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A Randomized Trial of Calcium Supplementation for Childhood Lead Poisoning

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ABSTRACT. *Objective.* Lead (Pb) poisoning remains a common disease among children despite successful public health efforts that have reduced its prevalence. Treatment options for children with blood Pb levels (BPbs) $<45 \mu\text{g/dL}$ are limited because chelation therapy is generally not indicated. Calcium (Ca) and Pb interactions are well documented. Competition for binding to Ca-binding proteins may underlie a mechanism for Pb absorption. The purpose of this study was to determine the role, if any, of supplemental Ca at reducing BPbs in moderately poisoned children.

Methods. Children aged 1 to 6 years with BPbs 10 to $45 \mu\text{g/dL}$ were enrolled in a double-blinded, placebo-controlled trial of the effects of Ca supplementation on BPbs. Children received either a Ca-containing liquid or an indistinguishable placebo. Dosage was adjusted bi-weekly on the basis of responses to a dietary Ca intake questionnaire to reach 1800 mg in the Ca-supplemented group. Samples for BPbs and measures to assess safety were collected before and after 3 months of supplementation and after an additional 3 months of follow-up. Bivariate and multiple regression analyses were performed.

Results. A total of 67 of 88 enrolled children with a mean age of 3.6 years completed 3 months of supplementation. There were no statistically significant differences between groups on hematologic and biochemical measures, including serum and urinary Ca, at any time points. The average compliance rate was estimated to be 80% for each group during the 3-month supplementation period.

Conclusions. At enrollment, the average daily Ca intake in this group of inner-city children was greater than the recommended daily intake for age. Although BPbs declined during a 3-month period in both groups, Ca supplementation aimed at providing 1800 mg of Ca/day had no effect on the change in BPbs. Ca supplementation should not be routinely prescribed for mild to moderately Pb-poisoned children who are dietarily Ca sufficient. *Pediatrics* 2004;113:e34–e39. URL: <http://www.pediatrics.org/cgi/content/full/113/1/e34>; lead, lead poisoning, calcium, calcium supplementation.

ABBREVIATIONS. Pb, lead; BPb, blood lead level; CDC, Centers for Disease Control and Prevention; EP, erythrocyte protoporphyria; AAS, atomic absorption spectrometry; SD, standard deviation; sCa, serum calcium; uCa, urinary calcium; uCr, urinary creatinine.

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Childhood lead (Pb) poisoning is prevalent worldwide. In the United States alone, an estimated 0.5 million preschool-aged children have elevated blood Pb levels (BPbs; $\geq 10 \mu\text{g/dL}$).¹ The poisoning of this large number of children is, in large part, the consequence of the widespread presence of leaded paint in US residential housing. The National Academy of Sciences estimates that there are 3 million tons of leaded paint in housing built primarily before 1960.² Outside the US, the continued use of leaded gasoline is associated with elevated BPbs in urban populations.³ A study completed recently in India found that average BPbs in 5 major cities were comparable to that in the United States 30 years ago, when leaded gasoline was in common usage; mean BPbs were in the 10 to $20 \mu\text{g/dL}$ range.⁴ Biochemical and neurodevelopmental deficits in children have been reported to occur even at levels below the current Centers for Disease Control and Prevention's (CDC's) threshold of concern of $10 \mu\text{g/dL}$.^{5,6}

The main route of Pb entry into children is by ingestion. As painted surfaces containing Pb deteriorate, leaded chips are released and contaminate household dust. Similarly, the use of leaded gasoline contaminates soils and is incorporated into or onto vegetables. This soil contamination may persist well after the elimination of leaded gasoline usage.⁷ The percentage of ingested Pb that is absorbed from the intestine depends on several factors but is estimated to approach 50% in children and $<10\%$ in adults.^{8,9} The presence of food in the intestine, especially minerals, and the sufficiency in the body's stores of nutrients such as iron may reduce these percentages.¹⁰

In nonintervention studies, an inverse association between BPbs at age 2 (all $<25 \mu\text{g/dL}$) and cognitive test scores obtained up to 10 years later was observed.¹¹ This suggests that cognitive deficits from Pb poisoning are permanent. However, in a previous study of moderately Pb-poisoned children (initial BPbs: $25\text{--}55 \mu\text{g/dL}$) in which children were treated aggressively to reduce BPbs over a 6-month period, we found that BPbs fell and cognitive test scores improved, especially in iron-sufficient children.^{12,13} This could not be attributed to chelation therapy with CaNa_2EDTA . A multicenter, placebo-controlled trial of succimer in Pb-poisoned 2-year-olds (BPbs: $20\text{--}44 \mu\text{g/dL}$) also failed to find a benefit of chelation on cognitive outcomes tested at 4 years of age.¹⁴ However, change in BPbs over the time period was

again associated inversely with change in cognitive scores.¹⁵ Thus, in intervention studies, a reversible component of Pb toxicity may have been identified but was not attributable to chelation therapy.

