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Lead Neurotoxicity and Socioeconomic Status: Conceptual and Analytical Issues

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Abstract

Socioeconomic status (SES) is usually considered to be a potential confounder of the association between lead exposure and children's neurodevelopment, but experimental and epidemiological data suggest that SES might also modify lead neurotoxicity. The basis of this effect modification is uncertain, but might include differences among SES strata in co-exposures to other neurotoxicants, genetic susceptibilities, environmental enrichment, and stress. The role of SES in the causal nexus is likely to include other dimensions, however. It conveys information about lead exposure opportunities as well as about predictors of child outcome that are correlated with but causally independent of lead. Failure to distinguish these aspects of SES will lead to an underestimate of lead's contribution, and might even result in attributing to SES health effects that should be attributed to lead. Conventional models, which treat SES and SES-related factors solely as potential confounders, do not capture the possibility that a child's early lead exposure alters the behaviors that the child elicits from others. Failure to model lead's contribution to such time-varying covariates will also tend to bias estimates of lead neurotoxicity toward the null. On a transgenerational level, low SES might be a proxy for vulnerability to lead. To estimate the burden of lead-associated neurotoxicity on a population level, we need to apply analytical approaches that model a child's development and its context as a complex system of interdependent relationships that change over time.

Socioeconomic status (SES) has played a central role in efforts to characterize the magnitude of the risk that lead poses to children. Because exposure is often greater among children of low SES (Baghurst et al., 1999) and low SES is a powerful predictor of neurodevelopment (Tong et al., 2007), it has long been recognized that due consideration must be given to the possibility that any observed association between lead exposure and neurodevelopment is, in part, an artifact of residual confounding, and thus reflects a Type I error of inference. Indeed, adjusting for SES and related covariates can result in reductions of 50% or more in the magnitude of lead's regression coefficient (e.g., Bellinger et al., 1992). Whether an investigator adequately handled this issue, avoiding a Type I error of inference, became one of the central determinants of whether the inferences drawn from a lead study were viewed as credible.

The role of SES in lead studies is likely to be much more complex than that of solely a confounder, however. Two dimensions of this issue are discussed in this paper. The first section summarizes epidemiologic and experimental findings suggesting that SES and SES-related aspects of a child's social environment modify the neurotoxicity of lead such that children of

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low SES are more vulnerable. The second section addresses conceptual aspects of the relationships among lead, SES, and neurodevelopment and, in particular, their implications for data analytic strategies. I argue that the approaches conventionally used to adjust for potential confounding by SES might be leading us to commit Type II errors of inference, i.e., underestimating the magnitude of lead's contributions to neurodevelopmental morbidity. In part, this might be due to a form of publication bias that encourages investigators to employ conservative modeling strategies that minimize the risk of drawing inferences that are false positives. But insofar as the goal of risk assessment is to provide accurate quantitative, and not merely qualitative, estimates of risk, especially to sensitive subgroups of the population such as children, Type II errors are not of mere academic interest and might have considerable public health import. After all, the costs of Type II errors are borne by the population exposed, in the form of diminished health, while the costs of Type I errors tend to be economic and primarily borne by corporate entities.

While the issues raised are discussed in the context of lead and SES, they pertain to any exposure that is not random with regard to important antecedents and correlates of the outcomes of interest.

SES as a modifier of the association between lead and children's neurodevelopment

Several early studies reported that a given blood or tooth lead level was associated with neurodevelopmental deficits of greater magnitude or persistence among children from the lower socioeconomic strata (Winneke and Kraemer, 1984; Harvey et al., 1984; Bellinger et al., 1988, 1990; Tong et al., 2000). For instance, in one prospective study, the dose-effect relationship differed according to SES beginning in the second year of life, when socioeconomic influences on child development are typically first evident. Specifically, children growing up in less advantaged circumstances expressed a lead-associated deficit at a cord blood lead level of 6 to 7 μg/dL, whereas more advantaged children expressed a deficit only when cord blood lead level exceeded 10 μg/dL. SES also modified children's neurodevelopmental prognosis. Children of higher SES showed greater improvement over time than did children from lower SES, regardless of blood lead history. However, the difference between high and low SES was greatest among children who had a cord blood lead level >10 ug/dL. Among children above the median SES, the mean score increased by more than 0.4 standard deviations between ages 2 and 5. Among children below the median SES, the mean score decreased by nearly the same amount over this period (Bellinger et al., 1990). Children from more advantaged families therefore appeared to be more able to compensate or recover from an early lead-associated neurodevelopmental deficit.

