The "Lead Diet": Can Dietary Approaches Prevent or Treat Lead Exposure?

Katarzyna Kordas, PhD

Although blood lead levels (BLLs) have been declining in the US for decades, pediatric lead exposure is an ongoing public health issue.[1] Given the well-documented cognitive deficits at BLLs <10 μg/dL, in 2012 the Centers for Disease Control and Prevention (CDC) called for renewed efforts for the primary prevention of any lead exposure in children.[2] Recent events in Flint, Michigan, also have served to refocus the public and health professionals on the seriousness of lead exposure. According to CDC statistics for years 2010-2014, 0.5%-0.6% of children (13 000-26 000) had confirmed BLLs ≥10 μg/dL and 4%-6% (106 000-282 000) ≥5 μg/dL.[3] Only 10%-18% of all children in the US aged <6 years, however, had a BLL test during that period. A recent study based on a national clinical laboratory database reported an overall prevalence of BLLs ≥10 μg/dL at 0.58% and ≥5 μg/dL at 2.95% for the years 2009-2015, with certain US states and cities particularly affected.[4]

See related article, p •••

Whether through contaminated water, lead-based paint, or a combination of sources, the problem of lead exposure resurfaces periodically in US municipalities like Flint, Michigan, Washington, DC, or Buffalo, New York,[5-7] highlighting issues of aging infrastructures, under-resourced communities, poor decision making, and environmental injustice. Overlaid on these systemic causes are personal poverty and complex family situations, potentially creating multiple threats to optimal child health and development, including factors such as poor diet or low developmental stimulation.

Parents and frontline health workers often are left to figure out how to help affected children, posing questions regarding effective interventions. Because dietary approaches seem relatively easy to implement compared with, for example, lead abatement or replacing old plumbing infrastructure, the conversation often turns to dietary recommendations. The 2012 CDC report highlights the role of pediatricians in educating families on nutrition as one primary prevention approach.[2] It should be emphasized that the prevention of lead exposure among vulnerable populations is the best solution to this problem and that intervening in exposure via dietary approaches does not address the root cause. Furthermore, careful examination of the links between nutrition (nutritional status, nutrients, diet) and lead exposure reveals limited and tenuous evidence.

BLL	Blood lead level
CaT1	Calcium transport protein 1
CDC	Centers for Disease Control and Prevention
DMT1	Divalent metal transporter 1
RCT	Randomized controlled trials

It is important for pediatricians, public health workers, and researchers to understand the state of the evidence so that recommendations to affected communities can be formulated appropriately. This is particularly important in the face of crises such as Flint, Michigan, which lend understandable urgency to the needs of frontline health workers to offer concrete guidance to anxious families.

This commentary will briefly review the state of the science, critically appraise the quality of the evidence, and highlight research gaps. A systematic and exhaustive review of the literature is beyond the scope of this commentary. Publications included in the review were identified through searches in PubMed via use of key words such as "diet," "nutrition," and "nutrient" in combination with "lead" and "blood lead." Reference sections of publications were scanned for further sources of information.

My objective is to create a deeper awareness of the existing evidence and, based on this body of work, a reasonable expectation with regard to the effectiveness of dietary approaches for children exposed to lead. The evidence is first organized by type of dietary component (for example, specific nutrients), followed by a discussion of the potential for prevention of exposure vs lowering of already-elevated BLLs. Because each nutrient-based study may include findings with respect to nutritional status or intake (and therefore different aspects of nutriture and metabolism), it is important to caution that studies of underlying nutritional deficiencies may produce different findings from evaluating intake. I will focus on the literature related to children to provide an accurate reflection of the state of evidence in the population group to which current recommendations apply. When data from studies with human children or adults are scarce, animal-based studies are included. It is also important to acknowledge that exposure in utero may be a common scenario and that separate literature exists on potential links between diet, nutrition, metabolism, and lead exposure during pregnancy.

Current Recommendations

In 2002, the CDC published guidelines on the medical and nutritional management of children with elevated BLLs.[8] The

From the Department of Epidemiology and Environmental Health, University at Buffalo, Buffalo, NY

The author declares no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.01.069

nutrient/food-specific interventions contained in that document are to advise and encourage caregivers to provide children with an adequate intake of iron-containing foods, vitamin C-containing foods, and calcium. Specifically, to address the recommendation on iron-rich foods, the CDC promotes introducing pureed meats as soon as the child is developmentally ready and providing 1 serving of lean red meat per day to older children. For vitamin C-rich foods, the recommendation is to give 2 servings of fruit juices or fruits daily. To ensure adequate intake of calcium, 2 servings daily of dairy products or other calcium-rich foods are recommended. Supplements should only be given under supervision of a physician or a nutritionist, and in the case of iron, only when anemia or iron deficiency has been diagnosed.

The CDC document is careful to point out that "nutritional measures have not yet been proven to have a clinically important impact on elevated blood lead levels in children" (p. 61), and that the aforementioned recommendations are based on "generally accepted nutritional principles, as well as on the results of adult human, animal, or cross-sectional studies" (pg. 62).[8] As stated previously, evidence on the links between diet and lead exposure is limited—very few well-designed and conclusive studies on this subject have been published. Yet, given that dietary recommendations are made routinely to parents, it appears that the tenuous nature of the evidence has been lost. Therefore, it is important to emphasize that, based on currently available evidence, there is little to suggest that making dietary changes or adopting dietary measures would lower children's BLLs substantially.

