Iron Deficiency Associated with Higher Blood Lead in Children Living in Contaminated Environments

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The evidence that iron deficiency increases lead child exposure is based primarily on animal data and limited human studies, and some of this evidence is contradictory. No studies of iron status and blood lead levels in children have accounted for environmental lead contamination and, therefore, the source of their exposure. Thus, no studies have directly determined whether iron deficiency modifies the relationship of environmental lead and blood lead. In this study, we compared blood lead levels of iron-deficient and iron-replete children living in low, medium, or highly contaminated environments. Measurements of lead in paint, soil, dust, and blood, age of housing, and iron status were collected from 319 children ages 1–5. We developed two lead exposure factors to summarize the correlated exposure variables: Factor 1 summarized all environmental measures, and Factor 2 was weighted for lead loading of house dust. The geometric mean blood lead level was 4.9 µg/dL; 14% exceeded 10 µg/dL. Many of the children were iron deficient (24% with ferritin < 12 ng/dL). Seventeen percent of soil leads exceeded 500 µg/g, and 23% and 63% of interior and exterior paint samples exceeded 5,000 µg/g. The unadjusted geometric mean blood lead level for iron-deficient children was higher by 1 µg/dL; this difference was greater (1.8 µg/dL) after excluding Asians. Blood lead levels were higher for iron-deficient children for each tertile of exposure as estimated by Factors 1 and 2 for non-Asian children. Elevated blood lead among iron-deficient children persisted after adjusting for potential confounders by multivariate regression; the largest difference in blood lead levels between iron-deficient and -replete children, approximately 3 µg/dL, was among those living in the most contaminated environments. Asian children had a paradoxical association of sufficient iron status and higher blood lead level, which warrants further investigation. Improving iron status, along with reducing exposures, may help reduce blood lead levels among most children, especially those living in the most contaminated environments. *Key words*: **children, environmental exposure, epidemiology, iron deficiency, lead poisoning.** *Environ Health Perspect* **109:1079–1084 (2001). [Online 1 October 2001]**
http://ehpnet1.niehs.nih.gov/docs/2001/109p1079-1084bradman/abstract.html

Childhood lead exposure is one of the most significant environmental health threats that affect children(*1–3*). Adverse effects of lead include cognitive deficits, neurotoxicity, behavior disorders, slowed growth, reduced heme synthesis, and impaired hearing (*1,3–9*). Although health and regulatory programs designed to reduce lead exposure are proving successful (*10*), many young children in the United States still have blood lead levels > 10 µg/dL, the Centers for Disease Control and Prevention (CDC) level of concern (*1,10–12*). The prevalence of elevated blood lead levels among minority, low-income inner-city children remains several times the national average (*10–12*). These same children are also more likely than others to be iron deficient, a condition that affects up to 6% of young children nationally (*13–16*), with insufficient iron intake in up to one-third of children in some communities (*17*).

It is biologically plausible that iron deficiency could lead to higher lead levels in children. Controlled animal studies consistently demonstrate higher lead levels in iron-deficient animals than in iron-replete controls (*18–23*). The mechanism for enhanced absorption is likely to be substitution of Fe^{+2} with Pb^{+2} and increased active transport into the body (*19,22,24,25*). Similarly, it is possible that Pb^{+2} may occupy vacant Fe^{+2} sites in the hematopoeitic system, thereby reducing lead excretion. Clinical studies of chelation therapy suggest that iron-deficient children may retain more lead in their bodies (*26,27*). It is also possible that iron deficiency modifies behavior, increasing pica or hand-to-mouth behavior in children and thereby increasing ingestion exposures to lead in their environment (*28,29*).

Despite the consistency of results in animal studies, the findings in human studies are less definitive. Experimental studies of iron deficiency and lead uptake in human adults are not consistent (*19,30–33*). Several epidemiologic studies in children support a correlation between iron deficiency and higher blood lead (*15,34–36*). Other studies have found no relationship between iron intake or low iron stores and blood lead in children (*37,38*); however, these studies either used diet to measure iron status (*38*) or studied older children (10–18 years) and did not control for age (*37*), which is an important factor affecting lead absorption (*39*).

To date, no studies examining iron status and blood lead in children account for environmental lead contamination, and thus the source of a child's exposure. Iron deficiency may be directly associated with lead uptake and systemic retention, or lead and iron deficiency may be independent factors, both of which may be related to another factor, such as poverty. Because the sociodemographic characteristics of children who are likely to be iron deficient also puts them at higher risk of lead exposure (*10*), it is not certain to what extent iron deficiency directly affects blood lead levels. Nor have any studies attempted to quantify the level of protection that sufficient iron status may confer on a child. In this study we evaluate whether iron deficiency is related to increased blood lead in children living in contaminated environments; we also account for major covariates, including socioeconomic status and child age.