These studies provided little insight, however, into why low SES increases a child's susceptibility to lead neurotoxicity. SES is a multifaceted abstract construct, and its measurement is attended by considerable uncertainty (Braveman et al., 2005). It casts a wide net, serving as a proxy index of many diverse aspects of a child's developmental environment. This omnibus and undifferentiated nature makes it valuable from the standpoint of controlling for confounding but serves as an impediment to understanding which aspects of SES are critical with respect to its effect modifying influence. From a policy standpoint, we cannot identify steps that would increase the resilience of children from low SES strata until we deconstruct SES and appreciate the extent to which its different components contribute to this process.

We can hypothesize roles for several types of factors. One is co-exposures to neurotoxicants other than lead (Weiss & Bellinger, 2006). Children living in poverty are known to suffer greater exposures to many chemical contaminants than do more affluent children (e.g., Naess et al., 2007). Data on the effects of joint exposures to lead and other chemicals are very limited,

however, and most come from experimental animal studies. Co-administration of lead and manganese to rats increases brain lead levels approximately 3-fold (Chandra et al., 1981; Malhotra et al., 1984; Shukla & Chandra, 1987), perhaps because co-administration increases the affinity of lead-binding proteins (Kalia et al., 1984). Compared to rats exposed to only one of these metals, those co-exposed have lower birth weight and brain weight (Chandra et al., 1983), increased spontaneous motor activity, and slower learning of conditioned avoidance responses (Chandra et al., 1981). In a study of children in Mexico City, a steeper inverse dose-effect relationship between blood lead and neurodevelopment was observed among those with higher blood manganese levels (Claus Henn et al., 2007).

Genetics might also be contributory. Perhaps lead is more neurotoxic to children of low SES because they more frequently carry genes associated with greater susceptibility or because increased exposure to lead affects gene expression, by means of epigenetic processes such as DNA methylation, in ways that threaten neurodevelopment (Wright and Baccarelli, 2007). These are only conjectures, however, because of uncertainties regarding the SES distribution of polymorphisms of interest or lead's role in altering gene expression. Certain genotypes do appear to confer increased risk of lead neurotoxicity. For instance, the adverse impact of lead on executive functioning (rule learning and reversal) is greater among boys, but not girls, who lack the dopamine receptor D4-7 VNTR (Froehlich et al., 2007). If low SES boys are more likely than high SES boys to have the D4-7 VNTR, this could contribute to effect modification by SES.

Differences among SES strata in the richness and variety of the opportunities for stimulation afforded by the social environment within which a child develops might also be important. In particular, an environment that is relatively impoverished in such opportunities might render a child more vulnerable to lead. In an experimental study, rats exposed to lead but reared in an enriched environment, which permitted greater opportunities for social interaction and exploration of materials, learned a water maze more quickly than did rats exposed to placebo but raised alone in a largely barren cage. The lead-exposed rats raised in isolation failed to show any improvement in their maze performance. Being lead-exposed but reared in an enriched environment also resulted in recovery of deficits in NMDA receptor gene expression and increased induction of brain-derived neurotrophic factor in the hippocampus and granule cell layer of the dentate gyrus (Guilarte et al., 2003). Environmental enrichment appeared to prevent lead neurotoxicity or to foster greater recovery of function, both behaviorally and biochemically.

Nutritional status is another potential contributor to socioeconomic differences in susceptibility to lead neurotoxicity, because of specific metabolic interactions between lead and essential micronutrients such as calcium and iron, or because nutritional deficiencies render children less able to weather the additional insult represented by lead exposure (Kordas et al., 2007).

Increased stress or reduced resources for coping with stress have been proposed as potential explanations for poorer health among individuals of low SES (Gallo and Matthews, 2003). Stress exacerbates the toxicity of many contaminants (Hougaard and Hansen, 2007; Relyea and Mills, 2001; Verwer et al., 2007), including lead. Maternal stress, induced by novelty, restraint, or cold, modulates the effects of prenatal lead exposure on offspring performance on FI schedule-controlled responding, as well as basal and stress-induced corticosterone response (Cory-Slechta, 2005; Virgolini et al., 2005; Virgolini et al., 2006). In these studies, the effects of combined exposure to lead and stress were detected in the absence of an effect of either factor alone, and the profile of effects of the combined exposure differed notably from the effects of lead alone.