Iron Status, Intake, and Supplementation

There is strong epidemiologic evidence that children's underlying nutritional deficiencies, particularly iron deficiency, are associated with elevated BLLs.[9] There is also good biological plausibility, because lead competes for absorption in the gut with several divalent metals. The divalent metal transporter 1 (DMT1) has been shown to shuttle both iron and lead across cell membranes.[10] Furthermore, when yeast cells are incubated in buffer containing lead but also low iron concentrations, lead absorption increases; conversely, lead absorption is reduced when greater iron concentrations are present, indicating that iron blocks the uptake of lead by the DMT1.[10]

Consistent with this finding, a longitudinal study of iron status at 2 clinic visits separated by approximately 1 year suggests that iron deficiency increases lead absorption in children,[11] but most of the evidence is cross-sectional. Work on polymorphisms in genes regulating the expression of proteins related to iron metabolism also suggests a modest but potentially causal association.[12,13] The DMT1, however, is not the only intestinal transporter used by lead to access the body. A DMT1-knockout study demonstrated that elimination of this transporter resulted in lower, but not completely reduced, absorption of lead.[14] It is also possible that instead of being causally related, iron deficiency and elevated BLLs share common behavioral or environmental risk factors, including the larger systemic issues referred to previously.[8] The recommendations issued by the CDC on the nutritional management of children exposed to lead are based on the premise that iron deficiency co-occurs with elevated BLLs in many population groups, with insufficient evidence to establish causal links.[8]

In a longitudinal, observational study, Schell et al[15] reported an inverse association between dietary iron intake at 3-6 months of age and 6-month BLLs, and between dietary iron intake at 9-12 months of age and 12-month BLLs, as well as rate of change in BLL from 6 to 12 months. In another study (cross-sectional), greater iron intake was associated modestly with lower BLL in preschool children.[16] Costa Rican children (13-24 months of age) with BLLs < 25 μg/dL and varying severity of iron deficiency and anemia were assigned nonrandomly to receive oral iron supplements for 12 weeks. Only children without anemia who had depleted iron stores (low serum ferritin) experienced a decrease in BLLs following iron supplementation, with no other groups benefitting.[17] In the same study, children with sufficient iron status received placebo drops. They had greater BLLs after 12 weeks compared with pretreatment, but this difference disappeared when initial BLLs were taken into account.[17]

Three randomized controlled trials (RCTs) of iron supplementation or fortification were conducted among pre- and school-aged children. One trial tested the efficacy of iron supplements (30 mg of ferrous fumarate for 6 months) in lowering BLLs in Mexican children with moderately high levels of exposure, but fairly low prevalence of iron deficiency, and showed little benefit.[18] Another evaluated the efficacy of iron-fortified rice (~15 mg iron as ferric pyrophosphate for ~4 months) against a control meal among Indian children with iron deficiency and found a reduction in the prevalence of BLLs ≥10 μg/dL in the group consuming iron-fortified meals.[19] Moroccan children (3-14 years old) received biscuits fortified with ~8 mg of iron ($FeSO_4$), ~ 41 mg of sodium EDTA (Na_2EDTA), both together, or placebo for ~7 months. Iron and Na_2EDTA each independently resulted in modest but statistically significant reductions in children's BLLs.[20]

The trials in Mexico and India enrolled children with similar BLLs (mean of 11.4 and 12.0 μg/dL, respectively), and Moroccan children had lower BLLs (adjusted geometric mean of 4.3 μg/dL). In contrast, 12% of the Mexican children, ~70% of the Indian children, and 32% of Moroccan children had iron deficiency. These trials represent mixed findings, and design differences among them prevent direct comparisons; however, they suggest the possibility that iron fortification may benefit children exposed to lead by effecting reductions in BLLs. These findings are fairly consistent with the observational literature but need to be confirmed in future studies along with other details, such as formulation, dosage, and timing (fasting or with food) of iron delivery. Furthermore, the additional iron may be most beneficial to children with moderate-to-high iron deficiency. This is an important consideration in the US context, where the prevalence of iron deficiency is likely to be similar or even lower than in the Mexican study. Finally, based on the totality of iron-related evidence, it is still difficult to recommend any changes to typical dietary intakes as the basis for treating or reducing lead exposure in children.

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017

An additional caveat in considering iron-based approaches for addressing lead exposure in children is understanding the role heme vs non-heme iron may play in improving iron status or potentially blocking the absorption of lead. The 2002 CDC guidelines recommend the consumption of pureed meats for infants and a daily serving of red meat for older children. Red meats are an excellent source of heme iron, whereas plant-based foods (and supplements) provide non-heme iron. Heme iron is absorbed and regulated through distinct mechanisms and is more bioavailable and used more efficiently than non-heme iron.[21] If followed, current recommendations would benefit iron status among children exposed to lead, but their direct impact on BLLs is likely to be limited because heme iron will not compete for absorption with lead by the DMT1. Food sources of non-heme iron may be more appropriate, but no evidence currently exists as to their efficacy in preventing the absorption of lead. In addition, non-heme iron often is accompanied in plant foods by absorption inhibitors such as phytates, which could limit how well iron interacts with lead.

