ASSOCIATION BETWEEN IRON DEFICIENCY AND BLOOD LEAD LEVEL IN A LONGITUDINAL ANALYSIS OF CHILDREN FOLLOWED IN AN URBAN PRIMARY CARE CLINIC

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Objective To determine if iron deficiency (ID) is longitudinally associated with lead poisoning.

Study design Blood lead levels, hemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), insurance status, and age were determined for 1275 children. ID was defined as MCV <70 fl and RDW >14.5 if age was <2 years and MCV <73 fl and RDW >14.5 if age was ≥2 years. Logistic regression models were constructed by using the second-visit blood lead levels dichotomized at ≥0.48 μm/L (10 μg/dL) as the outcome.

Results The odds ratio (OR) for baseline ID predicting lead poisoning at the second visit was 4.12 (95% CI, 1.96-8.65). In the second model, using children who were iron-replete at both visits as the referent group, for children with ID at both visits, the OR for predicting lead poisoning at the second visit was 5.54 (95% CI, 2.25-13.62). For children with ID at the first visit and iron-replete at the second visit, the OR was 2.73 (95% CI, 0.90-8.27), and for children iron-replete at the first visit and ID at the second visit, the OR was 0.81 (95% CI, 0.10-6.30).

Conclusions ID is associated with subsequent lead poisoning. These data are consistent with a biological mechanism of increased lead absorption among iron deficient children. *(J Pediatr 2003;142:9-14)*

Both iron deficiency (ID) and lead poisoning are detrimental to early development and may have lasting and profound neurologic and developmental effects.[1-4] Both disproportionately affect children under 5 years of age, children from lower socioeconomic groups, and children living in the inner city.[5,6] Previous studies suggest a link between ID and elevated blood lead levels,[7-10] whereas other studies have disputed the association.[11-14] Because of these conflicting studies, it remains unclear whether ID has a causal association with lead poisoning or whether it merely is a marker of high environmental lead. Whether such an association is causative is an important factor to consider when developing lead poisoning prevention programs. If the association is causative, then preventing ID in targeted high-risk populations might prevent lead poisoning.[9,10,15,16]

One strategy for assessing the causality of this relation would be to establish the temporal effect of ID on subsequent lead poisoning. To determine whether an association between lead poisoning and preexisting ID exists, we conducted a longitudinal analysis of data from children being screened for lead poisoning and ID in an urban primary care clinic.

CBC	Complete blood cell count
CDC	Centers for Disease Control
ID	Iron deficiency
MCV	Mean corpuscular volume
OR	Odds ratio
RDW	Red cell distribution width

See editorial, p 3.

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Table I. Selected demographic characteristics and laboratory measures

Variable	Visit 1 Mean ± SD	Visit 2 Mean ± SD
Age (y)	1.7 ± 0.8	2.6 ± 0.8
Hemoglobin (g/dL)	11.4 ± 0.9	11.4 ± 0.9
MCV (fl)	75.6 ± 5.1	76.2 ± 5.0
RDW	14.3 ± 1.3	14.1 ± 1.0
Insurance status, n (%)		
MassHealth (Medicaid)	837 (65.6)	780 (64.3)
Private insurance	268 (21.0)	288 (23.7)
Self-pay	170 (13.3)	146 (12.0)
Iron status n(%)		
Not iron-deficient	1104 (88.7)	1099 (90.5)
Iron-deficient	141 (11.3)	115 (9.5)
Blood lead n(%)		
0.48 mm/L (10 mg/dL)	1099 (86.2)	1097 (90.4)
≥0.48mm/L (10 mg/dL)	176 (13.8)	117 (9.6)
Total n	1275	1214

Iron deficiency is defined as MCV <73, RDW >14.5 if age is <2 years and MCV <70, RDW >14.5 if age is ≥2 years.
Thirty subjects did not have CBC data at visit 1.