Currently, the specific treatment of childhood Pb poisoning varies with the degree of intoxication. More than 90% of affected children have mild to moderately elevated BPbs between 10 and 44 $\mu\text{g}/\text{dL}$.¹ The mainstays of therapy consist of the elimination of all sources of exposure, modifying behaviors such as pica to reduce ingestion, and nutritional support.¹⁶ Of these approaches, only the effectiveness of eliminating the environmental source of Pb has been tested in controlled studies.^{17–19} Surprising is that the contributions of the other 2 components—behavior modification and nutritional support—to the management of childhood Pb poisoning have not been assessed in randomized, controlled trials. Once children have been identified as Pb poisoned and these therapeutic efforts have been initiated, BPbs fall slowly over months in most children.²⁰

Awareness of a metabolic interaction between calcium (Ca) and Pb has existed for many years. Pb and Ca competition for absorption from the intestine has been documented in animal models.^{21–25} Ca intake and BPbs are inversely related in children.^{26–29} Ca intake is well below the daily recommended intake in other countries such as China.³⁰ However, a therapeutic role of supplemental Ca for the large group of children for whom no specific medical treatment is available currently (BPbs: 10–44 $\mu\text{g}/\text{dL}$) has not been examined. This study tested the hypothesis that Ca supplementation to achieve 1800 mg/day as a component in the treatment of childhood Pb poisoning (BPbs values of 10–44 $\mu\text{g}/\text{dL}$) would result in a greater fall in BPbs over 3 months than those in unsupplemented children.

METHODS

To test the hypothesis, we used a prospective, randomized, placebo-controlled study design. Children who were referred to the Environmental Sciences Clinic at the Montefiore Medical Center with BPbs between 10 and 44 $\mu\text{g}/\text{dL}$ were eligible. These boundaries were chosen because the current definition of undue Pb absorption is a BPb of 10 $\mu\text{g}/\text{dL}$, and at BPbs $\geq 45 \mu\text{g}/\text{dL}$, chelation therapy is indicated.¹⁶ The inclusion and exclusion criteria are given in Table 1. All of the children received the usual components of our treatment intervention, which include educational materials, behavioral and nutritional counseling, and coordination with the responsible Departments of Health to determine and reduce the sources of exposure.

In both cross-sectional and longitudinal studies, BPbs are reported to increase from birth to ~3 years of age and then decline.^{31,32} We therefore stratified eligible children by age into 2 groups: 12 to 35 months and 36 to 72 months.³³ A separate restricted randomization list that was prepared before the trial was used by the pharmacist to assign enrollees into treatment groups after stratification. Both the investigators and the parents were

blinded to assignment group. Children were to receive Ca as Ca gluconate, 115 mg of elemental Ca/5 mL, or placebo for 3 months. Both groups were then followed for an additional 3 months without supplements. Supplement quantity was adjusted on the basis of a 24-hour dietary recall questionnaire that was administered biweekly. Specific and quantitative details of Ca-containing foods (including liquids) consumed during the previous day were recorded, and the Ca content was calculated using the software Nutribase Professional Nutrition Manager, version 1.0 (Cybersoft Inc, Phoenix, AZ). The responses to the questionnaire were verified by comparing the answers to the types and quantities of food described by the caregiver to the research team during scheduled home visits.

The goal of treatment was to provide 1800 mg Ca/day between supplement and diet. This amount was used in our pilot study and in a published study of Ca supplementation in non-Pb-poisoned children.³⁴ It was found to be safe and potentially effective. The dose was calculated as follows: daily supplement dosage = 1800 (mg) – daily dietary Ca intake by history (mg).

The placebo was a Ca-free solution that was comparable in sweetness and color to the Ca supplement. Both supplements were given to the parents in graduated, brown, half-liter bottles with a dispenser cap. Training on dispensing it and how to determine the amount remaining in the bottle was given to the caregiver at the first home visit by the research coordinator. The dose was divided into 3 portions to be given immediately before meals to enhance compliance.

The main outcome measure was BPbs measured at enrollment, at 3 months (after 3 months of supplementation), and at 6 months (an additional 3 months after completion of supplementation). The hypotheses to be tested were that BPbs would be lower at 3 and 6 months in the Ca-supplemented group.

Three home visits were scheduled: within 1 week of enrollment and at 3 and 6 months. The main purpose of these visits was 1) to determine whether there was Pb in the home and 2) to observe the hand-to-mouth behavior of the child.

At the first home visit, each child's caregiver completed a questionnaire that asked about medical, demographic, and environmental information. The Caldwell Home Scale was used as a sociologic measure of the home.³⁵

For home Pb assessments, a visual inspection of the surfaces was made and the Pb content on painted surfaces was measured using x-ray fluorescence instrumentation (XRF). The visual inspection was scored on a scale of 0 to 9, higher numbers indicating greater potential risk from the surface. The XRF protocol used was modified from our previous studies.^{12,20,36} We used a MAP 4 Pb paint analyzer that provides K and L-XRF readings (Scitex, Kennewick, WA). Readings (in mg/cm²) were made at 3 sites on each surface of 1 wall per room. The mean of these readings was multiplied by the visual inspection score of that surface. The sum of the products from all of the surfaces provided us with an estimate of Pb paint hazard in the home. This sum score is the Home Pb Environmental Score.