The relationships among lead exposure, SES-related risk factors, and neurodevelopment are likely to be quite complex. Indeed, while SES might modify the association between lead and neurodevelopment, the converse might also be true. The plausibility of this hypothesis is supported by evidence that lead exposure impairs the capacity for structural and functional plasticity in response to a later insult. For example, in rats, early lead exposure increased the motor impairments produced by a subsequent photochemically-induced ischemic stroke in the hind limb sensorimotor parietal cortex (Schneider and DeCamp, 2007). Lead exposure also disrupts the reorganization of the rat barrel field somatosensory cortex following whisker follicle ablation, leaving clusters of denervated neurons that remain active but dysfunctional (Wilson et al., 2006). These examples raise the possibility, discussed in the next section, that early lead exposure modifies associations among factors within a child's developmental context, most importantly associations between these factors and neurodevelopment. The assumption that these associations are completely independent of lead provides the basis for treating such factors solely as potential confounders.

Conceptual and analytical issues germane to the role of SES in lead neurotoxicity

This section raises several questions about the way in which SES and related factors have been conceptualized in lead studies: Does the way in which we adjust for SES adequately reflect its role(s) in the causal nexus? Are we mistaking effects of lead for effects of SES, thereby underestimating the role of lead? Are we adequately representing time-varying aspects of SES and the social environment? Does lead exposure contribute to a child's SES?

As noted, in lead studies, the only role traditionally attributed to SES has been that of a potential confounder of the association between a lead biomarker and a child outcome such as IQ. What are the implications of this? All of the IQ variance that is shared by SES and lead has, in effect, been considered to belong to SES. This is conservative, as it assumes that lead is not responsible for any of the SES-associated variance in IQ. It seems more likely that at least two components of the IQ variance shared by SES and lead must be distinguished. First, SES conveys information about factors such as parental IQ, stimulation opportunities, access to medical care, quality of schools, neighborhood characteristics, etc. These are presumably largely independent of lead, although the possibility that this is not invariably true is discussed later. Second, SES also conveys information about the lead exposure opportunities in a child's proximal environment and thus the child's internal lead dose. Therefore, the IQ variance that is shared by lead and SES should be partitioned into the portion of SES that is a proxy for lead exposure/dose and the portion of SES that is not causally related to lead but only correlated. For the purposes of reducing bias due to confounding, it is only the latter area that we need be concerned about and which should be represented by a term in the model. Inclusion of a term that also represents the portion of SES that reflects lead exposure/dose would result in over-adjustment, i.e., produce an underestimate of lead's association with IQ.

In principle, the residuals of the regression of SES on measurements of potential sources and pathways of lead exposure in the environment would provide an estimate of the IQ variance that is shared by lead and SES but that is causally unrelated to lead sources and pathways. This strategy is applied in nutritional epidemiology studies in order, for example, to obtain an estimate of nutrient intake that is independent of energy intake (total caloric intake) (Willett, 1998). In a toxicologic setting, an example is the use of the residual method to obtain an estimate of dietary intake of arsenic that was independent of water arsenic concentration (Kile et al., 2007).

Given this conceptualization, is it possible that, as a result of the way in which SES is handled analytically, we might be attributing to SES what is predominantly a lead effect on health

outcomes? A recent study of cardiovascular reactivity in children provides evidence that the usual practice might be resulting in such errors of inference. Gump and colleagues (2007) showed that the oft-observed association between SES and cardiovascular reactivity in children was severely attenuated when adjustment was made for the children's blood lead levels, raising the possibility that lead mediates this association. This is perhaps not surprising. Being abstract, SES does not "cause" anything, and any associations it has with health outcomes must be explained by one of its proximal constituents. The study of Gump et al. suggests that differences across SES strata in exposures to common contaminants such as lead might contribute to socioeconomic disparities in certain health disorders.

The models typically fit in lead studies also fail to capture potentially important time-varying processes. We appear to assume that altered child health is the only effect of a child's lead exposure, ignoring the possibility that it might also alter other SES-related aspects of the child's developmental system as it evolves over time. The transactional model of child development emphasizes reciprocal, bidirectional processes of that system such that a child's environment changes over time, in part in response to the child's behaviors and characteristics (Sameroff and Mackenzie, 2003). For example, a child with a difficult temperament might elicit quite different behaviors from a parent than does a child with an easy temperament. This parenting might, in turn, exacerbate the child's behavioral difficulties, in turn eliciting even less positive parenting. The eventual result of this cycle might be child behavior that is sufficient to meet criteria for ADHD, conduct disorder, or some other diagnosis. This is relevant to lead studies because increased exposure has been associated with less optimal behavior in very young children (Sciarillo et al., 1992; Wasserman et al., 1998) and with increased aggression, oppositional behaviors, and juvenile delinquency in older children (Needleman et al., 1996; Needleman et al., 2002). What happens to the developmental environment as a lead-exposed child ages has largely been ignored, specifically the possibility that parenting behaviors changed over time, at least in part, as a result of a child's early lead exposure. If this is so, parenting behavior measured at the later time, when child outcome is classified, should be considered not only as a potential confounder but also as a mediator of the association between early lead exposure and late child outcome. Treating concurrent parenting solely as a confounder, which implies a belief that lead is not causally involved in any of the child outcome variance that they share, would produce an underestimate of lead's contribution to that late outcome. This is a model specification error and would result in an error of inference.