METHODS

This study was approved by the Children's Hospital, Boston, Institutional Review Board. We retrospectively examined screening data from the hospital's outpatient primary care clinics from computerized records collected from April 1994 until December 1996. Children followed in this clinic live primarily in an urban setting. During the study period, measurements of venous whole blood lead and complete blood counts were routinely performed to screen for both lead poisoning and anemia. Massachusetts state law mandates that all children must be screened for lead poisoning beginning at 9 to 12 months of age and annually thereafter until 4 years of age. Routine annual screening for anemia with complete blood counts (CBCs) is also performed concurrently, providing us with a measure of ID status. The study population consisted of children followed for primary care (age range, 9-42 months) over a 3-year period. Children seen for 2 consecutive visits whose blood was drawn simultaneously for screening of blood lead and complete blood counts were included in the study. If subjects were seen for more than 2 visits during the study period, only the initial 2 visits were included.

Sample Analysis

A sample of venous blood for whole blood lead and complete blood count determination was collected simultaneously. Samples were drawn into a 2-mL Vacutainer containing lithium heparin (45 USP units) (Becton-Dickinson Co, Franklin Lakes, NJ) for blood lead determination and a 2-mL Vacutainer containing EDTA (K3, 0.04 mL, 7.5%) for CBC determination. All blood samples were analyzed in the clinical laboratory of Boston Children's Hospital with a Coulter Microdiff 16 (Coulter, Miami, Fla) to determine hemoglobin concentration, red blood cell mean corpuscular volume (MCV), and red blood cell distribution width (RDW). Whole blood lead concentration was measured with an atomic absorption spectrophotometer (Perkins Elmer 5000 Zeeman HGA-500 spectrophotometer, Norwalk, Conn). By laboratory protocol, samples with blood lead concentrations between 0 and 4 μg/dL are reported as <5 μg/dL (0.24 μmol/L). This laboratory participated in the Centers for Disease Control (CDC) blood lead quality assurance program without any out-of-bounds measurements during the study period. The intraclass correlation between our laboratory measurements and the CDC standards was $R = 0.999$.

Information on insurance status and date of birth was collected during registration for each clinic visit. Insurance status was separated into 1 of 3 categories: MassHealth (Medicaid), self-pay, and private insurance. Insurance status is commonly used as a marker of socioeconomic status,[18] and prior studies have demonstrated that it is associated with household income.[17-19] ID was defined a priori at each visit by established American Academy of Pediatrics (AAP) criteria for MCV and RDW.[20] Children were classified as having ID if MCV was <70 fl and RDW was >14.5 if age was <2 years and MCV was <73 fl and RDW was >14.5 if age was ≥2 years.[20,21] Such a definition is useful in identifying patients with early ID who are not yet anemic and has been demonstrated to improve the distinction between heterozygous thalassemia and anemia of chronic disease from early ID.[21-23] Using these criteria, the change in iron status was categorized into 4 groups: iron-replete at both visits (referent group), iron-replete at the first visit and iron-deficient at the second visit, iron-deficient at the first visit and iron-replete at the second visit, and iron-deficient at both visits. We also used iron-deficient at the first visit without respect to change in ID status as an independent variable in some analyses. Lead poisoning was defined as a blood lead level of ≥0.48 μm/L (10 μg/dL), the current CDC screening standard.[24]

Univariate and bivariate analyses were performed to examine covariate distributions and bivariate associations among baseline age, blood lead level, ID status, insurance status, and hemoglobin as predictors of subsequent lead poisoning. Categoric variables were assessed by means of the χ^2 test, with continuity correction and continuous variables assessed by means of the unpaired Student t test or 1-way analysis of variance as appropriate. Analyses were performed both when including subjects with baseline blood lead levels >10 μg/dL and when excluding such subjects.

We determined the longitudinal effect of ID on subsequent lead poisoning as follows. First, a logistic regression model was constructed to determine associations between baseline ID in predicting lead poisoning at the second visit controlling for appropriate covariates (baseline blood lead level, baseline insurance status, baseline age, and concurrent hemoglobin concentration). Next, a second logistic regression model was constructed to determine the effect of change in ID status in predicting subsequent lead poisoning, controlling