Dust samples were collected from the center of each room and from 1 window sill and 1 window well per room according to guidelines published by Department of Housing and Urban Development and the CDC.^{16,37} Wipes without aloe and without alcohol (KMart) were used for this purpose. One package was opened and used in each subject's home. Data are expressed as μg of Pb/foot.² A dust sample was obtained from the child by wiping the dominant hand with the diaper wipes. At 3 and 6 months, return visits to the home were made to assess any changes in the environment as a result of renovation, cleaning, or additional deterioration.

For assessing hand/object-to-mouth behavior, a 15-minute period of free play in the home was videotaped by the research

TABLE 1. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Initial BPbs 10–44 $\mu\text{g}/\text{dL}$	Chelation in the past 3 mo
Age 1–6 y	Concomitant Fe deficiency (ferritin <16 ng/mL)
Normal intake history and physical	Hemoglobin < 10.5 g/dL from any cause
Availability of telephone contact	Metabolic bone disease
	Medications affecting mineral metabolism, such as steroids, diuretics, large doses of vitamins

coordinator at the first home visit. Site selection for videotaping was made in conjunction with the parent who identified the area most used by the child during waking hours. Videotapes were coded by an evaluator who was blind to supplement status. The major measure coded for this study was the frequency of hand/object-to-mouth activities independent of food ingestion per unit of time observed.

Compliance was measured in 2 ways. At all contacts, questions related to compliance were asked: 1) how many doses were missed per day during the preceding 2 weeks, and 2) what is the amount remaining on the bottle? At each clinic visit, the old bottles were brought and the remaining liquid was measured. At each contact, beginning at 2 weeks, the caregiver was asked whether the subject had symptoms possibly related to treatment. These included 1) gastrointestinal: abdominal complaints of pain, anorexia, constipation; or 2) central nervous system: changes in behavior, headaches; or, 3) genitourinary: increased drinking and urination, blood in the urine.

Visits to our Environmental Sciences Clinic were scheduled at 0, 3, and 6 months for all enrollees. Children with initial BPbs between 25 and 44 $\mu\text{g}/\text{dL}$ had an additional clinic visit scheduled at 6 weeks. At each clinic visit, anthropomorphic measurements were made and an interval history was obtained. A 5.0-mL venous blood sample was taken to determine the BPbs, erythrocyte protoporphyrin (EP), serum 25-hydroxyvitamin D, magnesium, Ca, phosphorus, serum blood urea nitrogen, creatinine, total protein, albumin, alkaline phosphatase, ferritin, and complete blood count. A spot morning urine sample was collected for urinary Ca (uCa), creatinine, and urinalyses. All of the clinic practices pertaining to the identification of Pb sources, teaching caregivers about Pb's toxic effects, and providing information on how to ameliorate them were conducted. Several of the personnel at the clinic are housing specialists and act as ombudsmen for the patients in their interactions with the public health agencies of New York City and Westchester County.

BPbs were measured by flameless atomic absorption spectrometry (AAS) on a Perkin Elmer (Wellesley, MA) atomic absorption spectrometer (model 4110 ZL). The laboratory participates successfully in proficiency testing programs administered by the New York State Department of Health and the CDC. The error of the method is $\pm 1 \mu\text{g}/\text{dL}$ (99% confidence limits).³⁶ EP is a measure of the toxic effects of Pb and/or iron deficiency. Levels $>35 \mu\text{g}/\text{dL}$, in the absence of iron deficiency or recent inflammatory illnesses, are consistent with Pb toxicity, usually at BPbs $>25 \mu\text{g}/\text{dL}$. EP is measured by the extraction method of Piomelli.³⁸ The error of the method is $\pm 1 \mu\text{g}/\text{dL}$.

Dust collected with the wipe procedure was stored in Pb-free 50-mL sealable centrifuge tubes. Analyses were performed at the Hematology and Environmental Lab at the University of Cincinnati under the direction of Dr S. Roda. Environmental dust samples were measured using flame AAS after nitric acid digestion. Hand wipe samples were assessed for Pb content by graphite furnace AAS. The error of the method for dust Pb for a sample in the 250 μg range is $\pm 0.03125 \mu\text{g}$.