Zinc Status, Intake, and Supplementation

The links between lead exposure and zinc deficiency have not been well studied in children or adults, partly because there are no good indicators of subclinical zinc deficiency. In young rats receiving lead acetate in drinking water (200 mg Pb/L), a marginal zinc diet (8 mg zinc/kg diet) resulted in greater lead concentrations in body tissues than a control diet (30 mg zinc/kg diet).[22] A cross-sectional study of 2-year-old Mexican children documented no difference in BLLs among those who were zinc deficient compared with those who were zinc replete.[23] Although zinc is a divalent metal and could be transported via the DMT1,[24] there is no indication that zinc competes with lead absorption by this transporter. Intestinal zinc transporters (ZIP4 is responsible for increasing and ZnT for lowering cellular zinc concentrations) are expressed along the entirety of the gastrointestinal tract and are the primary mode of zinc transport.[25] There is no indication, however, that lead uses these transporters for intestinal absorption.[26] Furthermore, although zinc transporter expression is upregulated in a state of deficiency,[25] a major mode of the body's response to low zinc intakes or a zinc-deficient state is to reduce endogenous zinc losses.[27] Given these considerations, it is unclear what mechanisms could be responsible for greater body zinc levels observed in animals fed marginal-zinc diets. In light of the null association between zinc status and BLLs among children,[23] shared risk factors for zinc deficiency and lead exposure, such as lower maternal education or lower socioeconomic status, cannot be discounted completely.

Zinc supplementation of animals exposed to lead has resulted in lower body lead burdens. One study tested the effects of marginal (8 mg Zn/kg diet) or supplemental (300 mg Zn/kg diet) zinc intake on bone lead accumulation in rat pups consuming lead acetate (200 mg Pb/L) in drinking water. Marginal zinc intake was associated with greater bone lead, whereas supplemental zinc was associated with lower bone lead levels compared with control animals.[28] In another study, high-level zinc supplementation (200 mg Zn/kg diet) reduced the absorption of lead from food.[29] Furthermore, zinc supplementation (1 mg/kg body weight) of male rats exposed to lead (50 mg lead acetate/kg body weight) restored the activity of enzymes delta aminolevulinic acid dehydratase and superoxide dismutase in testicular tissue.[30] Most of these supplemental regimens, however, would be considered toxic. Where many studies in animals provided 200-300 mg Zn/kg of diet, for children (6 months to 18 years), the total recommended daily allowance ranges from 3 to 12 mg per day, and the tolerable upper intake ranges from 5 to 34 mg per day.[31] Therefore, although high-level zinc supplementation has been successful in preventing lead exposure or lead-induced toxicity in animals, it is impractical and even dangerous in humans.

In contrast, there is little evidence that typical zinc intake from the diet or zinc supplementation in human children or adults is associated with BLLs. In a longitudinal, observational study of young infants, greater dietary zinc intake at 3-6 months of age was associated with lower 6-month BLLs, but there was no association between zinc consumption and BLL at 12 months.[15] In the RCT mentioned previously, BLLs of Mexican children who received 30 mg of zinc oxide daily for 6 months did not differ from BLLs of children not receiving zinc.[18] The CDC document on managing elevated BLLs does not recommend adding zinc to children's diets.[8] This recommendation is prudent, given that 2 observational studies in very young children, one unsuccessful RCT in school children, and a number of studies in animals that provided supraphysiological doses of zinc do not permit any conclusions on the role of zinc in children's lead exposure.

Vitamin C Status, Intake, and Supplementation

There are reasons to believe that greater intake of foods and juices containing vitamin C would be beneficial for children exposed to lead, particularly if these children also have iron deficiency. Ascorbic acid enhances the intestinal absorption of non-heme iron (plant-based) because it reduces the naturally occurring ferric (Fe^{+3}) to ferrous (Fe^{+2}) iron, a necessary step for transport via DMT1.[32] Field studies in schoolchildren show that the addition of ascorbic acid to test meals or drinks improves non-heme iron absorption.[33,34] One study tested the ability of fruits and fruit juices to enhance the absorption of iron from a rice meal among women with iron deficiency and found great variability, suggesting that not all types of fruit are equally beneficial. Iron absorption was correlated with the ascorbic acid content of the fruit and juices.[35]

In one study of children aged 6-16 years participating in National Health and Nutrition Examination Survey III (large sample, but cross-sectional), there was an inverse association between serum ascorbic acid concentrations and the prevalence of elevated BLLs (defined as BLL >15 μg/dL), in that children in the highest tertile of ascorbic acid concentrations had an 89% lower likelihood of having an elevated BLL.[36] In contrast, there was no linear association between serum ascorbic acid and BLL.[36] Dietary intake of vitamin C was not

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017

associated with the prevalence of elevated BLLs.[36] Studies in animals suggest that supplementation with ascorbic acid could reduce BLLs,[37] as well as anemia and oxidative stress resulting from lead intoxication,[38] but these findings would need to be confirmed in children.

Calcium Intake and Supplementation

The link between calcium and lead has been discussed along with the merits of calcium supplementation as a means to reduce lead toxicity in children.[39] Calcium is absorbed via passive transport through epithelial cell tight junctions, and via active, vitamin D-regulated, transport, which predominates, especially when intake levels are low to moderate.[40] Lead uses both these mechanisms to cross intestinal cells, and the luminal calcium transport protein 1 (CaT1) exhibits high affinity for both calcium and lead.[39] Therefore, competition between lead and calcium exists at the active transporter, and it makes sense that low calcium intake would be related to greater lead absorption. Because the expression of CaT1 is dependent on vitamin D, however, the status of this vitamin would play an important role in lead absorption.