We should also consider the possibility that in addition to SES being a proxy for lead exposure, it might also be, in part, a result of lead exposure. Low SES is associated with an increased prevalence of various psychiatric disorders, for which two explanatory models have been proposed. The social causation model posits that the adversities and stressors associated with low SES are responsible, while the social selection model posits that over time individuals who are genetically predisposed to psychiatric disorders drift downward into lower SES strata or fail to rise out of them. These models are not mutually exclusive, and the evidence suggests disease-specificity. The social causation model best accounts for the distribution of depression, anxiety, and personality disorders, and the social selection model best accounts for the distribution of schizophrenia and other psychotic disorders (Dohrenwend et al., 1992; Johnson et al., 1999; Ritsher et al. 2001).

In lead studies, SES has traditionally been handled in a manner consistent with the social causation model. The myriad developmental risk factors associated with low SES have been thought to be responsible for an apparent association of poor outcome with increased lead exposure (i.e., as a result of residual confounding) or to exacerbate lead neurotoxicity (i.e., as a result of effect modification). Could social selection also be at work? As noted previously, certain genetic polymorphisms appear to confer increased susceptibility to lead, and the possibility has been raised that lead adversely affects gene expression. The resulting lead-

associated impairments in aptitude, educational achievement, and occupational possibilities could cause a family to drift downward in SES over generations. To the extent that this occurs, low SES would be a proxy for vulnerability to lead. If so, controlling for SES in the typical manner would, again, produce an underestimate of the extent to which lead is, ultimately, responsible for poor outcomes. Achieving a full characterization of lead's contributions to the burden of disease thus requires moving beyond cross-sectional analyses of individual generations to consider possible trans-generational effects. This poses a formidable challenge but one that must be addressed if we are to accurately estimate the burden of lead-associated disease on a population level.

Summary and Conclusions

Some epidemiological evidence suggests that the neurotoxicity of lead is modified by SES, such that children from less advantaged families are at greater risk. Because of the omnibus nature of SES, however, it is not clear which biological, psychological, or sociological factor (s) subsumed by it are responsible. Therefore, deconstructing SES and identifying the factor (s) is an important research need, one that must be met in order to design and target secondary prevention programs to mitigate the neurodevelopmental effects of lead.

Our models likely fail to capture salient aspects of the different roles that SES plays in the causal nexus. Adjusting for SES in the usual manner when estimating the association between lead and neurodevelopment most likely results in over-adjustment to some extent because a portion of the outcome variance that SES shares with lead reflects exposure opportunities and, thus, should not be allocated to SES. In the extreme case, an association observed between SES and a health outcome might be an unrecognized lead effect. From a trans-generational perspective, a family's SES might reflect a lead-associated downward drift over time due to an enhanced susceptibility due to genetic or epigenetic processes.

Our models typically fail to take account of the transactional nature of development, specifically the possibility that lead exposure affects not only the child but, indirectly as a result of the altered stimulus properties the child provides, factors that contribute to the child's subsequent developmental context. Treating such factors solely as potential confounders and ignoring their potential role in mediating lead's association with child outcome will result in erroneous inferences about that association.

The distinction between independent and dependent variables becomes blurred when we consider a child's development and its context as a system that changes over time. Cross-sectional analytical methods, i.e., those that estimate associations among variables based on a "snapshot in time," likely fail to represent accurately the interplay among the direct and indirect influences generating the changes. To achieve a more holistic appreciation of these issues, we need methods that can model more than a single relationship at a time, methods that are not limited, as multiple regression is, to an "equation-by-equation" approach. Ecologists studying the complex dynamics of species distribution, population sizes, and the effects of invasions have developed approaches to address complex systems. It might be fruitful to consider whether such approaches, or aspects of them, could be applied to neurotoxicological data sets. In the epidemiologic literature, new methods for drawing causal inferences from observational data, such as structural nested models, appear useful in estimating effect modification by time-varying covariates (Robins et al., 2007).

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