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Environmental lead exposure and children's cognitive function

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Summary

Recent research has substantially increased knowledge about the effects of low-level lead exposure on children's neurobehavioral development. This update article focuses on two specific areas of recent research: low-level effects on cognitive function, and results from experimental and observational studies designed to prevent or reverse the damaging effects of lead on intellectual development, either through chelation therapy or micronutrient supplementation. Taken as a whole, these studies suggest that there is no safe level of lead exposure for young children and, although small, these effects are enduring and possibly permanent.

Keywords

Lead; Cognition; Child; Intelligence; Nutrition

Lead (Pb) is a naturally occurring element that has been mined for several millennia and used to create products that meet a broad range of human needs. Its value as a gasoline additive, as a pigment for paints and glazes and its usefulness in many other products has led to widespread distribution of lead in the environment. Along with widespread use of lead has come substantial human exposure. Unfortunately, lead adversely affects nearly every system in the human body and appears to be particularly harmful to the developing nervous system [1]. Although symptoms of lead poisoning were described more than 1,000 years ago, only in the last 25–30 years has it become widely accepted that lead exposure at levels that do not produce overt symptoms can cause subtle and possibly permanent damage to children's cognitive functioning.

In the following review we provide an update on recent research into the neurobehavioral effects of low-level pediatric lead exposure. The review is organized around four basic questions that guide much of the research in this area. These questions are: (1) what are the health effects of pediatric lead exposure; (2) is there a level of exposure that is safe for the developing brain; (3) are lead effects permanent; and (4) are there effective interventions for preventing, reducing, or reversing lead-related neurobehavioral damage? Substantial progress has been made toward answering each of these questions. Taken together, the

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answers suggest that there may be no safe level of lead exposure and that primary prevention may be the only effective strategy for protecting children from this widespread toxin.

Health effects of pediatric lead exposure

More than a decade ago, the U.S. Centers for Disease Control and Prevention (CDC) identified lead poisoning as “one of the most common and preventable pediatric health problems” [1]. As a result of industrialization, lead remains one of the most prevalent toxic metals in the environment. Infants and young children are at particularly high risk of exposure because they engage in frequent hand-to-mouth behavior and spend a great deal of time where lead particles from deteriorating paint, gasoline emissions, and smelting operations are deposited (e.g. household floors exposed soil). Other prominent sources of exposure include inhalation of emissions from vehicles using leaded fuel, ingestion of water conveyed through lead plumbing, and consumption of food that has been stored in lead-soldered cans or lead-glazed ceramics. Dozens of other sources of lead pose a threat to children, depending on their geographical location and their family’s cultural practices, livelihood, and hobbies [1]. Also, because on a kilogram per kilogram basis children drink more fluids, breathe more air, and eat more food than adults, they will accumulate more lead than an adult who is exposed at a similar level.

Ingested or inhaled lead is first absorbed into the blood stream, then gets stored in soft tissue, and is eventually stored in bone and teeth where it can reside for a decade or more. High levels of lead exposure result in clinically observable symptoms, but controversy remains about what might be a safe or acceptable blood lead concentration for children. Extremely high lead exposures that cause a child’s blood lead level to rise to about 100 micrograms per deciliter (μg/dL) of whole blood result in very severe and readily observable symptoms, including convulsions, coma, and even death [2]. Substantially lower blood concentrations of 50 μg/dL or more can cause swelling of the brain, colic, anemia, and kidney damage [2]. Children in the U.S. who present with a blood lead concentration of 45 μg/dL or greater are referred for chelation drug therapy to rapidly lower their lead levels in hopes of avoiding the most serious of these health effects. Blood lead concentrations of 30 μg/dL or more can interfere with hemoglobin synthesis and vitamin D metabolism and can slow nerve conduction. Accompanying these high exposure levels are mild to profound intellectual deficits.