To complicate matters further, lead has been shown to inhibit the CaT1.[26] Cross-sectional studies in children have yielded mixed findings, with some showing negative and statistically significant correlations between dietary calcium intake and BLLs, some showing marginal associations, and some reporting null findings.[39] Thus, there is limited evidence of benefits from calcium supplementation, as stated by Ballew and Bowman,[39] suggesting that "diet can ameliorate the deleterious effects of environmental lead could provide a false sense of efficacy." Consistent with this conclusion, a recent cluster-randomized supplementation trial conducted among 12- to 18-month-old Nigerian children with moderately elevated BLLs found that providing calcium carbonate (400 mg/d) or ground dry fish (529 ± 109 mg Ca/d) did not significantly change BLLs 12-18 months later compared with placebo.[41] The CDC recommendations on the nutritional management of elevated BLLs among young children do not include calcium supplementation.[8]

Dietary Intake of Other Nutrients

BLLs of children (6-11 years old) and adult women living in Australia were examined in relation to a range of nutrients derived from a 6-day duplicate diet.[42] The intake of all the nutrients together (including copper, calcium, potassium, magnesium, sodium, and zinc) was not associated with BLLs. Because of small numbers of children in the study (n = 10), the associations could not be examined reliably for children alone. The authors concluded that the additional provision of most of these micronutrients would not benefit children with low-level lead exposure.[42] In a study of infants and young children with low-level lead exposure participating in the Women, Infants, and Children program, there was an inverse association between BLLs and the intake of phosphorus or vitamin E.[43] A small study of 12- to 47-month-old African American children from Philadelphia found no association between the dietary intake or serum concentrations of vitamin D in children with BLLs either below or above 30 μg/dL.[44]

Among 1-year-old children with median BLL of 4 μg/dL, greater energy intake was associated with greater BLLs in households with greater but not lower dust lead concentrations.[45] Similarly, greater energy intake and greater percent of energy from fat were associated with greater mean BLLs and greater likelihood of having a BLL > 15 μg/dL.[46] The study of participants in the Women, Infants, and Children program found a direct association between BLLs and protein intake.[43] In a longitudinal study of low-level lead exposure of infants from Albany, New York, protein intake was associated inconsistently (inversely at 6 months and positively at 12 months) with children's BLLs, possibly having to do with a transition to table foods and self-feeding.[15]

Dietary Patterns and Foods

There are no studies relating derived dietary patterns or diet quality to biomarkers of lead exposure in children. One study of young children from Jersey City, New Jersey, with moderately elevated BLLs found that the consumption of specific foods, such as hamburgers, doughnuts, and peanut butter and jelly sandwiches, was associated with greater BLLs in 13- to 24-month-old children,[47] potentially explaining the relationship between energy and fat intake and BLLs discussed previously. These foods are sticky and greasy and may aid in the transfer and ingestion of lead from children's hands.[47] In contrast, in that same study, 13- to 24- and 25- to 36-month-old children who consumed yogurt had lower BLLs.[47] It is unclear whether the basis for this inverse association with yogurt consumption is biological interaction between nutrients (for example, calcium) and lead, or more behavioral—yogurt typically is consumed with a spoon. In 2 studies conducted among adult volunteers, the consumption of skim[48] and full-fat milk[49] reduced the uptake of lead acetate by the gastrointestinal tract; however, there was greater uptake of lead with intake of either skim or full-fat milk than of a solution made to match the amount of calcium and phosphate salts found in milk.

Aside from the question of whether extrapolations can be made to children, these studies clearly illustrate that studying single nutrients does not approximate food/dietary consumption and its effect on lead absorption. A study in which children were randomized to consume food (ground fish) as a means of delivering greater dietary calcium showed no effect of this treatment on BLLs compared with placebo.[41] Therefore, it may be inappropriate to make recommendations about the intake of foods to address environmental exposures from studies that solely examined the intake of nutrients.

Meal Patterns

There is little evidence regarding meal patterns (frequency of meals, meal skipping) and BLLs in children. In adults, the

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017

uptake of lead acetate by the gastrointestinal tract was lower (4% vs 61%) when consumed with a balanced meal as opposed to prolonged fast.[48] This finding was consistent with another study following a shorter fast, where lead absorption was 3-5 times greater in the fasted state than when ingested with food.[50] Food components such as carbonate and phosphate form stable ligands with lead, which reduces lead's solubility and at least in part explains why less lead is absorbed in the fed vs fasted state.[51] The ability of balanced meals to reduce lead uptake was observed for up to 3 hours after a meal.[48] One study examined the association between regular (5 days/week) vs irregular breakfast consumption and BLLs of preschool children. There was a small but statistically significant difference in BLLs between the 2 groups.[52]

Furthermore, among young children not only what they eat but also how they eat it appears to be important. In one study, consuming foods picked up from the floor was associated with greater BLLs in 13- to 24-month-old children.[47] Children who prepared their own food had greater BLLs than children who did not. Conversely, eating foods with fingers or handwashing before meals was not associated with children's BLLs.[47] In another study involving preschool children, lead concentrations on hand wipes collected before meals were associated with lead content of duplicate diets.[53]

Food as a Source of Lead Exposure

Food and supplements[54] or methods of food preparation, such as the use of lead-glazed cookware,[55] may be a source of lead exposure, which is consistent with findings of greater BLLs in association with greater energy intake. Among young children living in the US and Mexico, lead concentration in candy was associated with BLLs.[56,57] Others have also found the potential for lead exposure from foods, including vegetables and cereals,[58-60] with some home-grown vegetables, particularly from urban gardens, being one possible source of exposure.[61] The Food and Agriculture Organization of the United Nations/World Health Organization guidance on food-based lead exposure, set at a provisional tolerable monthly intake of 25 μg/kg body weight, is now considered inadequate to protect human health.[62]

With water being an increasingly recognized source of lead,[63] the consumption of lead-contaminated water or foods prepared with such water also could contribute to exposure.[64,65] Because infants who are formula-fed consume greater amounts of water than infants who are breastfed,[66] the potential for lead exposure from water in early childhood cannot be ignored. The CDC makes specific recommendations for pregnant women and children to avoid the consumption of water that exceeds the current action level of 15 μg/L.[67] Both environmental lead exposure to the mother and mobilization of calcium (and deposited lead) from bone during pregnancy contribute to fetal exposure.[68] Lead exposure through breast milk is also an important health concern.[69] Knowledge of chemical contaminant levels in breast milk may influence maternal decisions on the timing of weaning,[70] thus depriving the infant of other benefits of breast milk and breastfeeding.