The database software used was Lotus 123 release 9 (IBM, White Plains, NY); statistical analyses were performed using Systat version 9 (Systat Software Inc, Richmond, CA). Variable means and standard deviations (SDs) were calculated. Two-group comparisons were made using either *t* tests or the Mann-Whitney test for data not normally distributed. Multiple regression models were constructed to control for possible confounders and to examine for possible interactions. On the basis of a pilot study of Ca effects, we expect a mean \pm SD change in BPbs of $8 \pm 4 \mu\text{g}/\text{dL}$ in the Ca-supplemented group and $3 \pm 6 \mu\text{g}/\text{dL}$ in the control group after 3 months of treatment. At an α of 0.05, a β of 0.80, and a 2-tailed test, the total sample size needed to detect a difference between the means was 46.³⁹ Because of concerns about possible attrition, we planned to oversample the population. This study was approved by the Montefiore institutional review board.

RESULTS

A total of 88 children were enrolled; 42 in the placebo and 46 in the Ca supplementation group. Of these, 67 completed 3 months of follow-up (32 and 35, respectively) and 58 completed 6 months of evaluation (24 and 34, respectively). Subjects who did not

complete the study either were lost to follow-up or did not return as per schedule requirements. For those who completed the supplementation period, the mean (\pm SD) dietary Ca intake at enrollment was $1108 \pm 465 \text{ mg}$ and $973 \pm 409 \text{ mg}$ for the placebo controls and supplemented groups, respectively, which was not statistically different. At the end of the supplementation period, total daily Ca intake averaged $1012 \pm 454 \text{ mg}$ for the placebo group and 1701 ± 121 for the Ca-supplemented group ($P = .00$). Compliance with supplement administration was comparable: $82 \pm 18\%$ and $84 \pm 16\%$ for the placebo and Ca groups, respectively. Mean and SD data at enrollment are given in Table 2. There were no statistically significant differences between the groups at enrollment on age, measures of home exposure, and hand/object-to-mouth behavior. Table 3 summarizes the biochemical data at the 3 time points. There were no significant differences between groups on any of these measures at any time point.

Although there were no differences between means of the 2 groups on any of the variables of interest except for average Ca intake during the supplementation period, we constructed a series of correlation matrices and multiple regression models to explore whether change in BPbs from enrollment to the end of the supplementation period was affected by Ca or by group, while controlling for behavior and environmental exposures. At enrollment, BPbs were inversely correlated to serum Ca (sCa) but not to Ca intake (Table 4).

The regression models assessed the contribution of variables to the change in BPbs during the 3-month intervention: each equation had BPbs at 3 months as the dependent variable while controlling for BPbs at enrollment. Addition of group assignment as a dichotomous variable, average Ca intake, or any of the housing exposure measures did not contribute significantly to the variance in BPbs at 3 months accounted for by the models. It is interesting that the sCa level at enrollment was again inversely related to the change in BPbs. There was no group by sCa level interaction.

We attempted to determine whether our failure to find a benefit of Ca supplementation was attributable to the relatively Ca-rich diets that the children were receiving at the time of enrollment. We repeated analyses in a subgroup of children with initial Ca intake $<750 \text{ mg}/\text{day}$. Unfortunately, this markedly reduced the number of subjects with data available

TABLE 2. Variables at Enrollment (\pm SD)

Variable	Placebo Group	Ca Group
Age (y)	3.7 ± 1.3	3.5 ± 1.7
Lead paint hazard score (Home Environmental Score)	44 ± 85	47 ± 83
Floor dust ($\mu\text{g}/\text{ft}^2$)	68 ± 110	48 ± 68
Window sill dust ($\mu\text{g}/\text{ft}^2$)	1818 ± 763	509 ± 815
Window well dust ($\mu\text{g}/\text{ft}^2$)	$19\ 733 \pm 34\ 315$	$23\ 303 \pm 46\ 078$
Hand dust ($\mu\text{g}/\text{hand}$)	4.9 ± 5.4	9.9 ± 24.6
Hand/object to mouth (touches/min)	0.4 ± 0.6	0.4 ± 0.5

TABLE 3. Biochemical Mean Values During the Course of the Study

	Enrollment Placebo	Enrollment Ca	3 Months Placebo	3 Months Ca	6 Months Placebo	6 Months Ca
BPbs ($\mu\text{g}/\text{dL}$)	21.4 \pm 8.7	20.7 \pm 5.8	16.6 \pm 7.2	15.1 \pm 6.3	14.4 \pm 6.8	14.0 \pm 7.2
EP ($\mu\text{g}/\text{dL}$)	60.4 \pm 49.3	40.2 \pm 20.8	41.7 \pm 24.3	31.7 \pm 11.1	37.7 \pm 23.4	32.3 \pm 16.2
Hemoglobin (g/dL)	12.0 \pm 0.9	12.2 \pm 0.9	12.2 \pm 0.7	12.3 \pm 1.1	12.3 \pm 0.9	12.3 \pm 0.8
Ferritin (ng/mL)	26.6 \pm 13.2	37.2 \pm 21.5	30.4 \pm 29.1	33.1 \pm 17.3	28.5 \pm 25.6	32.9 \pm 17.7
sCa (mg/dL)	9.7 \pm 0.3	9.6 \pm 0.4	9.8 \pm 0.4	9.8 \pm 0.4	9.5 \pm 0.4	9.7 \pm 0.4
Mg (mg/dL)	2.0 \pm 0.2	2.1 \pm 0.3	2.0 \pm 0.2	2.0 \pm 0.2	1.9 \pm 0.3	1.9 \pm 0.2
uCa/uCr ratio	0.1 \pm 0.1	0.1 \pm 0.1	0.1 \pm 0.1	0.1 \pm 0.1	0.1 \pm 0.1	0.1 \pm 0.1
Alkaline phosphatase (IU)	234.6 \pm 62.8	268.0 \pm 76.7	246.2 \pm 64.5	239.1 \pm 57.3	257.2 \pm 61.8	257.2 \pm 69.8
25-OH vitamin D (ng/mL)	26.0 \pm 11.7	30.7 \pm 9.6	23.8 \pm 8.0	31.2 \pm 12.8	26.3 \pm 6.8	29.5 \pm 15.3

