitation in the Gesell Developmental score (GDS) outcomes related to Hg. Indeed, using principal component analysis, we have found effects of prenatal and postnatal Hg from both EtHg (from vaccines) and MeHg (fish consumption) in exclusively breast-fed children that were also evaluated by GDS (Marques et al. 2008). Tang et al. (2008) showed that cord blood Hg was three times lower than that reported for the Faroe Island whale-eaters, thus attributing the 7.0 μg Hg/L to low fish consumption (only nine mothers consumed fish or shell fish); compared with the high concentrations of Hg in whale meat, the Hg levels in these non–fish-eating mothers are relatively high. In this context, it should be noted that recent studies have indicated that rice can significantly contribute to MeHg exposure in China (Feng et al. 2008; Qiu et al. 2008). A post hoc assessment of these issues can enrich Tang et al.'s study.

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Effects of Prenatal Exposure to Pollutants on Children's Development: Tang and Perera Respond

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The study we reported in our article "Effects of Prenatal Exposure to Coal-burning Pollutants on Children's Development in China" (Tang et al. 2008) was conducted in the Tongliang County of Chongqing City, an area in western China. In his letter, Dórea suggests that the children who participated in our study may have been exposed to thimerosal in vaccinations. Because the actual levels of thimerosal used in each vaccine are a trade secret, we were not able to directly control for possible exposure to thimerosal in our analysis. We note that in the United States, all routinely recommended vaccines for U.S. infants are available only as thimerosal-free formulations or contain only trace amounts of thimerosal. We do not know whether that has been the case for vaccines used in China. On the other hand, the children's vaccination schedule is well enforced in China, so any thimerosal exposure would have been similar among all the children who participated in our study. Therefore, this exposure would not have been likely to confound the observed relationship between Gesell Developmental scores (GDS) and

PAH–DNA adducts and lead concentrations in newborn umbilical cord blood.

We did not observe a significant adverse impact of the Hg levels in cord blood on neurodevelopment at 2 years of age. The main concern for mercury exposure and neurodevelopment concerns prenatal exposures to methylmercury in fish consumed by pregnant women, and the consumption of fish is low in Tongliang. Reports have shown high Hg levels in rice from a mining area of Guizhou, a province located in southwestern China (Qiu et al. 2008; Feng et al. 2008). The Hg levels in the rice from other areas in China did not seem to exceed normal levels (Zhang and Wang 2007). Our study area, Tongliang County, is not within the Hg mining areas of Guizhou Province; thus, it is unlikely that the consumption of rice could expose the study sample to notable Hg levels.

In reference to Dórea's suggestion to account for breast-feeding, we did incorporate a breast-feeding variable in our initial analysis. However, because the effect of breast-feeding was not generally statistically significant, the final model did not include a breastfeeding variable.

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Reduction in Measurement Error Confounds Cumulative Pollution Exposure

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Barraza-Villarreal et al. (2008) showed a convincing link between increased air pollution and reduced forced expiratory volume in 1 sec (FEV_1). However, the apparent stronger association between reduced FEV_1 and cumulative exposure over 1–5 days may be due in part to a reduction in measurement error of particulate matter < 2.5 μm ($PM_{2.5}$) and not a true cumulative effect (Barraza-Villarreal et al.'s Figure 3).

Air pollution studies are prone to measurement error. In the study of Barraza-Villarreal et al. (2008)—as in most others—the estimates of air pollution came from a network of fixed monitors. Each child's day-to-day exposure was assigned using the closest monitor, and no monitors were > 5 km from the child's home or school. However, even with a monitor near the child's location, the estimate cannot be perfect because of variation in individual exposure (e.g., time spent outdoors).

I evaluated the effect of measurement error using a simulation study. I assumed that the 158 asthmatic children had a $PM_{2.5}$ exposure given by

$$PM_{2.5}^{c} = 28.9 + b_c,$$
$$c = 1, \ldots, 158,$$
$$b_c \sim N(0, \sigma_b^2).$$

The mean $PM_{2.5}$ exposure is 28.9 μg/m^3, and each child (c) varies around this mean (b). This between-child variation means that some children live in more polluted areas than others.

The children's FEV_1 was observed at repeated times, which was simulated using

$$FEV_1^{ct} = 1.89 + f_{ct} + \alpha PM_{2.5}^{c},$$
$$c = 1, \ldots, 158,$$
$$t = 1, \ldots, n_c,$$
$$f_{ct} \sim N(0, \sigma_f^2),$$

where 1.89 L/sec is the mean FEV_1, t is time, n_c is the number of observations for child c, and f_{ct} is the measurement error in FEV_1. The parameter α controls the change in FEV_1 due to $PM_{2.5}$ exposure.