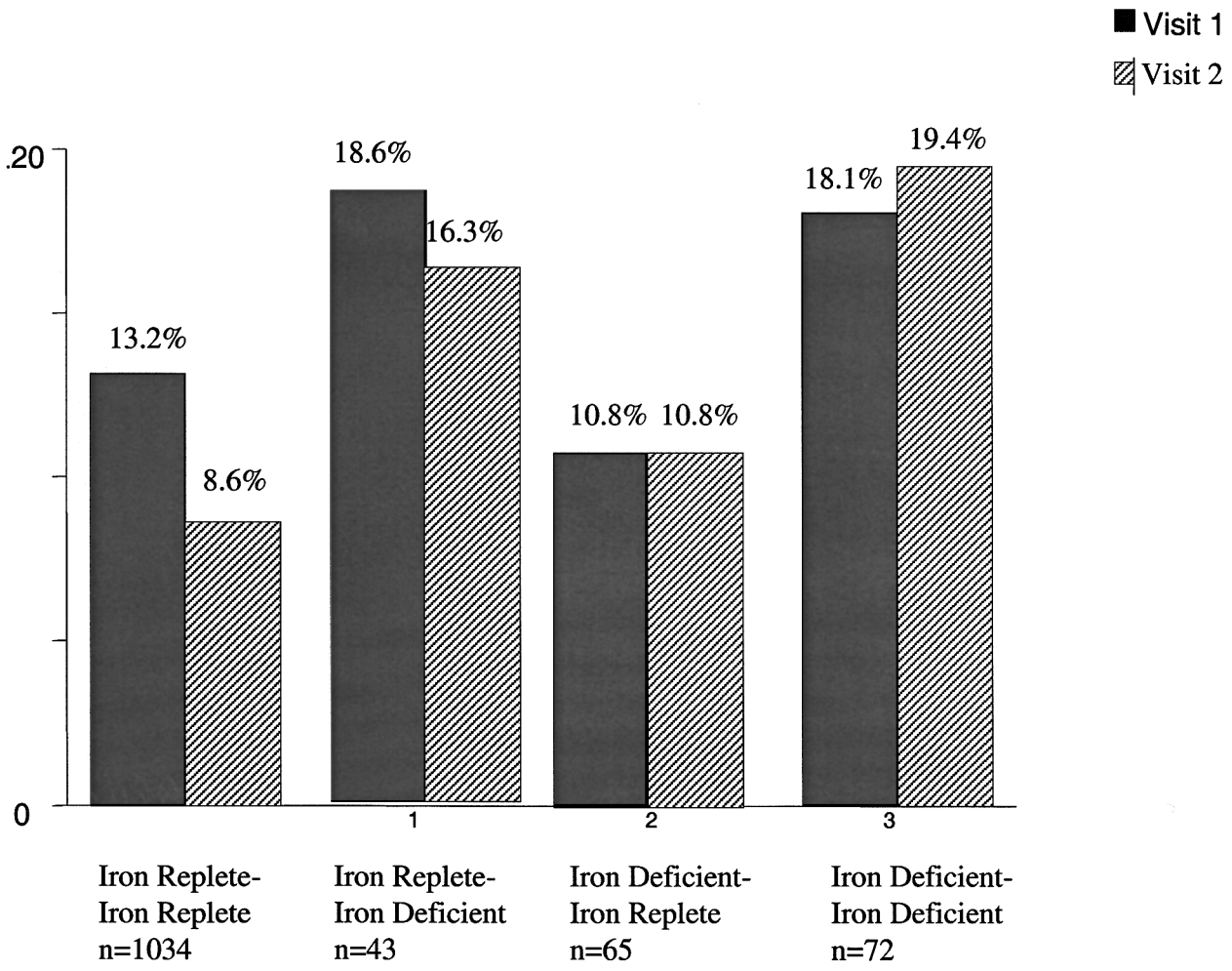

Figure. Change in percentage of subjects with blood lead levels ≥0.48 mm/L (10 mg/dL) at visit 1 and visit 2 within each category of change in iron deficiency status. Data are for all subjects with complete data at 2 visits (overall n = 1214).