Neurobehavioral effects of low-level lead exposure

Low-level lead exposure typically refers to blood lead at concentrations less than 30 μg/dL in asymptomatic children. The existence and nature of effects associated with such exposures has been the focus of much research and also a source of considerable controversy [34]. Early attempts to demonstrate an association between low-level exposure and children’s cognitive function employed cross-sectional research designs in which intelligence test scores and blood lead concentrations are measured at the same time, typically after age 5 or 6 years [5]. Because there is a myriad of genetic and environmental factors that influence cognitive development, independent of lead exposure, additional measures are also typically taken to quantify the influence of other factors that affect

cognitive development and that can confound the relation between children's intelligence and their blood lead concentration. Parental measures such as maternal intelligence, education, socioeconomic status, and provision of an intellectually stimulating home environment, and child variables such as pregnancy and birth complications, birthweight, and gestational age, can be used to provide for statistical control of possible confounders, though care must be taken not to include variables that are consequences, rather than antecedents, of lead exposure. Pocock and colleagues conducted a comprehensive meta-analysis of cross-sectional studies published prior to 1994 and concluded that an increase in blood lead concentration in children from 10 to 20 μg/dL is associated with a 1 to 2 point decline in their score on an intelligence test [5]. An important limitation of most cross-sectional studies is that blood lead is measured at only one point in time during middle or late childhood. However, blood lead levels typically peak at about 2 years of age and then decline in older children as they engage in less frequent hand-to-mouth behavior.

Because the half-life of lead in blood is approximately 35 days, a single blood lead measure during childhood might not accurately reflect the magnitude of exposure at an earlier age point, and this early exposure might have the strongest effects on brain development and function. In a review of more recent cross-sectional studies, Koller et al. [4] found that the results from cross-sectional studies were inconsistent and, considering their methodological limitations, concluded that cross-sectional studies are of little value in the debate about the effects of low-level lead exposure. For the purpose of determining what might be a safe level of exposure, it is important to estimate the child's maximum blood lead concentration at any age. Because the maximum exposure nearly always occurs at an age before intelligence can be reliably measured, cross-sectional designs do not allow one to estimate what is a safe maximum blood lead level.

Several prospective cohort studies of early lead exposure were initiated in the late 1970's and 1980's. These studies followed children, typically from birth, to ascertain blood lead concentrations and measure neurobehavioral performance throughout infancy and childhood. The primary outcome examined in these studies was children's cognitive performance during early childhood, as measured by a standardized test of intelligence. Other outcomes examined in one or more studies include performance on tests of visual-spatial representation, memory, reasoning, executive functioning, and social-behavioral conduct. Cohort studies were initiated in Boston [6] and Cincinnati [7] in the U.S., Pristina and Mitrovica in the former Yugoslavia [8], in Mexico City [9], and Port Pirie [10] and Sydney [11] in Australia. Also, though originally designed to examine the effects of prenatal substance abuse, a cohort study conducted in Cleveland also examined lead exposure and children's cognitive development [12]. Among the cohort studies, the Boston study was unique in that the average blood lead concentration of participants was consistently below 10 μg/dL [13], which contrasts with the higher lead levels found in Cincinnati [14], Cleveland [15], Sydney [11], and in Port Pirie [16]. In the Yugoslavia study, approximately half of the subjects (the "exposed" group) resided near a lead smelter, a refinery, and a battery manufacturing plant, while the comparison town (the "unexposed" group) had little environmental exposure, thus blood lead concentrations ranged considerably from 1 to 70 μg/dL in that study [17]. Four of the six cohort studies reported that low-level exposure, measured as cumulative exposure or exposure at a particular age during infancy was associated with lower intelligence test

scores. Moreover, every study that reported adverse lead effects also replicated their findings at 2 or more testing ages. The studies conducted in Sydney [11,18] and Cleveland [15,19] found no statistically significant associations. Taken together, the cohort studies indicate that an increase in blood lead from 10 to 20 μg/dL is associated with a small but statistically significant decrease in children's intelligence test scores of about 1–3 points [5,20,21]. When the results of these studies began to emerge, the CDC evaluated the available evidence and concluded that a blood lead concentration as low as 10 μg/dL in children was a cause for concern.

Is there a safe level of exposure to lead?