TABLE 4. Correlations (Pearson) at Enrollment

	sCa	Alkaline Phosphatase	25-(OH) Vitamin D	Ca Intake
Alkaline phosphatase	0.39†			
25-(OH) vitamin D	-0.32*	-0.11		
Ca intake	-0.11	-0.13	0.37†	
Blood Pb	-0.22*	0.04	0.06	0.19

* $P \leq .05$.† $P \leq .01$.

for analyses to 6 control subjects and 10 Ca-supplemented cases. Overall, there was no group difference between mean BPbs at either of the 2 time points, but these analyses had little power.

There were no serious adverse events. Abdominal pain complaints occurred infrequently in both groups. Three children had uCa/uCr ratios between 0.34 and 0.39 at enrollment, all with initial Ca intakes of 1600 to 1800 mg/day. Two of these children were in the placebo group; their ratios declined to <0.1 . The Ca-supplemented child had a uCa/urinary creatinine (uCr) of 0.36 at enrollment and after 3 months. This child had an enrollment Ca intake of 1620 mg/day and an average Ca intake during supplementation of 1800 mg. None of the children had hematuria. There was no effect of Ca supplementation on hematologic measures or serum ferritin levels.

DISCUSSION

Considerable experimental data support the premise of a potential role for Ca supplementation in the amelioration of Pb poisoning. Ca-binding proteins have a high affinity for Pb.^{40,41} In rodent studies, BPbs in exposed animals are higher in those fed Ca-deficient diets.⁴² Studies using stable isotopes of Pb fed simultaneously with Ca to adults showed a decrease in Pb absorption.⁴³ Increasing dietary Ca is associated with decreases in gastrointestinal Pb absorption and BPbs in some studies^{8,26,28,44,45} but not in others.^{46,47} In a recent longitudinal study, Lanphear et al⁴⁷ found a marginal correlation between BPbs and Ca intake in a cohort of 12- to 24-month-old children who received ~ 900 mg of Ca per day.

Furthermore, an interventional study aimed at preventing Pb accumulation in infants in which formula-fed non-Pb-poisoned infants were supplemented with Ca glycerophosphate (1800 mg/L vs 465 mg/L) did not find a benefit over 9 months of

treatment.³⁴ BPbs increased 2.4 $\mu\text{g}/\text{dL}$ in the unsupplemented and 2.0 $\mu\text{g}/\text{dL}$ in the supplemented group. Of interest, there was no effect of supplementation on urinary Ca excretion or iron status. Sargent et al³⁴ suggested that a controlled trial was needed in children with BPbs in the range of 10 to 20 $\mu\text{g}/\text{dL}$.

The published data supporting a potential role of Ca supplementation in the treatment of mildly to moderately Pb-poisoned children are limited. A single uncontrolled study examined the potential effects of Ca supplementation on a Ca-deficient and Pb-poisoned population in China. The source of Pb exposure in this group was from leaded gasoline usage and industrial pollution, not leaded paint. Shen et al⁴⁸ provided a total daily intake of 800 mg Ca (the current recommended dietary allowance for this age group) to a group of 35 children who were aged 49 to 70 months and whose pretreatment Ca intake was ~ 300 mg/day. A 10 $\mu\text{g}/\text{dL}$ fall in BPbs was observed over a 2-month period, although Pb exposure was presumably ongoing and unchanged.

In our pilot study using 1800 mg/day as a Ca intake target, we found a 5 $\mu\text{g}/\text{dL}$ difference in BPbs after 3 months of follow-up between Ca-supplemented children and unsupplemented control subjects. This formed the basis of our power calculation. A total of 1800 mg was also a level unlikely to be associated with toxicity. This approach was validated by the lack of clinical and laboratory findings of any detrimental effects attributable to the supplement during the course of the pilot of this study.