Prevention vs Treatment

Most of the studies examining nutrient intakes or nutritional interventions in relation to children's BLLs involved children who already were exposed to lead, and some studies, especially those conducted in the 1980s and 1990s, enrolled children with moderately high lead levels. In that respect, they are more able to address the issue of effectiveness of dietary "treatment" for lowering BLLs once exposure has occurred, than of prevention. Complete prevention of lead exposure via dietary means is not possible. With sufficient exposure, well-nourished children will present with detectable and possibly elevated BLLs. In one RCT involving iron fortification, 18% of children in the fortification group had elevated BLLs at the end of the trial,[19] suggesting that even if treatment is effective, not all children benefit. Part of the reason for this is that lead uses multiple types of transporters as well as tight junctions to cross epithelial cells in the intestine. Existing evidence cannot address the question of whether nutritional approaches would be more effective in acute-exposure scenarios.

Tempering Expectations

The evidence on the relationship between "nutrition" and lead exposure stems from 4 types of studies, testing the associations of BLLs with children's nutritional status (for example, biomarkers of iron status or zinc deficiency); dietary intake of single components, such as energy, protein, and fat or specific nutrients, such as iron, calcium, or vitamin C; typical intake of specific foods, such as milk, or food patterns; and the provision of single nutrients in randomized or nonrandomized trials. Unfortunately for the recommendations made to families, what is missing is the systematic evaluation of interventions involving foods or even observational studies of food consumption/diet quality in relation to children's BLLs. Also of importance is the fact that some recommendations (like those for vitamin C) appear to be based largely on findings derived from studies in animals or epidemiologic studies in adults.

Several issues need to be considered when critically appraising the existing evidence, aside from potential methodologic problems, such as low sample sizes, exclusion of large proportions of the enrolled participants, and limited covariate control. First, many of the studies conducted to date have been cross-sectional, which means that little can be said regarding the causal relationship between the intake of dietary components and children's BLLs. Well-designed RCTs and longitudinal studies can provide stronger evidence for causal links, but only few have been conducted.

Second, many of the studies examining the intake of dietary components in relation to children's BLLs have taken the single-nutrient approach, for the most part neglecting to examine how multiple nutrients would interact with one another as agonists or antagonists. Furthermore, rarely were whole foods or dietary patterns examined, which is a problem because people plan meals to consume foods, not nutrients.[71] Importantly, there have been no tests of food-based interventions. Yet, when recommendations are made, they are framed in terms of

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017

increasing intake of foods rich in specific nutrients. Although this approach seems reasonable, it is important to recognize the disconnect between the evidence base and the recommendations. Third, many studies conducted to date included children with greater BLLs than those encountered typically in pediatric practice today. The recent RCT of iron fortification is a notable exception.[20] There is an implicit assumption that the recommendations are appropriate for children with low or very low lead exposure; this assumption needs to be tested further.

Implications for Public Health Practice

So, where does the evidence leave frontline health workers making recommendations to anxious parents? Opinions may vary, but it seems prudent to adhere to current recommendations, with the understanding that they represent a benefit for children's nutritional status. The guidelines on iron-rich foods or iron supplements to correct existing iron deficiency in children exposed to lead, especially in children 2-3 years old or younger, who are growing rapidly and have high physiological demand for iron, may be particularly important. Because fasting and meal skipping was associated with greater BLLs in children and more efficient lead absorption in adults, regular meals should be recommended. Finally, it also is good practice to make sure children eat their foods with clean hands.

The uncertainty with respect to the basis for the current recommendations for preventing or lowering lead exposure needs to be recognized (**Table**; available at www.jpeds.com). The uncertainty needs to be communicated clearly to families. Whereas children with iron deficiency are more likely to experience elevated BLLs, iron supplementation or fortification of food does not guarantee that all children will be protected from lead. For vitamin C, although encouraging the intake of 2 servings of fruits or fruit juices is consistent with healthy dietary recommendations, we have absolutely no evidence on the efficacy of vitamin C supplementation or the provision of vitamin C-rich foods with respect to lowering BLLs in children. An expectation that any nutrient-rich food will prevent lead absorption or increase lead excretion in children is not based on empirical evidence.

The true number of children at risk for lead exposure is unknown. The aging infrastructure in the US, coupled with limited resources, increases the possibility of future environmental emergencies. In addition to an urgent need for developing primary prevention strategies, understanding the impact of diet and nutrition on response to lead exposure in children is important. Additional research is needed on the relationship between the consumption of foods and dietary patterns (rather than nutrients) and children's BLLs to close the knowledge gaps on dietary approaches for the prevention and reduction of lead exposure in children and to ensure they are consistent with other healthy lifestyle recommendations. In addition, studies are needed to understand the determinants of optimal response to interventions, including underlying deficiencies, genetic susceptibilities, and age-related differences in routes of exposure, rates of intestinal lead absorption, or physiological needs for specific nutrients. An additional issue to consider is access to healthcare and healthy foods, the latter being essential for scaling-up any promising dietary interventions. Finally, any trials of interventions need to reflect the current definitions and prevalence of elevated BLLs in the pediatric population. This knowledge will need to be integrated with evidence regarding other strategies to decrease lead exposure. ■