Because the evidence about effects of lead at concentrations below 10 μg/dL was insufficient at the time, the CDC report explicitly acknowledged that 10 μg/dL could not be considered a safe exposure level, labeling it instead a "level of concern" [1]. The report also noted that no existing studies provided evidence for any sort of threshold blood lead concentration below which the effects are nonexistent. The results of the Boston study [13] were published subsequent to the CDC report, and it was the only study that focused on a cohort of children with blood lead concentrations consistently below 10 μg/dL. Surprisingly, the effect size reported for this very low exposure cohort was larger than for the other more highly exposed groups. The Boston cohort showed that a 10 μg/dL increase in blood lead concentration measured at age 2 years was associated with a 5.8 point decline in the intelligence test score. Using these data, Schwartz [20] conducted a threshold analysis and found no support for the existence of a threshold below which there were no neurobehavioral effects, at least down to 1 μg/dL of blood lead. The relatively small sample size available for this analysis weakened the conclusion, but the results supported the view that even very low lead levels are a cause for some concern. An attempt to gather additional evidence about the effects of blood lead levels less than 10 μg/dL was carried out using data from a cross sectional study of more than 5,000 U.S. children ages 6–17 years who participated in the third National Health And Nutrition Examination Survey (NHANES III). Lanphear and colleagues [22] reported lower cognitive performance as a function of increasing blood lead for children with very low blood lead concentrations. Specifically, across the range of 0 to 5 μg/dL, children with higher blood lead concentrations performed more poorly on tests of nonverbal reasoning, short-term memory, arithmetic, and reading skills. Although the sample size was large, data were not available to control important potential confounders, such as maternal intelligence and intellectual stimulation in the home environment [23]. Moreover, as noted previously, the cross-sectional design allowed only a single concurrent blood lead measure during later childhood and it is likely that the children had much higher lead concentrations during infancy.

Concerns about adverse neurobehavioral effects from very low level lead exposure were heightened by the results of a recent prospective cohort study of children living in Rochester, NY, the majority of whom had maximum blood lead concentrations less than 10 μg/dL through 6 years of age. Canfield and colleagues reported that intelligence test scores, measured in the same children at both 3 and 5 years of age, were inversely associated with their lifetime average blood lead concentrations [24]. More specifically, after controlling for 9 pre-specified covariates, they found that as lifetime average blood lead levels increased from

1 to 10 μg/dL, children's intelligence test scores declined by an estimated 7.4 points. To directly address the question of whether blood lead concentrations less than 10 μg/dL adversely affect children's intellectual functioning, a secondary analysis was conducted using only the subsample of 101 children who had blood lead levels less than 10 μg/dL at every assessment (i.e., at 6, 12, 18, 24, 36, 48, and 60 months of age). Even in this restricted subsample of children with very low exposure throughout infancy and early childhood, there was a statistically significant decrease in intelligence test scores as lead levels increased from 1 to 10 μg/dL. Moreover, the estimated effect size was larger in this subsample than in the full sample. As confirmed using semiparametric regression modeling, the dose-effect relation appeared to be nonlinear, such that the effects of lead appeared to be proportionally greater at concentrations below 10 μg/dL than above that value. The findings from the Rochester study appeared to corroborate and extend the findings from the Boston cohort by showing that for the only two studies that were based on very low exposure cohorts, both reported larger lead effects than did studies based on more highly exposed children. Furthermore, after publication of the Rochester study, Bellinger and Needleman [25] reported a re-analysis of data from 48 children from the Boston study whose blood lead concentrations were always less than 10 μg/dL (i.e., at 6, 12, 18, 24, 57, and 120 months of age). Remarkably, data from this study mirrored those from the Rochester study in that the estimated decline in intelligence was greater for this subsample of 48 children than it was for the full sample. Moreover, the magnitude of the effect size for lead was nearly identical to that estimated from the Rochester study.

Although the consistency of the findings from these two studies was noteworthy, both studies were limited by a small sample size. When combined, they included fewer than 150 children with peak blood lead concentrations less than 10 μg/dL. Moreover, in neither study was there a sufficient range of blood lead values to describe a dose-response relation across the 10 to 30 μg/dL, which was the focus of the cohort studies. In response to these limitations, the investigators of the longitudinal cohort studies of pediatric lead exposure were invited to contribute their data towards a pooled analysis designed to examine the association between intelligence test scores and blood lead concentration, especially for children who had maximal measured blood lead levels less than 10 μg/dL. Data were collected from 1,333 children who participated in seven international population-based cohort studies, where participants were followed from birth or early infancy until 5–10 years of age. The full-scale IQ score was the primary outcome measure.