Unfortunately, we also did not find any benefit from this Ca dose. The change in mean BPbs over 3 and 6 months of follow-up was comparable in both groups. There are several possible explanations. First, BPbs declined in both groups, and this is consistent with a successful environmental intervention to reduce Pb exposure. If a main site of Pb-Ca competition is at the level of the gut, then the reduction of Pb exposure would attenuate the effects of any potential downstream interventions because less Pb would be ingested. Second and related, this population of inner-city children, unlike historic reports, were receiving a Ca-rich diet at the time of enrollment. Thus, it is possible that a maximal Ca intake effect on Pb absorption in children had already been achieved by the time of enrollment in the study. In other words, on a molar basis, there was already a greater amount of Ca in the diet as compared with Pb and additional Ca therefore would have minimal additional impact. We can estimate that average Ca

intake increased from ~25 mmol daily at enrollment to ~45 mmol during treatment in the Ca-supplemented group. The actual Pb intake before and during the study was unknown, but considerable exposure was documented at enrollment. During the study period, it is possible that ingested Pb was reduced to the micromolar range because concomitant efforts to reduce Pb exposure were ongoing and largely successful; hand and floor wipe dust Pb content declined in 57% and 70% of the children, respectively. Pb is an effective competitor with Ca for protein binding when equimolar concentrations are used in the test tube.^{49,50} If there had been a 1000-fold difference in the molar concentrations of these metals presented to the gut, then additional Ca would not be expected to have a demonstrable additional effect on reducing absorption. This leaves open the possibility that Ca supplementation may still play a role in the treatment of Pb-poisoned children who are dietarily Ca deficient. However, the limited data in our study from children with initially lower Ca intakes (but still sufficient by recommended dietary allowance or Dietary Reference Intake standards) do not support this hypothesis.

Another possibility to consider is the schedule used for Ca administration. We chose to give the supplements in 3 divided doses with meals to enhance compliance. These may not have been times in close proximity to episodic Pb ingestion. In both humans and rodents, concomitant administration of Ca and Pb was most effective in reducing Pb absorption; the effect was attenuated when the dose of Pb was administered 90 minutes later.^{51,52} Because we had no control over the time of Pb ingestion, if it was ongoing, then we could not relate our Ca supplementation schedule directly to this ingestion. It therefore is possible that dividing the total daily dose into smaller but more frequent administrations could still have an effect on BPbs. This approach might provide an opportunity for Ca and Pb ingestion to be coupled.

We found a dissociation between measures of sCa and Ca intake and BPbs before and during Ca supplementation. Ca intake before or during the study was not a predictor of BPbs or changes in those levels, consistent with the findings of Lanphear et al.⁴⁷ Ca supplementation did not significantly improve BPbs more than placebo, which was consistent with the study by Sargent et al.³⁴

In contrast, sCa levels at enrollment were predictive of initial and subsequent change in BPbs. To explore mechanisms for these associations, we analyzed the measure of bone activity, alkaline phosphatase—a marker of osteoblast activity—and the marker of vitamin D nutritional sufficiency—the 25-hydroxy vitamin D level. Bivariate correlations were significant (uncorrected for multiple tests) between Ca intake at enrollment and 25-hydroxy vitamin D levels. This was expected because milk ingestion accounted for most Ca intake, and milk is vitamin D fortified. sCa was related to alkaline phosphatase and inversely related to 25-hydroxy vitamin D; the last 2 were not statistically intercorrelated: in a regression model, both remained significant predictors

of sCa1 with no interaction. If we interpret this finding to mean that increased bone turnover raises sCa levels, then this occurred without increasing (measurable) Pb release because BPbs were not related to sCa in this regression model. This is contrary to expectations because increased bone resorption is associated with increasing BPbs.^{53,54} Similarly, lower vitamin D levels, although not in the range of vitamin D deficiency, were associated with higher sCa levels but not alkaline phosphatase. If the D and Ca levels were physiologically related, then lower D levels could influence sCa indirectly by increasing bone resorption via secondary hyperparathyroidism. Again, if this mechanism were operating, then Pb should have been released from bone as well, thereby increasing BPbs. This was not observed using graphite furnace AAS. The sCa/BPbs relationship does not seem to have been mediated by bone turnover or vitamin D status. We thus have no explanation for these sCa associations.

By design, our main outcome measure was the change in BPbs. Assessment of BPbs remains the gold standard for evaluating children; however, it does not necessarily predict tissue Pb.⁵⁵ It remains possible that treatment did have an effect on the Pb content in the soft tissues, and that remains to be studied in animal models. We did collect data on a measure of Pb's biochemical effect, the EP level. Again, we failed to find an effect of Ca supplementation on the progression of EP levels over the course of the study.

Several additional considerations remain. The Ca formulation that we chose was selected because it is effective in the treatment of hypocalcemic patients, it is in liquid form, and it is palatable to young children. It is possible that other formulations may have different efficiencies in competing with Pb. In addition, a more restricted age range to younger children who are more likely to ingest and absorb a greater percentage of minerals may find Ca supplementation more efficacious. We conclude that Ca supplementation to achieve 1800 mg/day is not effective for the treatment of children who are 1 to 6 years of age, have BPbs between 10 and 44 $\mu\text{g}/\text{dL}$, and are receiving Ca-rich diets.