In the study of Barraza-Villarreal et al. (2008), FEV_1 was dependent on $PM_{2.5}$ exposure from the previous 1–5 days. Daily $PM_{2.5}$ values are subject to measurement error (e), which I simulated using

$$PM_{2.5}^{ct} = PM_{2.5}^{c} + e_{ct},$$
$$e_{ct} \sim N(0, \sigma_e^2).$$

Barraza-Villarreal et al. (2008) used a mixed model to estimate the effect of $PM_{2.5}$ on FEV_1 and controlled for the repeated FEV_1 results from the same child. They also controlled for a number of covariates; however, for this simulation study I simply regressed the simulated daily values, FEV_1^{ct}, against the simulated daily pollution values, $PM_{2.5}^{ct}$, and included a random intercept for each child.

I assumed a between-child variation in $PM_{2.5}$ of $\sigma_b^2 = 2.8^2$ and an equal measurement error in $PM_{2.5}$ of $\sigma_e^2 = 2.8^2$ (by naively using the standard deviation in $PM_{2.5}$). I assumed a measurement error variation in FEV_1 of $\sigma_e^2 = 0.66^2$. I simulated data for 158 children and random sampled the number of observations per child (n_c) by rounding a randomly generated value from a normal distribution $N(11,2.2^2)$.

The results of 100 simulations are shown in Figure 1. Longer exposure lags gave estimated reductions that more closely approximated the true effect. On face value, longer exposure appears to be more damaging to health, but the simulated data had no cumulative effect. The stronger effect occurred because of the regression dilution bias and a reduction in the measurement error of $PM_{2.5}$ exposure from using multiple days (MacMahon et al. 1990). Although different simulation results can be obtained by varying the strength of the pollution effect and measurement errors, the trend will always be to increased effects with increasing exposure periods.

The results of this simulation show that care should be taken when summing repeated measurements. Cumulative measurements are confounded by reductions in measurement error, which makes interpretation difficult.

The results of this simulation in no way invalidate the results found by Barraza-Villarreal et al. (2008). There is strong evidence that increased exposure to air pollution damages lung function. However, it is difficult to estimate how much of this reduction is due to a cumulative effect, thus requiring methodological development.

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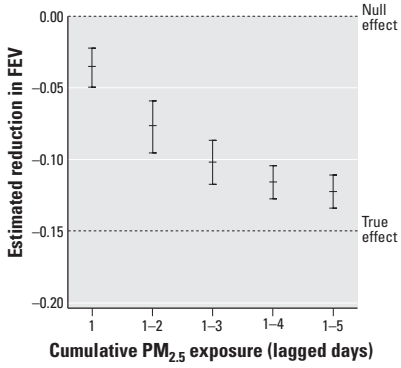

Figure 1. Increase in the estimated effect of $PM_{2.5}$ with increasing lag using a simulation study. Vertical lines are the mean estimate and 95% confidence interval.

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Reduction in Measurement Error: Barraza-Villarreal et al. Respond

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We thank Barnett for his comments on our article (Barraza-Villarreal et al. 2008), in which we reported associations between ambient air pollution and adverse lung function outcomes in a cohort of schoolchildren in Mexico City, Mexico. In the last several years, the adverse effects of air pollution on lung function, such as decrement in forced expiratory volume in 1 sec (FEV_1) has been clearly demonstrated (Gauderman et al. 2007; Romieu et al. 1997). Before our study, there were reports of associations between cumulative particulate matter [PM < 10 μm (PM_{10}) and < 2.5 μm ($PM_{2.5}$) in aerodynamic diameter] and gaseous (ozone, sulfur dioxide, and nitrogen dioxide) air pollutant exposure and decrease in lung function in other studies (Downs et al. 2007; Romieu et al. 2006). Replication of these findings in different populations under different conditions of exposure is an important aspect of epidemiologic research, with consistency of results strengthening the weight of evidence for a true association between exposure and outcome.

However, air pollution exposure assessment is always a critical factor in environmental epidemiology. Like other studies of air pollution and lung health, our study (Barraza-Villarreal et al. 2008) relied on ecologic rather than personal indicators of exposure. Exposure misclassification due to the use of fixed-site ambient monitors rather than personal dosimeters is likely to underestimate rather than overestimate the effect of air pollution on lung function.

In his letter Barnett mentions that "the apparent stronger association between reduced FEV_1 and cumulative exposure over 1–5 days may be due in part to a reduction in measurement error of particulate matter < 2.5 μm ($PM_{2.5}$) and not a true cumulative effect." He attempted to verify this assertion by carrying out a simulation study; however, we see several problems with it. First, in his simulations, Barnett assumed a normal distribution (Figure 1). Several distributions have been reported as adequate for $PM_{2.5}$, among them log-logistic, log-normal, and gamma. Using the data from our study (Barraza-Villarreal et al. 2008), we carried out an exercise similar to Barnett's, but we fitted different distributions (data not shown). The one that best fit our data was the gamma distribution. Second, when considering cumulative exposure, it is important to take into account the correlation between the observations on consecutive days; it is not enough to simulate from a distribution and then add the exposure. The models presented by Barnett did not take into account this correlation. Third, we reproduced the simulation of FEV_1 as presented by Barnett (data not shown) and observed that it could produce negative value for FEV_1 because it does not take into account the correlation of observations within children, although a sample size for each child was simulated and an artificial mixed model was fitted.