For the entire group of children, the geometric mean blood lead concentration peaked at 17.8 μg/dL when children were about 2.5 years and then declined to 9.4 μg/dL by 5–7 years of age. A total of 244 (18%) children had a maximal blood lead concentration of less than 10 μg/dL maximal. After covariate adjustment there was a statistically significant inverse association between blood lead concentration and IQ score. Estimated using a loglinear model, an increase in concurrent blood lead levels from 2.4 to 30 μg/dL was associated with a 6.9 IQ point decrement (to avoid influence of extremely high or low lead values, only data from the 5^{th} to the 95^{th} percentile were included in the model fit). The decline in IQ associated with a blood lead increase from 2.4 to 10 μg/dL was 3.9 points. In comparison, blood lead increases from 10 to 20 μg/dL and 20 to 30 μg/dL were associated with IQ declines of only 1.9 and 1.1 points, respectively. Thus, what was true for the Rochester and

Boston studies individually was reflected in the pooled analysis also. The slope of the dose-response function was steeper at lower blood lead levels.

Although the exact mechanism for this seemingly counterintuitive dose-response relation is not known, if the slope of the blood lead-intelligence relation is negative, even for children who never had a blood lead measure as high as 10 μg/dL, then it suggests that there is no safe level of lead exposure for young children. Moreover, the nonlinear relation suggests that proportionally more damage may be done by the initial exposure to lead than by a subsequent exposure of equal size that happens after the primary damage has occurred. Both of these conclusions argue for the importance of primary prevention.

Are the effects of early lead exposure transient or permanent?

It is possible that lead exposure during infancy disrupts cognitive functioning during early childhood, but that children recover function later in life. This issue has been addressed using a number of methodologies. A simple approach to this question is to follow the children who participated in the longitudinal cohort studies into adolescence when intelligence test scores become more stable predictors of adult IQ. This approach has been used for the Boston and Port Pirie cohorts. Children in the Boston cohort were re-assessed at age 10 years and it was found that blood lead concentration at age 2 years was predictive of 10-year intelligence and achievement test scores [13]. Even though their lead levels had declined, their blood lead concentration at age 2 remained predictive of their later performance. Indeed, the effects of lead appeared stronger than they were at the previous assessment at age 5 years [26]. In the Port Pirie cohort, children were re-assessed for intelligence at 11 to 13 years of age. Similar to what was found at ages 2 and 5 years, lead exposure during infancy was predictive of cognitive function during early adolescence [16]. These results suggest that lead effects are enduring.

A more specific question about enduring effects was investigated in the Port Pirie cohort data. Tong and colleagues [27] sought to learn whether changes in an individual child's blood lead concentration over time was linked to an improvement in cognitive performance. As noted above, blood lead concentration tends to increase from infancy through toddlerhood and then decrease significantly after about age 3 years. If the effects of lead are transient and dependent primarily on concurrent exposure then cognitive function should increase as lead levels subside, and they should increase most for children whose lead levels declined most. Tong and colleagues tested this hypothesis by asking whether the degree of cognitive improvement from the time of the 2-year or 4-year cognitive assessments to the time of the 11- to 13-year assessment was linked to the amount of decline in blood lead. They reported no association between declining blood lead concentrations and changes in IQ scores across this age period.

Chelation therapy and recovery of cognitive function

One hope for the treatment of highly exposed children is that chelation therapy can be used to rapidly reduce body lead burdens and allow them to avoid at least some of the intellectual dysfunction caused by lead. Evaluating the empirical basis for this hope has been the subject of the Treatment of Lead-Exposed Children study (TLC), a multi-site randomized, double-

blind, placebo controlled trial of 780 children between the ages of 12 and 33 months with a confirmed blood lead concentration between 20 and 44 μg/dL [28]. The objective of the study was to determine if administration of succimer (dimercaptosuccinic acid) in these children has neurodevelopmental benefits.