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REFERENCES

1. Rogan WJ, Ware JH. Exposure to lead in children—how low is low enough? *N Engl J Med.* 2003;348:16
2. Committee on Measuring Lead in Critical Populations, Board on Environmental Studies and Toxicology, Commission on Life Sciences. *Measuring Lead Exposure in Infants, Children, and Other Sensitive Populations.* Washington, DC: National Academy Press; 1993
3. Yan C, Wu S, Shen X, et al. The trends of changes in children's blood lead levels since the introduction of lead free gasoline in Shanghai. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2002;23:172-174
4. The George Foundation. Project Lead Free: a study of lead poisoning in major Indian cities. In: *Proceedings of the International Conference on Lead Poisoning Prevention and Treatment: Implementing A National Program in Developing Countries, February 8-10, 1999, Bangalore, India.* Bangalore, India: The George Foundation; 1999:79-85

5. Needleman HL, Gatsonis CA. Low-level lead exposure and the IQ of children. *JAMA*. 1990;263:673–678
6. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 µg per deciliter. *N Engl J Med*. 2003;348:1517–1526
7. Bosque MA, Schuhmacher M, Domingo JL, Llobet JM. Concentrations of lead and cadmium in edible vegetables from Tarragona Province, Spain. *Sci Total Environ*. 1990;95:61–67
8. Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, Fomon SJ. Absorption and retention of lead by infants. *Pediatr Res*. 1978;12:29–34
9. Kehoe RA. The metabolism of lead in man in health and disease. II. The metabolism of lead under abnormal conditions. *J R Inst Public Health Hyg*. 1961;24:101
10. Maddaloni M, Lolocono N, Manton W, Blum C, Drexler J, Graziano J. Bioavailability of soilborne lead in adults, by stable isotope dilution. *Environ Health Perspect*. 1998;106(suppl 6):1589–1594
11. Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. *Pediatrics*. 1992;90:855–861
12. Ruff HA, Bijur PE, Markowitz ME, Ma Y, Rosen JF. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. *JAMA*. 1993;269:1641–1646
13. Ruff HA, Markowitz ME, Kurtzberg D, Bijur PE, Rosen JF. Relationships among blood lead levels, iron deficiency, and cognitive development in two-year-old children. *Environ Health Perspect*. 1996;104:180–185
14. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med*. 2001;344:1421–1426
15. Liu X, Dietrich KN, Radcliffe J, Ragan NB, Rhoads GG, Rogan WJ. Do children with falling blood lead levels have improved cognition? *Pediatrics*. 2002;110:787–791
16. US Centers for Disease Control. *Preventing Lead Poisoning in Young Children: A Statement by the Centers for Disease Control*. Atlanta, GA: US Centers for Disease Control; 1991
17. Farfel MR, Chisolm JJ Jr. Health and environmental outcomes of traditional and modified practices for abatement of residential lead-based paint. *Am J Public Health*. 1990;80:1240–1245
18. Weitzman M, Aschengrau A, Bellinger D, Jones R, Hamlin JS, Beiser A. Lead contaminated soil abatement and urban children's blood lead levels. *JAMA*. 1993;269:1647–1654
19. Haynes E, Lanphear BP, Tohn E, Farr N, Rhoads GG. The effect of interior lead hazard controls on children's blood lead concentrations: a systematic evaluation. *Environ Health Perspect*. 2002;110:103–107
20. Markowitz ME, Bijur PE, Ruff HA, Rosen, JF. Moderate lead poisoning: trends in blood lead levels in unchelated children. *Environ Health Perspect*. 1996;104:968–972
21. Barton JC, Conrad ME, Harrison L, Nuby S. Effects of calcium on the absorption and retention of lead. *J Lab Clin Med*. 1978;91:366–376
22. Six KM, Goyer RA. Experimental enhancement of lead toxicity by low dietary calcium. *J Lab Clin Med*. 1970;76:933–942
23. Mahaffey KR, Goyer RA, Haseman J. Dose-response to lead ingestion on rats on low dietary calcium. *J Lab Clin Med*. 1973;89:92–100
24. Fullmer CS. Intestinal calcium and lead absorption: effects of dietary lead and calcium. *Environ Res*. 1991;54:159–169
25. Lederer LG, Franklin CB. Effect of calcium and phosphorus on retention of lead by growing organisms. *JAMA*. 1940;114:2457–2461
26. Sorrel M, Rosen JF, Roginsky MR. Interactions of lead, calcium, vitamin D and nutrition in lead-burdened children. *Arch Environ Health*. 1977;32:160–164
27. Johnson NE, Tenuta K. Zinc, iron and calcium intakes of lead poisoned children who practice pica. *Environ Res*. 1978;18:369–376
