CORRESPONDENCE

Intellectual Impairment and Blood Lead Levels

TO THE EDITOR: In the light of the report on intellectual impairment and blood lead levels by Canfield et al. (April 17 issue),[1] we reanalyzed data from our prospective cohort study,[2] focusing on 48 children whose blood lead levels never exceeded 10 μg per deciliter at birth or at 6, 12, 18, 24, 57, or 120 months. The IQ at 120 months was inversely related to the lead level at 24 months with adjustment for covariates (P=0.03). Nonparametric smoothing analyses suggested that the inverse association persisted at blood lead levels below 5 μg per deciliter.[3] The blood lead coefficient (−1.56) was greater than that derived from analyses including children with peak levels above 10 μg per deciliter (−0.58). Thus, in our study as well, the inverse slope might be greater at lower blood lead levels than at higher blood lead levels. This finding is puzzling, and the magnitude of the decrease in IQ seems implausibly large. Because some of it presumably reflects residual confounding, the precise shape of the dose–effect relation at lead levels below 10 μg per deciliter remains uncertain. Nevertheless, despite the success of recent initiatives in reducing the population's exposure to lead, it is increasingly clear that children's IQ scores are reduced, without an apparent threshold, at lead levels that are still prevalent among children in the United States.[4]

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1. Canfield RL, Henderson CA Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Engl J Med 2003;348:1517-26.
2. Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 1992;90:855-61.
3. Schwartz J. Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ Res 1994;65:42-55.
4. Blood lead levels in young children — United States and selected states, 1996–1999. MMWR Morb Mortal Wkly Rep 2000;49:1133-7.

TO THE EDITOR: Relevant to the results of Canfield et al. is a recent report[1] showing a clear association between iron deficiency and increased lead absorption. Iron-deficient toddlers were found to be at greater risk for the consequences of increased lead absorption than were those who had sufficient levels of iron. Unfortunately, iron deficiency remains a substantial problem in children who are one to three years old — the age group in which the ingestion of lead appears to be greatest.[2] The case for the primary prevention of iron deficiency in toddlers[2] with routine daily iron supplementation, rather than adherence to the current secondary-prevention screening and treatment recommendations of the American Academy of Pediatrics,[3] has been greatly strengthened by the findings of the study by Canfield et al.

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THIS WEEK'S LETTERS

1. Wright RO, Tsaih SW, Schwartz J, Wright RJ, Hu H. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. J Pediatr 2003;142:9-14.
2. Eden AN, Mir MA. Iron deficiency in 1- to 3-year-old children: a pediatric failure. Arch Pediatr Adolesc Med 1997;151:986-8.
3. Kleinman RE, ed. Pediatric nutrition handbook. 4th ed. Elk Grove Village, Ill.: American Academy of Pediatrics, 1998.

TO THE EDITOR: Given the *Journal*'s international readership, Canfield et al., Selevan et al.,[1] and Rogan and Ware[2] should have acknowledged the effects of the toxicity of environmental lead in residents of developing countries. These people, who are usually poor and frequently lack basic health care, face much higher levels of exposure than do residents of wealthier nations.[3,4] Although the United States and the European Union have phased out leaded gasoline, 30 to 95 percent of the gasoline sold in Latin America, Asia, and Africa still contains lead.[3] Other sources include pollution from military sources and importation (read "dumping") of lead-laden toxic substances (e.g., old computers, fertilizers, and industrial waste).[3,4] Despite evidence of cost savings with the use of unleaded gasoline and calls from respected scientists and the World Bank for the elimination of leaded fuels, the highly profitable lead industry has lobbied against a phase-out.[3] The world's governments should support prevention through the elimination of fuel-based and industrial sources of lead, and developed nations should stop exporting toxic wastes to already beleaguered poorer countries.

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1. Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J. Blood lead concentration and delayed puberty in girls. N Engl J Med 2003;348:1527-36.
2. Rogan WJ, Ware JH. Exposure to lead in children — how low is low enough? N Engl J Med 2003;348:1515-6.
3. Kitman JL. The secret history of lead: special report. The Nation. March 20, 2000:11-30.
4. Donohoe MT. Causes and health consequences of environmental degradation and social injustice. Soc Sci Med 2003;56:573-87.

THE AUTHORS REPLY: The results of the secondary analysis of data from the prospective study by Bellinger and Needleman are consistent with the results we reported. Specifically, the inverse slope of the blood lead–IQ relation is greater at lower lead levels. Among children whose recorded peak blood lead level was never as high as 10 μg per deciliter, the estimate of the linear slope (−1.56) is very close to the estimate in our study (−1.37). We agree that both estimates are extremely large. As we reported, however, the shape of the dose–effect relation is nonlinear, so a linear analysis involving the use of truncated data will yield an overestimate of the true association. Our best (semiparametric) model indicated that the decrease in IQ occurring at blood lead levels of less than 10 μg per deciliter is about half as large as the decrease we found using the same range of data with a linear model.