Submitted for publication Sep 6, 2016; last revision received Dec 29, 2016; accepted Jan 27, 2017

Reprint requests: Katarzyna Kordas, PhD, Department of Epidemiology and Environmental Health, University at Buffalo, 270 Farber Hall, Buffalo, NY 14214. E-mail: kkordas@buffalo.edu

References

1. Rosen M. Lead's damage can last a lifetime, or longer. ScienceNews. February 15, 2016.
2. Centers for Disease Control and Prevention. Low level lead exposure harms children: a renewed call for primary prevention; 2012. https://www.cdc.gov/nceh/lead/acclpp/final_document_030712.pdf. Accessed February 21, 2017.
3. Centers for Disease Control and Prevention. CDC's National Surveillance Data (1997-2014), 2016 [updated July 11, 2016]. https://www.cdc.gov/nceh/lead/data/national.htm. Accessed February 21, 2017.
4. McClure LF, Niles JK, Kaufman HW. Blood lead levels in young children: US, 2009-2015. J Pediatr 2016;175:173-81.
5. Guidotti TL, Calhoun T, Davies-Cole JD, Knuckles ME, Stokes L, Glymph C, et al. Elevated lead in drinking water in Washington, DC, 2003-2004: the public health response. Environ Health Perspect 2007;115:695-701.
6. Hanna-Attisha M, LaChance J, Sadler RC, Schnepp AC. Elevated blood lead levels in children associated with the Flint drinking water crisis: a spatial analysis of risk and public health response. Am J Public Health 2016;106:283-90.
7. Zremski J. Rate of lead poisoning for children in WNY far exceeds that of Flint, Mich. 2016. The Buffalo News. 24 February 2016;Sect. City & Region.
8. Centers for Disease Control and Prevention. Managing elevated blood lead levels among young children: recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. Atlanta (GA): Centers for Disease Control and Prevention; 2002.
9. Kordas K. Iron, lead, and children's behavior and cognition. Annu Rev Nutr 2010;30:123-48.
10. Bannon DI, Portnoy ME, Olivi L, Lees PS, Culotta VC, Bressler JP. Uptake of lead and iron by divalent metal transporter 1 in yeast and mammalian cells. Biochem Biophys Res Commun 2002;295:978-84.
11. 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.
12. Karwowski MP, Just AC, Bellinger DC, Jim R, Hatley EL, Ettinger AS, et al. Maternal iron metabolism gene variants modify umbilical cord blood lead levels by gene-environment interaction: a birth cohort study. Environ Health 2014;13.
13. Hopkins MR, Ettinger AS, Hernandez Avila M, Schwartz J, Tellez Rojo MM, Lamadrid-Figueroa H, et al. Variants in iron metabolism genes predict higher blood lead levels in young children. Environ Health Perspect 2008;116:1261-6.
14. Bannon DI, Abounader R, Lees PS, Bressler JP. Effect of DMT1 knockdown on iron, cadmium, and lead uptake in Caco-2 cells. Am J Physiol Cell Physiol 2003;284:C44-50.
15. Schell LM, Denham M, Stark AD, Ravenscroft J, Parsons P, Schulte E. Relationship between blood lead concentration and dietary intakes of infants from 3 to 12 months of age. Environ Res 2004;96:264-73.
16. Hammad TA, Sexton M, Langenberg P. Relationship between blood lead and dietary iron intake in preschool children. A cross-sectional study. Ann Epidemiol 1996;6:30-3.