for the same covariates. By using this dichotomized cut-point for blood lead levels of 0.48 μm/L (10 μg/dL), indicator terms for ID (or change in ID status, depending on the model), baseline insurance status (with private insurance patients as the referent group), baseline blood lead level, baseline age, and concurrent hemoglobin were entered into the logistic regression models. Because the baseline blood lead level was by far the strongest predictor of subsequent lead poisoning at visit 2, we repeated the analysis, excluding all subjects with baseline blood lead levels >0.48 μm/L (10 μg/dL) to avoid the problem of residual confounding. Finally, the mean "time between visits" was also considered as a potential confounder of our results. That is, subjects with ID might be seen more or less frequently than iron-replete subjects, and this might confound our results as blood lead levels change with time as the result of changes in child behavior and changes in environmental lead levels. To evaluate this potential confounder, we calculated the mean time between visits for each of the 4 categories of "change in ID status." This variable was added to the models to determine whether the ID coefficients were confounded by differences in "time between visits."

RESULTS

During the study period, 1275 children of this age range were seen in the primary care clinic for at least 2 well child care visits (Table I). The overall mean time between the 2 visits was 0.84 ± 0.39 years (9.6 ± 4.7 months). Of the 1275 subjects with at least 2 visits, 1214 had complete data on CBC values, blood lead levels, and covariates. After excluding all subjects with baseline blood lead levels ≥0.48 μm/L (10 μg/dL), 1050 subjects were included in the final analysis. The prevalence of ID and lead poisoning at each of the 2 visits is shown in Table I. We categorized the change in ID status by using MCV and RDW criteria, as outlined above at each visit. Based on this difference, we calculated the number of subjects with lead poisoning in each category.

Although the number of subjects with lead poisoning who were iron-replete at each visit declined markedly (Table II), the number of subjects with lead poisoning who were iron-deficient at one or both visits was more stable over time (Figure). Baseline blood lead concentration ranged from <5 μg/dL to 40 μg/dL (median <5 μg/dL [0.24 μmol/L] and range <0.24 to 2.10 μmol/L), and blood lead concentration at

Table II. Comparison of baseline iron status with blood lead concentration, patient demographics, and laboratory measures

	Iron-replete at baseline	Iron-deficient at baseline
*Blood Pb visit 1	n = 1077	n = 137‡
<0.48 mm/L (10 mg/dL)	933	117
≥0.48 mm/L (10 mg/dL)	144	20
†Blood Pb visit 2		
<0.48 mm/L (10 mg/dL)	981	116
≥0.48 mm/L (10 mg/dL)	96	21
Baseline age (y)	1.75 (0.76)	1.79 (0.67)
Insurance status visit 1		
Private	239 (22.2)	19 (13.9)
Medicaid	687 (63.8)	102 (74.5)
Self-pay	151 (14.0)	16 (11.7)
Hemoglobin visit 2	11.5 (0.8)	10.9 (0.9)

Data restricted to subjects with complete data on all variables (n = 1214).
*P = .79, c2 for association of iron deficiency and blood lead at visit 1.
†P = .025, c2 for association of iron deficiency categories and blood lead at visit 2.
‡Four subjects with iron deficiency at baseline did not have complete data on blood lead, insurance, and age at visit 2.

the second visit ranged from <5 μg/dL to 25 μg/dL (median <5 μg/dL [0.24 μmol/L] and range <0.24-1.38 μmol/L). Table II also shows the results of the crude association between baseline ID status and lead poisoning as experienced at visit 1 and visit 2. The association between change in ID status and lead poisoning was only significant at visit 2. When the analysis was restricted to subjects with baseline blood lead levels <10 μg/dL (0.48 μmol/L), the crude association between baseline ID and lead poisoning at visit 2 was still significant (χ^{-}_{2df} = 9.2; P = .002, n = 1050).

The mean time between visits were similar for all groups and ranged from 0.76 ± 0.33 years to 0.90 ± 0.42 years (iron-deficient/iron-replete and iron-replete/iron-deficient, respectively). This difference was borderline significant in a 1-way analysis of variance (P = .058). However, when the time between visits was entered into the logistic regression models as a continuous covariate, none of the odds ratios for ID status in any of the regression models changed by >10%, suggesting a lack of confounding. We therefore dropped the variable "time between visits" from the final regression models.