At baseline, children in the TLC trial were given tests of intelligence, behavior, and neuropsychological function, and then randomized to treatment or placebo. Treatment consisted of up to three 26-day courses of succimer, administered orally. After 3 years of follow-up, children's cognitive function was reassessed. Although blood lead concentrations were significantly lower in the treated group, scores on cognitive, behavioral, and neuropsychological tests were similar in both groups, suggesting that according to this protocol succimer does not reduce or reverse the effects of earlier elevated blood lead concentrations [29]. A second round of cognitive assessments was conducted when children were 7 years old, an age when cognitive tests are much more stable predictors of adult functioning [30]. Consistent with the earlier findings, succimer therapy was found to have no benefit to cognitive, behavioral, or neuromotor development. The implications of the TLC trial are clear: chelation therapy with succimer, as currently prescribed, cannot be recommended for young children with blood lead concentrations in the range studied [30].

The rigorous and highly focused design of the TLC trial demanded a highly focused question and produced an extremely valuable albeit necessarily narrow conclusion. A number of additional questions remain; primary among them is whether a different chelation protocol might have produced different results. It appears that the TLC protocol might not have reduced the treated children's blood lead levels enough to affect their cognitive function to a measurable degree. For example, although the protocol succeeded in producing a rapid and significant decrease of 11 μg/dL in the succimer group one week after treatment, this effect was reduced to only 2.7 μg/dL after only 12 months. By the age of 7 years the average blood lead levels of treated children did not differ from those receiving the placebo (both were 8.0 μg/dL). A more aggressive regimen of chelation therapy almost certainly would have caused a larger group difference in lifetime average blood lead levels. Whether such a regimen would be deemed safe and whether it would produce measurable long-term differences in children's cognitive outcomes remain open questions. Given the available evidence however, the results from the TLC trial underscore the importance of taking effective environmental action to prevent children from being exposed to lead.

Nutritional interventions for lead exposure

An additional approach to preventing or reducing the toxic effects of lead exposure in children is through nutritional intervention. Although primary prevention is optimal, it may not be feasible when exposure is persistent and ubiquitous or when it involves sources not under the control of the caregiver or community. Worldwide, the awareness of effects of lead on health is growing but many countries do not have policies or infrastructures in place to protect their most vulnerable populations. As demonstrated by the TLC trial, even in the United States where resources dedicated to the treatment of lead-exposed children are considerable, short-term chelation therapy is ineffective, and is not appropriate for persistent, low-level exposure.

Animal and epidemiological studies in humans provide strong evidence for a relationship between nutritional status and markers of lead exposure. Most notably, two recent reviews summarize findings on iron-lead interactions, including some early supplementation trials [3132]. Also notable is the longitudinal assessment of iron deficient (ID) children from an urban clinic [33]. This study demonstrated that ID at one clinic visit was predictive of elevated blood lead subsequently. Ballew and Bowman [34] reviewed studies on the relationship between calcium intake/status and lead exposure. The relationship between zinc status and lead toxicity in humans is not well characterized, but zinc seems to play an important role in preventing or reversing the inhibitory effects of lead on key hemesynthesis enzymes [35], and it may also prevent accumulation of lead in soft tissues [36].

Although originating mostly from animal work or cross-sectional studies in humans, many of these findings have been taken to suggest that nutritional interventions could successfully reduce blood lead concentrations in children. Supplementation with iron, zinc or calcium, especially in children consuming diets with inadequate supplies of these nutrients has been proposed as a possible solution to the problem of pediatric lead exposure. Several trials have been conducted since the early 1990s, both in infants and older children. Two studies examined the efficacy of calcium, three of iron, and one of zinc. All studies investigated the effects of supplementation on blood lead concentration, two on cognitive function and/or behavior, and in one study iron was used as an adjunct to chelation therapy.

Evidence from iron supplementation studies

Ruff et al. [37] examined the change over 7 weeks and 6 months in blood lead and cognitive index of children aged 13–87 months who were treated with either 1) calcium disodium edetate (EDTA) at least once, 2) 6 mg/kg/d iron, 3) both EDTA and iron, or (4) not treated at all. Treatment was not randomized; EDTA was given based on the lead mobilization test and iron was given only in case of ID (60% children). There were no main effects of EDTA on cognition and no interactions with iron supplements. Blood lead levels declined and cognitive performance improved over time. There was no difference in the magnitude of change in either lead or cognitive index between children who were ID versus non-ID at enrollment.