We also agree that residual confounding must be considered when these results are interpreted, as in any observational study. In both studies, a broad range of potential confounders were included, but the identification of additional confounders is an important direction for future research. However, the close correspondence between our findings and those reported by Bellinger and Needleman is informative in the following regard: their study participants were primarily from middle-class and upper-middle-class, two-parent families, whereas many of the participants in our study were relatively disadvantaged. To the extent that residual confounding may have inflated the estimates of the inverse slope in both studies, it would seem that the sources of confounding are not closely related to conditions of social advantage or disadvantage.

The prevention of iron deficiency has well-documented benefits for children's health, and as Dr. Eden suggests, iron intake may play a part in reducing lead absorption.[1] Similar research suggests that dietary intake of calcium, zinc, and possibly other essential minerals may also modify the absorption of lead.[2] However, the existing evidence does not warrant the use of dietary interventions as a major strategy for reducing exposure to lead.[3] Instead, improvement of children's diets should accompany efforts to eliminate their exposure to lead.

We agree with Dr. Donohoe that there is adequate evidence to support policies aimed at the global elimination of exposure to lead during childhood. Banning the use of leaded gasoline and all other nonessential uses of lead would be a good beginning.

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1. Wright RO, Tsaih SW, Schwartz J, Wright RJ, Hu H. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. J Pediatr 2003;142:9-14.
2. Osman K, Schütz A, Åkesson B, Maciag A, Vahter M. Interactions between essential and toxic elements in lead exposed children in Katowice, Poland. Clin Biochem 1998;31:657-65.
3. Ballew C, Bowman B. Recommending calcium to reduce lead toxicity in children: a critical review. Nutr Rev 2001;59:71-9.

Obesity and Cancer

TO THE EDITOR: In the abstract of their article on overweight, obesity, and mortality from cancer, Calle et al. (April 24 issue)[1] conclude, "Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites." However, if one looks at the data for men (alas, this does not hold true for women), one sees that the relative risk of cancer among men who were "grade 1 overweight" (body-mass index [the weight in kilograms divided by the square of the height in meters], 25.0 to 29.9), as compared with men in the "normal range" (body-mass index, 18.5 to 24.9) is 0.97. Since 29,227 of the men studied fell into these two categories of body-mass index, whereas only 3076 had a higher body-mass index, this conclusion is diametrically opposed to what the data show to be true for more than 90 percent of this population of men — and presumably for any similarly stratified population of men. Thus, the advice implied in the conclusion of the abstract is exactly contrary to what the data suggest would be good advice.

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1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.

TO THE EDITOR: Calle et al. attempt to estimate the fraction of deaths due to cancer in the U.S. population that are attributable to overweight and obesity by using multivariate-adjusted relative risks and the distribution of body-mass index in the subgroup of the current population that is 50 to 69 years old. The formula they cite for the calculation of the population attributable fraction is appropriate for unadjusted relative risks[1]; the use of adjusted relative risks in this formula is incorrect and can result in biased estimates.[2,3] With adjusted relative risks, the population attributable fraction should be calculated on the basis of the distribution of body-mass index among persons who have died of cancer. Both the distribution of body-mass index and the rate of death due to cancer vary according to age, race, smoking status, and other confounding factors. When there is confounding, the expected distribution of body-mass index among persons who have died of cancer cannot be calculated directly from the distribution of body-mass index in the general population, because the distribution of confounding factors will also affect the distribution of body-mass index among persons who died of cancer. Estimates of the population attributable fraction that are calculated on the basis of adjusted relative risks and the distribution of body-mass index in the general population without taking into account the distribution of confounding factors may be biased.

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1. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. Belmont, Calif.: Lifetime Learning, 1982.
2. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Pub Health 1998;88:15-9.
3. Benichou J. A review of adjusted estimators of attributable risk. Stat Methods Med Res 2001;10:195-216.

TO THE EDITOR: Calle et al. report that obesity is a risk factor for cancer-related death, but although they adjusted their analyses for multiple potential confounders, they did not address two important statistical issues: the sensitivity of relative risk to proportional hazards and the potential for artifacts in evaluations of cancer-specific risk among adults who may have other diseases. Since the authors did not give readers access to their raw data or present a summary of the data that is adequate for an evaluation of these phenomena, a simulation must suffice to demonstrate these points. Suppose