Univariate analysis of ID with respect to blood lead concentration demonstrated that the crude odds ratio (OR) for baseline ID predicting a subsequent blood lead concentration ≥0.48 μmol/L (10 μg/dL) was 2.77 (95% CI, 1.40-5.47). This effect was even greater in the logistic regression model (Table III). The ORs ratios for "change in ID status" (using iron-replete at both visits as the referent group) in predicting lead poisoning were similar in trend and effect size to the ORs in the multivariate logistic regression model and are therefore not shown. Results of the logistic regression modeling are presented in Tables III and IV. We also looked at a test of trend in which we looked at change in ID as an ordinal variable in the logistic regression models. The order of this variable was iron-replete to iron-replete, iron-replete to iron-deplete, iron-deplete to iron-replete, and iron- deplete to iron-deplete, scored from 1 to 4 as an integer. This variable was highly significant in the logistic regression models (P = .001), suggesting an increasing effect of combined decreased body iron stores/dietary iron intake.

DISCUSSION

We are unaware of previous studies that have demonstrated that laboratory evidence of baseline ID is longitudinally associated with lead poisoning. All studies of which we are aware have been cross-sectional and cannot determine whether ID preceded lead poisoning or vice versa.[7-14] Not only are these studies cross-sectional, but their results have been mixed, with some finding associations between ID and lead poisoning[7-10,25] and others disputing the association.[11-14,26] Of note, our results suggest that the risk of subsequent lead poisoning associated with ID is quite large, with 4- to 5-fold increases in baseline risk of lead poisoning.

With respect to nonobservational research, experimental studies have demonstrated that iron-deficient animals absorb a greater percentage of ingested lead than iron-replete animals.[27,28] Barton et al[28] suggested that the effects of ID on lead absorption are mediated through a common absorptive receptor. In contrast, at least one controlled clinical study[25] has failed to demonstrate this effect, causing some investigators to argue that the association may be due to confounding.[11,14] A second controlled study did find increased lead absorption in iron-deficient subjects.[26] Both diseases do occur more frequently in lower socioeconomic classes; thus, the relation may be secondary to common environmental risk factors, and ID may therefore merely be a marker of high environmental lead levels. Previous clinical studies have been cross-sectional; this study addresses that issue by looking at pre-existing ID as a risk factor for subsequent lead poisoning. The argument that ID is "causally" associated with lead poisoning is strengthened by our ability to demonstrate this temporal relation between ID and lead poisoning. Subjects with baseline ID have an increased risk of lead poisoning even if they become iron-replete, but the risk does decrease relative to subjects who remain iron-deficient. Subjects who are iron-replete at baseline did not have a greater risk of subsequent lead poisoning even if they became iron-deplete. However, the mean time between visits of 8 months does not preclude that prolonged ID did not increase eventual risk of lead poisoning. The stepwise progression of the ORs demonstrates a dose effect, whereby there is an increased risk of lead poisoning associated with both decreased dietary iron/decreased baseline iron stores but that baseline iron stores have the greater effect. Nevertheless, the results suggest that increasing body iron stores can mitigate the risk of subsequent lead poisoning, as the greatest risk was seen for subjects who remained iron-deficient at both visits.

Bradman et al[10] placed the potential association between ID and lead poisoning in biologic context. That is, ID

Table III. Logistic regression modeling of the association between baseline iron deficiency and subsequent lead poisoning

Independent variable	Adjusted OR (95% CI) for blood lead ≥0.48 mm/L (10 mg/dL) at visit 2	*P* value
Baseline iron deficiency	4.12 (1.96–8.65)	< .0001
Age at baseline visit (y)	0.43 (0.23–0.70)	.001
Hemoglobin at visit 2 (g/dL)	1.53 (1.08–2.17)	.02
Insurance status, SP*	0.81 (0.40–1.61)	.55
Insurance status, PR†	0.58 (0.20–1.69)	.32

SP, No insurance (self-pay); PR, private.
Lead poisoning was defined as blood lead level ≥0.48 mm/L (10 mg/dL). For multivariate analysis, n = 1050 as subjects with baseline blood lead level ≥0.48 mm/L (10 mg/dL) were excluded. There were 94 subjects with iron deficiency at baseline. Baseline iron deficiency is defined as MCV <73, RDW >14.5 if age is <2 years and MCV <70, RDW >14.5 if age is ≥2 years at visit 1.
*Dichotomized as self-pay vs MassHealth.
†Dichotomized as private insurance vs MassHealth.