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017

17. Wolf AW, Jimenez E, Lozoff B. Effects of iron therapy on infant blood lead levels. J Pediatr 2003;143:789-95.
18. Rosado JL, Lopez P, Kordas K, Garcia-Vargas G, Ronquillo D, Alatorre J, et al. Iron and/or zinc supplementation did not reduce blood lead concentrations in children in a randomized, placebo-controlled trial. J Nutr 2006;136:2378-83.
19. Zimmermann MB, Muthayya S, Moretti D, Kurpad A, Hurrell RF. Iron fortification reduces blood lead levels in children in Bangalore, India. Pediatrics 2006;117:2014-21.
20. Bouhouch RR, El-Fadeli S, Andersson M, Aboussad A, Chabaa L, Zeder C, et al. Effects of wheat-flour biscuits fortified with iron and EDTA, alone and in combination, on blood lead concentration, iron status, and cognition in children: a double-blind randomized controlled trial. Am J Clin Nutr 2016;104:1318-26.
21. Young MF, Griffin I, Pressman E, McIntyre AW, Cooper E, McNanley T, et al. Utilization of iron from an animal-based iron source is greater than that of ferrous sulfate in pregnant and non-pregnant women. J Nutr 2010;140:2162-6.
22. Jamieson JA, Shuhyta JN, Taylor CG. Lead does not affect transcription of intestinal zinc-binding proteins in growing rats. Exp Biol Med (Maywood) 2007;232:744-53.
23. Cantoral A, Téllez-Rojo MM, Levy TS, Hernández-Ávila M, Schnaas L, Hu H, et al. Differential association of lead on length by zinc status in two-year old Mexican children. Environ Health 2015;14.
24. Gunshin H, Mackenzie B, Berger UV, Gunshin Y, Romero MF, Boron WF, et al. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. Nature 1997;388:482-8.
25. Cousins RJ. Gastrointestinal factors influencing zinc absorption and homeostasis. Int J Vitam Nutr Res 2010;80:243-8.
26. Bressler JP, Olivi L, Cheong JH, Kim Y, Maerten A, Bannon D. Metal transporters in intestine and brain: their involvement in metal-associated neurotoxicities. Hum Exp Toxicol 2007;26:221-9.
27. King J. Does zinc absorption reflect zinc status? Int J Vitam Nutr Res 2010;80:300-6.
28. Jamieson JA, Taylor CG, Weiler HA. Marginal zinc deficiency exacerbates bone lead accumulation and high dietary zinc attenuates lead accumulation at the expense of bone density in growing rats. Toxicol Sci 2006;91:286-94.
29. Cerklewski FL, Forbes RM. Influence of dietary zinc on lead toxicity in the rat. J Nutr 1976;106:689-96.
30. Batra N, Nehru B, Bansal MP. The effect of zinc supplementation on the effects of lead on the rat testes. Reprod Toxicol 1998;12:535-40.
31. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. A report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Washington (DC): National Academies Press; 2001.
32. Teucher B, Olivares M, Cori H. Enhancers of iron absorption: ascorbic acid and other organic acids. Int J Vitam Nutr Res 2004;74:403-19.
33. Davidsson L, Walczyk T, Zavaleta N, Hurrell RF. Improving iron absorption from a Peruvian school breakfast meal by adding ascorbic acid or Na_2EDTA. Am J Clin Nutr 2001;73:283-7.
34. Davidsson L, Walczyk T, Morris A, Hurrell RF. Influence of ascorbic acid on iron absorption from an iron-fortified, chocolate-flavored milk drink in Jamaican children. Am J Clin Nutr 1998;67.
35. Ballot D, Baynes RD, Bothwell TH, Gillooly M, Macfarlane BJ, Macphail AP, et al. The effects of fruit juices and fruits on the absorption of iron from a rice meal. Br J Nutr 1987;57:331-43.
36. Simon JA, Hudes ES. Relationship of ascorbic acid to blood lead levels. JAMA 1999;281:2289-93.
37. Vij AG, Satija NK, Flora SJ. Lead induced disorders in hematopoietic and drug metabolizing enzyme system and their protection by ascorbic acid supplementation. Biomed Environ Sci 1998;11:7-14.
38. Farooq Y, Farooq MA, Hussain A. Role of ascorbic acid supplement in amelioration of anaemia in lead intoxication. J Pak Med Assoc 2016;66:1073-6.
39. Ballew C, Bowman B. Recommending calcium to reduce lead toxicity in children: a critical review. Nutr Rev 2001;59:71-9.
40. Bronner F. Mechanisms of intestinal calcium absorption. J Cell Biochem 2003;88:387-93.
41. Keating EM, Fischer PR, Pettifor JM, Pfitzner M, Isichei CO, Thacher TD. The effect of calcium supplementation on blood lead levels in Nigerian children. J Pediatr 2011;159:845-50.
42. Gulson BL, Mizon KJ, Korsch MJ, Taylor AJ. Low blood lead levels do not appear to be further reduced by dietary supplements. Environ Health Perspect 2006;114:1186-92.
43. Penuela N, Blemings KP, Fitch CW. Protein, phosphorus, and vitamin E intakes are associated with blood lead levels among WIC infants in rural West Virginia. Nutr Res 2006;26:96-9.
44. Laraque D, McCormick M, Norman M, Taylor A, Weller SC, Karp J. Blood lead, calcium status, and behavior in preschool children. Am J Dis Child 1990;144:186-9.
45. Gallicchio L, Scherer RW, Sexton M. Influence of nutrient intake on blood lead levels of young children at risk for lead poisoning. Environ Health Perspect 2002;110:A767-72.
46. Lucas SR, Sexton M, Langenberg P. Relationship between blood lead and nutritional factors in preschool children: a cross-sectional study. Pediatrics 1996;97:74-8.
47. Freeman NC, Ettinger A, Berry M, Rhoads G. Hygiene- and food-related behaviors associated with blood lead levels of young children from lead-contaminated homes. J Expo Anal Environ Epidemiol 1997;7:103-18.
48. James HM, Hilburn ME, Blair JA. Effects of meals and meal times on uptake of lead from the gastrointestinal tract in humans. Hum Toxicol 1985;4:401-7.
49. Blake KCH, Mann M. Effect of calcium and phosphorus on the gastrointestinal absorption of ^{203}Pb in man. Environ Res 1983;30:188-94.
50. Rabinowitz MB, Kopple JD, Wetherill GW. Effect of food intake and fasting on gastrointestinal lead absorption in humans. Am J Clin Nutr 1980;33:1784-8.
51. Holt AC, Partridge S, Morton AP, Blair JA, eds. The intestinal absorption of lead: the importance of lead speciation. Heavy metals in the environment: international conference. New Orleans (LA): Oak Ridge National Laboratory; 1987.
52. Liu J, McCauley L, Compher C, Yan C, Shen X, Needleman HL, et al. Regular breakfast and blood lead levels among preschool children. Environ Health 2011;10.
53. Stanek K, Manton W, Angle C, Eskridge K, Kuehneman A, Hanson C. Lead consumption of 18- to 36-month-old children as determined from duplicate diet collections: nutrient intakes, blood lead levels, and effects on growth. J Am Diet Assoc 1998;98:155-8.
54. US Food and Drug Administration. Survey data on lead in women's and children's vitamins, 2008. http://www.fda.gov/Food/FoodborneIllness Contaminants/Metals/ucm115941.htm. Accessed February 21, 2017.
55. Hernandez-Avila M, Romieu I, Rios C, Rivero A, Palazuelos E. Lead-glazed ceramics as major determinants of blood lead levels in Mexican women. Environ Health Perspect 1991;94:117-20.
56. Tamayo y Ortiz M, Téllez-Rojo MM, Hu H, Hernández-Ávila M, Wright R, Amarasiriwardena C, et al. Lead in candy consumed and blood lead levels of children living in Mexico City. Environ Res 2016;147:497-502.
57. Centers for Disease Control and Prevention (CDC). Childhood lead poisoning associated with tamarind candy and folk remedies—California, 1999-2000. MMWR Morb Mortal Wkly Rep 2002;51:684-6.
58. Callan A, Hinwood A, Devine A. Metals in commonly eaten groceries in Western Australia: a market basket survey and dietary assessment. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2014;31:1968-81.
59. Jin Y, Liu P, Sun J, Wang C, Min J, Zhang Y, et al. Dietary exposure and risk assessment to lead of the population of Jiangsu province, China. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2014;31:1187-95.
60. Chen C, Qian Y, Chen Q, Li C. Assessment of daily intake of toxic elements due to consumption of vegetables, fruits, meat, and seafood by inhabitants of Xiamen, China. J Food Sci 2011;76.