In conclusion, because Barnett's simulation of $PM_{2.5}$ was based on a normal distribution, it does not reproduce the original structure of our data (Figure 1) (Barraza-Villarreal et al. 2008); therefore, the conclusions obtained are not applicable.

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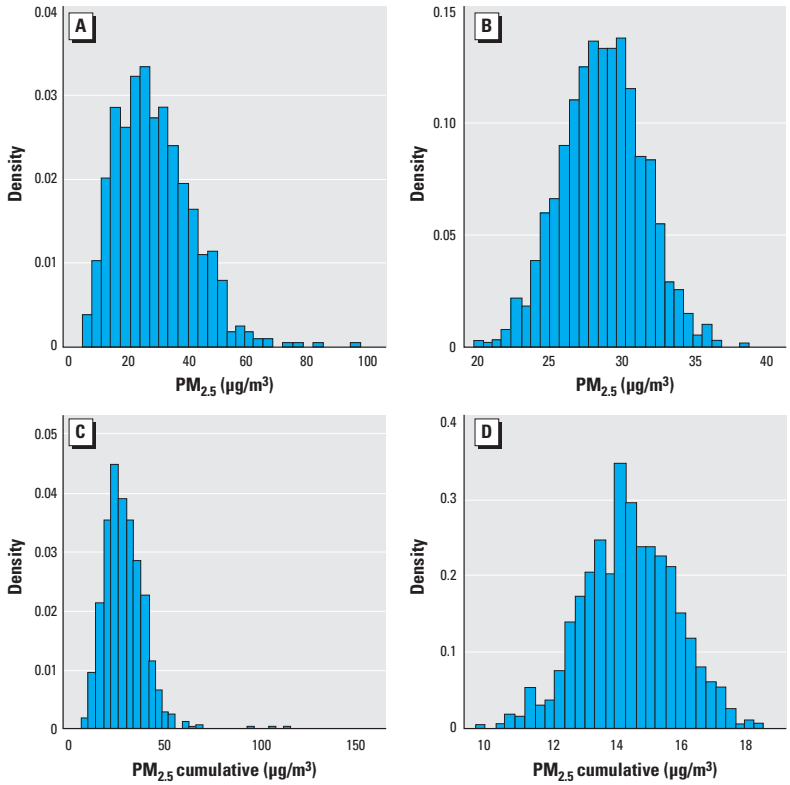

Figure 1. Same day (*A*,*B*) and 2-day cumulative (*C*,*D*) $PM_{2.5}$ distributions. (*A*,*C*) original data. (*B*,*D*) Simulated data.

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Errata

Chisholm et al. have reported an error in their article "Risk of Birth Defects in Australian Communities with High Brominated Disinfection By-product Levels" [Environ Health Perspect 116:1267–1273 (2008)]. In Table 1, the study design, reference, and exposure range given for the first study listed, "Retrospective cohort, Canada," were incorrect. The results are actually from a cross-sectional study carried out in the United States by Bove et al. (1995), and the exposure range is as follows: High (> 100 µg/L) versus low (< 20 µg/L) THM levels. The defect types and risk estimates (95% confidence intervals) were correct.

The full reference for this study is as follows:

Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. 1995. Public drinking water contamination and birth outcomes. Am J Epidemiol 141:850–862.

These errors were introduced during the final drafting stages of the publication; when a much larger table of past literature was reduced, the two studies were accidentally combined. The authors apologize for the errors and emphasize that these changes do not alter the concepts that they addressed in their article.

In the "Conclusion" of the Commentary by Vanderstraeten and Verschaeve [Environ Health Perspect 116:1131–1135 (2008)], "health," the last word in the first sentence, should be "exposure." The corrected sentence is as follows:

Because the overall results from the currently available literature are inconclusive and, in particular, because most of the reported positive findings are flawed by methodologic imperfections or shortcomings, uncertainty still prevails about the possible influence on gene and protein expression from RF exposure at intensities relevant to usual human exposure.

EHP regrets the error.

In the article by Zablotska et al. [Environ Health Perspect 116:1056–1062 (2008)], the units for vitamin A (mg/day) were incorrect in Tables 2–4; the units should be "IU/day." Also, the units for retinol equivalents in the Appendix should be "µg/day" instead of "mg/day."
The authors regret the errors.