28. Mahaffey KR, Gartside PS, Glueck CJ. Blood lead levels and dietary calcium intake in 1- to 11-year-old children: the Second National Health and Nutrition Examination Survey, 1976 to 1980. *Pediatrics*. 1986;78:257–262
29. Mahaffey KR. Role of nutrition in prevention of pediatric lead toxicity. In: Chisolm JJ Jr, O'Hara DM, eds. *Lead Absorption in Children, Management, Clinical and Environmental Aspects*. Baltimore, MD: Urban & Schwarzenberg; 1982:63–79
30. Xiaoming S. Some concepts on human nutrition of calcium. *J Appl Med* 1993;13:377 (Chinese)
31. Pirkle JL, Brody D, Gunter EW, et al. The decline in blood lead levels in the United States. *JAMA*. 1994;272:284–291
32. Mahaffey KR, Annett JL, Roberts J, Murphy RS. National estimates of blood lead levels: United States, 1976–1980. Association with selected demographic and socioeconomic factors. *N Engl J Med*. 1982;307:573–579
33. Pocock SJ. *Clinical Trials, A Practical Approach*. Chichester, NY, John Wiley & Sons; 1983:66–87
34. Sargent JD, Dalton M, O'Connor G, Olmstead E, Klein RZ. Randomized trial of calcium glycerophosphate-supplemented infant formula to prevent lead absorption. *Am J Clin Nutr*. 1999;69:1224–1230
35. Caldwell BM, Bradley R. *Home Observation for Measurement of the Environment*. Little Rock, AR: University of Arkansas at Little Rock; 1984
36. Markowitz ME, Shen XM. Assessment of bone lead in pregnancy. *Environ Res*. 2001;85:83–89
37. HUD (US Department of Housing and Urban Development) Comprehensive and Workable Plan for the Abatement of Lead-Based Paint in Privately Owned Housing: Report to Congress. Washington, DC: HUD; 1990
38. Markowitz ME, Bijur PE, Ruff HA, Rosen JF. Effects of calcium disodium versenate chelation in moderate childhood lead poisoning. *Pediatrics*. 1993;92:265–271
39. Ex-Sample, Version 3.0. Columbia, MO: The Idea Works, Inc; 1993
40. Simons TJB. Cellular interactions between lead and calcium. *Br Med Bull*. 1986;42:431–434
41. Fullmer CS, Edelstein S, Wasserman Rh. Lead-binding properties of intestinal calcium-binding proteins. *J Biol Chem*. 1985;260:6816–6819
42. Han S, Pfitzenmaier DH, Garcia E, et al. Effects of lead exposure before pregnancy and dietary calcium during pregnancy on fetal development and lead accumulation. *Environ Health Perspect*. 2000;108:527–531
43. Blake KCH, Barbezat GO, Mann M. Effect of dietary constituents on the gastrointestinal absorption of ²⁰³Pb in Man. *Environ Res*. 1983;30:182–187
44. Bogden JD, Gertner SB, Christakos S, Kemp FW, Yang Z, Datz SR, Chu C. Dietary calcium modifies concentrations of lead and other metals and renal calbindin in rats. *J Nutr*. 1992;122:1351–1360
45. Quarterman J, Morrison JN, Humphries WR. The influence of high dietary calcium and phosphate on lead uptake and release. *Environ Res*. 1978;17:60–67
46. Rosen JF, Chesney RW, Hamstra A, DeLuca HF, Mahaffey KR. Reduction in 1, 25-dihydroxyvitamin D in children with increased lead absorption. *N Engl J Med*. 1980;302:1128–1131
47. Lanphear BP, Hornung R, Ho M, Howard C, Eberle S, Knauf K. Environmental lead exposure during early childhood. *J Pediatr*. 2002;140:40–47
48. Shen XM, Guo D, Zhou J, Chonghui Y. Intervening role of calcium on lead toxicity in children: experimental study and clinical verification. *Chinese J Child Health*. 1993;1:157
49. Habermann E, Crowell K, Janicki P. Lead and other metals can substitute for Ca+2 in calmodulin. *Arch Toxicol*. 1983;54:61–70
50. Chao SH, Bu CH, Cheung WY. Activation of troponin C by Cd2+ and Pb2+. *Arch Toxicol*. 1990;64:490–496
51. Meredith PA, Moore MR, Goldber A. The effect of calcium on lead absorption in rats. *Biochem J*. 1977;166:531–537
52. Heard MJ, Chamberlain AC, Sherlock JC. Uptake of lead by humans and effect of minerals and food. *Sci Total Environ*. 1983;30:245–253
53. Markowitz ME, Rosen JF, Bijur PE. Effects of iron deficiency on lead metabolism in moderately lead toxic children. *J Pediatr*. 1990;116:360–364
54. Silbergeld EK, Schwartz J, Mahaffey K. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. *Environ Res*. 1988;47:79–94
55. Rosen JF, Crocetti AF, Balbi K, et al. Bone lead content assessed by L-line x-ray fluorescence in lead-exposed and non-lead-exposed suburban populations in the United States. *Proc Natl Acad Sci U S A*. 1993;90:2789–2792

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