Costa Rican infants (n = 165; 13–24 months) were randomized by anemia status to intramuscular (IM) iron, oral iron or oral placebo for 1 week [38]. Subsequently, iron-sufficient children were given placebo for 3 months, while all others received oral iron. The mean blood lead level at baseline ranged from 5.8 to 36.9 μg/dL; 57.6% had blood lead concentrations > 10 μg/dL. At the end of supplementation, non-anemic infants who began the study with depleted iron stores showed the most marked decline in lead levels (1.2 μg/dL, $p < 0.01$), followed by non-anemic and anemic ID children. The iron sufficient group had an increase in blood lead of 1.0 μg/dL after receiving placebo. Change in serum ferritin (SF) was closely associated with the change in blood lead concentration.

In a school-based supplementation study, 602 Mexican children (aged 6 to 8 years) were randomized to receive 30 mg iron, 30 mg zinc, both, or a placebo daily for 6 months. Baseline blood lead was 11.5 ± 6.1 μg/dL; 51% had lead levels ≥ 10 μg/dL. Children were

followed-up at the end of treatment and after another 6 months without supplementation. Iron supplementation (alone or with zinc) was associated with a greater decline in blood lead (1.7 ± 2.6 μg/dL) compared to those receiving no iron (1.3 ± 2.2 μg/dL, $p < 0.05$) [39], although these differences did not remain statistically significant at long-term follow-up. Iron had no effect on parent or teacher ratings of behavior [40] and did not produce consistent changes in cognitive performance [41]. Baseline lead status (< or ≥ 10 μg/dL) did not modify the effects of iron on any of these outcomes.

Evidence from calcium supplementation studies

The possible effect of calcium intake on children's blood lead concentrations has been examined in studies using either fortified formulas or the direct administration of calcium supplements. In one study, the blood lead concentrations of two groups of infants 3.5–6 months old were compared after 4 and then 9 months of consuming standard iron-fortified formula with or without additional calcium and phosphorus [42]. The standard formula contained 465 mg calcium and 317 mg P/L, whereas the supplemented formula had 1,800 mg calcium and 1,390 mg P/L. Of the 103 infants randomized to treatment, 81 completed the study. The higher calcium intake in the supplemented group helped delay an increase in blood lead after 4 (83% *vs.* 42% rise) but not after 9 months. At the end of the study the two groups had similar median blood lead levels.

In another study, 88 children aged 12–72 months were randomized to receive placebo or calcium supplements for 3 months [43]. Randomization was stratified by age (12–35 and 36–72 months). Level of calcium supplement was adjusted based on daily dietary recall to achieve a calcium intake of 1,800 mg/d. Blood lead was examined at the end of treatment and after another 3 months without supplementation. There were no group differences at either time point despite significantly higher calcium intake in the supplemented group.

Evidence from zinc supplementation

The study of Mexican children cited above also examined the effects of zinc supplementation on blood lead levels, behavior, and cognitive performance and found no main effects, either in the short or the long-term on blood lead [39], behavior [40], or cognition [41]. There were also no differences in the effects of zinc by baseline lead status.

Discussion of supplementation studies

Studies examining the effects of micronutrients on children's blood lead concentrations are scarce; some are not randomized, and some are underpowered. Thus, they offer limited evidence of nutrition-related alterations in children's blood lead concentrations. Additional research is needed to clarify whether the effectiveness of micronutrient supplementation depends on factors such as the age and duration of both the exposure and the supplementation, the total body lead burden, and on the child's initial nutritional status. In the Costa Rican study, for example, changes in SF were related to changes in blood lead concentration but it was the infants with depleted iron stores, rather than those with ID or ID anemia, that had the largest change in blood lead levels [39]. The basis for such an effect is unclear and requires further study. Similarly, the effect of calcium may be age-dependent.