Table IV. Logistic regression model of the association between change in iron deficiency status and subsequent lead poisoning

Independent variable	Adjusted OR (95% CI) for lead poisoning at visit 2	*P* value	n*
Iron-replete both visits	Referent group	—	898
Iron-replete–iron-deficient	0.81 (0.10–6.30)	.84	58
Iron-deficient–iron-replete	2.73 (0.90–8.27)	.08	35
Iron-deficient–iron-deficient	5.54 (2.25–13.62)	< .0001	59

ORs are adjusted for baseline age, insurance status, and concurrent hemoglobin level. Iron deficiency is defined as MCV <73, RDW >14.5 if age is <2 years and MCV <70, RDW >14.5 if age is ≥2 years. Lead poisoning is defined as blood lead level ≥0.48 mm/L (10 mg/dL). Test for trend for increasing risk in going from iron-replete both visits to iron-replete–iron-deficient to iron deficient–iron-replete to iron-deficient both visits; P = .001.
*Overall n for this model is 1050 because subjects with baseline blood lead level ≥0.48 mm/L (10 mg/dL) were excluded.

must be an effect modifier of the association between lead poisoning and environmental lead exposure. In a cross-sectional analysis, Bradman et al demonstrated that within strata of high, medium, and low lead exposure, iron-deficient children had significantly higher blood lead levels than iron-replete children. Our results, combined with those of Bradman et al, suggest that dietary iron supplements may be an effective preventative measure against lead poisoning in targeted populations.

There are both limitations and strengths to our study. We did not measure environmental lead levels and cannot comment on effect modification between ID and environmental lead. Therefore, a potential limitation is that our findings may be due to the effect of residual confounding by actual environmental lead exposure; that is, ID may still be a marker of poverty and greater environmental lead levels. However, the results of the change in iron status analysis in which subjects with baseline ID but who are subsequently iron-replete had a lower risk of lead poisoning than subjects with ID at both visits suggests that this factor did not confound our results. Exposure misclassification is a potential limitation and is always possible in studies of ID. Serum ferritin levels, for example, may misclassify subjects who are iron-deficient as iron-replete, given that it is an acute phase reactant.[21] In addition, our classification scheme for ID, although more specific than serum ferritin, may be less sensitive in detecting ID than serum iron/TIBC or serum ferritin.[21] However, it should be noted that this type of misclassification is likely to be nondifferential with respect to the null hypothesis of no association, as iron-deficient children who were lead-exposed and non–lead-exposed would be equally likely to be misclassified as iron-replete. The same is true regarding iron-replete children being misclassified as iron-deficient. Such a nondifferential misclassification error will tend to drive the overall effect toward a null finding (type II error) but will not drive a true null finding toward an effect (type I error).[29]

Although previous studies of calcium supplementation have not demonstrated efficacy in preventing lead poisoning,[30] the role of iron supplements, possibly in conjunction with calcium supplements, has not been explored. A recent randomized, controlled trial of chelation therapy demonstrated no clear beneficial effect on cognitive outcomes,[31] suggesting that prevention is the only means by which the neurotoxic effects of lead can be averted. Greater efforts at prevention are

needed.[32] If nutrient deficiencies predispose to lead poisoning, then their supplementation might be useful treatment adjuncts in lead poisoning prevention. Although nutritional supplementation is not a solution to lead exposure, the evidence that ID is associated with subsequent lead poisoning makes such an effect plausible. We would caution, however, that any study should be done in conjunction with environmental hazard reduction. The use of iron and calcium supplements to prevent subsequent elevations in blood lead levels may be a simple cost-effective strategy that could augment environmental remediation. A further public health impetus to study this question is the well-established adverse effect of ID on cognitive development.[3,4] Given this factor, the consequences of combined ID and lead poisoning on neurodevelopmental outcome may be potentially devastating.[33,34]

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