61. McBride MB, Shayler HA, Spiliethoff HM, Mitchell RG, Marquez-Bravo LG, Ferenz GS, et al. Concentrations of lead, cadmium and barium in urban garden-grown vegetables: the impact of soil variables. Environ Pollut 2014;194:254-61.
62. Food and Agriculture Organization of the United Nations, World Health Organization. Joint FAO/WHO expert committee on food additives, summary and conclusions; 2010. Geneva, Switzerland. Contract No.: JECFA/73/SC. http://www.who.int/foodsafety/publications/chem/summary73.pdf. Accessed February 21, 2017.
63. Brown MJ, Margolis S. Lead in drinking water and human blood lead levels in the United States. MMWR Morb Mortal Wkly Rep 2012;61:1-9.
64. Watt GC, Britton A, Gilmour WH, Moore MR, Murray GD, Robertson SJ, et al. Is lead in tap water still a public health problem? An observational study in Glasgow. Br Med J 1996;313:979-81.
65. Lanphear BP, Burgoon DA, Rust SW, Eberly S, Galke W. Environmental exposures to lead and urban children's blood lead levels. Environ Res 1998;76:120-30.
66. Hilbig A, Kersting M, Sichert-Hellert W. Measured consumption of tap water in German infants and young children as background for potential health risk assessments: data of the DONALD Study. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2002;19:829-36.
67. Centers for Disease Control and Prevention. Sources of Lead: Water, 2016. https://www.cdc.gov/nceh/lead/tips/water.htm. Accessed February 21, 2017.
68. Arbuckle TE, Liang CL, Morisset AS, Fisher M, Weiler H, Cirtiu CM, et al. Maternal and fetal exposure to cadmium, lead, manganese and mercury: the MIREC study. Chemosphere 2016;163:270-82.
69. Rebelo FM, Caldas ED. Arsenic, lead, mercury and cadmium: toxicity, levels in breast milk and the risks for breastfed infants. Environ Res 2016;151:671-88.
70. Geraghty SR, Khoury JC, Morrow AL, Lanphear BP. Reporting individual test results of environmental chemicals in breastmilk: potential for premature weaning. Breastfeed Med 2008;3:207-13.
71. Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc 2004;104:615-35.
72. Markowitz ME, Sinnett M, Rosen JF. A randomized trial of calcium supplementation for childhood lead poisoning. Pediatrics 2004;113:e34-9.
73. Sargent JD, Dalton MA, O'Connor GT, Olmstead EM, Klein RZ. Randomized trial of calcium glycerophosphate-supplemented infant formula to prevent lead absorption. Am J Clin Nutr 1999;69:1224-30.

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017

Table. Summary of evidence base for dietary interventions in children exposed to lead

Nutrients	Nutrient status	Typical dietary nutrient intake	Nutrient supplementation in experimental trials	Food-based intervention
Iron	Good evidence base. Iron status measured as serum ferritin, an indicator of stored iron levels, or hemoglobin, an indicator of functional iron.	A number of studies conducted in children of varying ages; examined dietary iron intake based on 24-h recalls or food frequency questionnaires; studies mostly cross-sectional.	Three well-designed RCTs (supplementation[18] and fortification[19,20]) conducted in school-age children. Fortification trials suggest benefit of additional iron. One nonrandomized trial of iron supplementation in young children showed benefit among iron-depleted, children without anemia but no other treatment group.[17]	No evidence base.
Calcium	Limited evidence base.	A number of studies (mostly cross-sectional and small) conducted in children of varying ages. One large, nationally representative sample. Examined dietary calcium intake based on 24-h recalls or food frequency questionnaires.	One trial among 1- to 6-y-old children receiving up to 1800 mg Ca/d for 6 mo had no effect on BLLs compared with placebo.[72] One trial among young children showed limited efficacy of calcium- and phosphorus-fortified infant formula but also experienced low participation.[73] One trial of calcium supplementation vs placebo in young children showed no differences in BLLs between groups.[41]	One RCT in young children involving a food source of calcium showed no efficacy compared with placebo.[41]
Vitamin C	Limited evidence base. Measured serum vitamin C concentrations.	Limited evidence base. Examined dietary vitamin C intake based on 24-h recalls.	No evidence base.	No evidence base.
Zinc	Limited evidence base. Measured serum zinc concentrations.	Limited evidence base. Examined dietary zinc intake based on 24-h recalls.	One well-designed RCT in schoolchildren showed no efficacy compared with placebo.[18]	No evidence base.

DIS 5.4.0 DTD ■ YMPD8991_proof ■ February 23, 2017