Calcium supplementation of infant formula slightly delayed increases in blood lead concentration when the infants were 7.5–10 months, but not when they were 12.5–15 months of age [42]. The onset of walking at about 12 months of age puts children at greater risk of coming into contact with lead, possibly diluting the effect of calcium supplementation. Supplementing older children with calcium also appeared ineffective for lowering their blood lead concentrations, but that finding was from a study with insufficient power to detect small treatment effects [43]. We are aware of no evidence that zinc supplementation can alter blood lead levels, but future research on micronutrient supplementation of lead-exposed children must be cognizant of these differential findings and work to clarify their basis.

Overall, these studies suggest that for school children lead toxicity may not be greatly affected by nutritional interventions alone. For infants and younger children, calcium, zinc or iron supplementation may be more promising as treatment or prevention of lead's toxicity, particularly for populations with inadequate intakes or stores of these nutrients. More randomized trials of micronutrients are needed to evaluate their relation to lead toxicity, especially because supplemented children would be expected to reap additional benefits of correcting nutritional deficiencies. Nevertheless, reliance on single nutrients for treating or preventing lead exposure is not a viable answer to this serious public health problem, pointing again to the importance of primary prevention.

The existing stand-alone nutritional interventions have shown limited effectiveness in reducing blood lead concentrations in children. However, adequately powered supplementation trials are needed to address the effectiveness of micronutrients in treating lead toxicity. It is also possible that calcium, zinc or iron supplementation in early childhood might delay or reduce age-related increases in blood lead. Moreover, nutritional supplementation of deficient children is also likely to have beneficial effects that are independent of any effect on blood lead concentration. Thus, the few existing studies of nutritional interventions in lead-exposed children have left many unanswered questions regarding the timing, duration, and dosage of supplementation that should be pursued with future trials.

Discussion

Acknowledging the limitations of observational study designs, evidence that very low level lead exposure adversely affects the neurobehavioral development of children is consistent and quite strong. These effects can be detected using nonspecific tests of general intelligence and achievement, and with tests designed to measure more specific cognitive functions. When data from all the existing longitudinal cohort studies that included substantial numbers of children with peak blood lead levels below 10 μg/dL are combined in a pooled analysis, the results suggest that there are small to modest-sized effects of lead exposure across the 0 to 10 μg/dL range [44], which is entirely below the currently accepted CDC and WHO levels of concern. Moreover, it appears that a given increase in lead may produce a greater amount of cognitive damage when a child's existing blood lead concentration is low (e.g., less than 10 μg/dL) than when it is higher than 10 to 15 μg/dL.

Although blood lead levels are lowered by chelation therapy, corresponding benefits to cognitive function have not been observed in randomized trials. This, along with results from longitudinal studies suggests that early lead exposure permanently harms children's cognitive functioning. It is possible, however, that the absence of cognitive benefits from the TLC chelation protocol could have been due to the small differences in lifetime average blood lead concentration between the groups, and that a more aggressive intervention might show some benefit.

The existing stand-alone nutritional interventions have shown limited effectiveness in reducing blood lead concentrations in children. However, adequately powered supplementation trials are needed to address the effectiveness of micronutrients in treating lead toxicity. It is also possible that calcium, zinc or iron supplementation in early childhood might delay or reduce age-related increases in blood lead. Moreover, nutritional supplementation of deficient children is also likely to have beneficial effects that are independent of any effect on blood lead concentration. Thus, the few existing studies of nutritional interventions in lead-exposed children have left many unanswered questions that should be pursued with future trials.

This update of the recent research on childhood low level lead exposure offers both encouragement and discouragement about our success at battling this long-time foe. It is discouraging that the amount of exposure needed to produce measurable adverse effects on children's cognitive functioning appears to be extremely low and that these effects appear to persist at least into early adolescence. It also disheartening to acknowledge our lack of success at treating the already-exposed child in a way that can reduce lead's adverse effects. It is encouraging, however, that the widespread elimination of leaded gasoline, lead plumbing, and lead-based paint have caused a dramatic decline in the average blood lead levels of children in much, although not all of the world. This affirms that pediatric lead toxicity is an entirely preventable problem and that by working to provide children with safer housing, freedom from exposure to industrial emissions and leaded gasoline, by continued efforts at public education in both industrialized and developing countries, and by reducing its unnecessary use, it is possible to remove lead exposure as a factor that limits children's opportunities to reach their full potential.

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