Methods

Selection of households and participants. Participants in the study were part of an epidemiologic study of childhood lead exposure in Sacramento, California, one of three

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We thank M. Haan for collaboration in conduct of the survey, L. Zahler for superb coordination of fieldwork, R. McLaughlin for data management, J. Irias for blood lead and iron parameter measurements, P. Flessel and G. Guirguis for environmental laboratory measurements and quality control, and S. Samuels for statistical consultation. We appreciate the advice of R.D. Schlag, D.F. Smith, and R.R. Neutra, who reviewed the questionnaire and study design; S. Cummins and B. Abrams for reviewing drafts of this manuscript; and B. Lubin for assistance on iron deficiency parameters.

This research was supported in part by the California Department of Health Services Childhood Lead Poisoning Prevention Program; NIEHS award P01 ES09605 and EPA award R826709.

Received 3 July 2000; accepted 4 April 2001.

California sites studied by the California Department of Health Services (CDHS) from 1988 to 1990. We used information from the 1980 census to identify specific census tracts with many children between ages 1 and 6 years and a high prevalence of lead risk factors, including a high proportion of older housing, low income, and minority ethnicity. We selected specific census tracts after discussions with local health officials and firsthand observation. Eligible households were enumerated by door-to-door survey. Any household with a child between 1 and 6 years of age was considered eligible. Seventy-nine percent of 2,220 households in the study area were enumerated; 483 were eligible, and 232 households participated with a total of 382 children. Of the 382 children, 28 were missing information on environmental exposure and 35 were missing measurements of ferritin, a measure of iron status, for a total of 319 children for this analysis.

Environmental measurements of lead contamination. We collected up to three interior and three exterior paint samples from different areas of peeling and/or chipping paint. We collected paint samples from intact surfaces if there was no peeling or chipping paint available. Interior and exterior trim and porches were sampled in preference to walls and siding. We used the maximum interior and exterior paint lead level to characterize the dwelling. We collected front, side, and rear-yard soil samples from the top 2.5 cm or less of soil, and used the geometric mean of these soil lead levels for the data analysis. We collected house dust samples with a vacuum cleaner with an in-line filter trapping particles > 0.3 mm at 98% efficiency. Each sample was collected from the center of a room, with preference given to areas where children were reported to spend time. Values for both concentration of lead in house dust (micrograms per gram) and loading (amount of lead per unit area, micrograms per square meter) were reported. Environmental samples were digested in nitric acid and analyzed by atomic absorption spectroscopy. Additional information is presented in Sutton et al. (*40*).

Environmental data, particularly dust measurements, were missing from several homes. Dust, paint, and soil lead measures were highly correlated (*40*). For homes with only one absent medium (i.e., dust, paint, or soil) (n = 69 children), we estimated the level of lead in the missing medium from multivariate regression equations derived from the other complete measurements. Housing age was ascertained from county tax assessor data.

Questionnaire. Interviews were administered in English, Spanish, Vietnamese, Cambodian, or Tagalog to the primary caregiver of each child. Questions addressed the child's risk factors for lead exposure, ethnicity, income, education, access to medical care, previous screening for lead poisoning, participation in day care or school, use of vitamins with iron, dwelling renovation, general health status, and a variety of other demographic and health information.

Blood lead and iron status measures. We measured lead levels and iron status in blood samples obtained by venipuncture. Lead and iron status measurements were conducted at the Metabolic Nutrition Laboratory (MNL) at Children's Hospital Oakland. We performed laboratory analysis for blood lead using graphite furnace atomic absorption spectroscopy with a detection limit of 1 µg/dL. MNL participates in the California Department of Health Services Lead Proficiency Testing Program, which, in turn, participates in national proficiency testing programs (*41*). The average percentage differences between measured and true concentrations for 46 external proficiency samples during batch runs was 9.2% for samples < 40 µg/dL. Lead concentrations in the quality control samples were established from the mean of values obtained by five nationally recognized reference laboratories. The coefficient of variation for internal quality control measurements was < 10%. Iron-related measures included ferritin, hematocrit (Hct), hemoglobin (Hgb), and mean corpuscular volume (MCV).

Ferritin is an iron-storage protein that maintains sufficient blood iron when dietary intake is inadequate. Ferritin levels may decrease, indicating low iron intake, while other measures of iron status remain normal. Therefore, low ferritin is a highly sensitive and specific indicator of iron deficiency with or without anemia. If ferritin levels are depleted, later signs of iron deficiency may develop, including low hematocrit, hemoglobin, and mean corpuscular volume (*42–44*). Using ferritin as the primary measure of iron status reduces the potential to misclassify low iron status. We chose ferritin levels, *a priori*, as the primary determinant of low iron status. For defining iron deficiency, we used a ferritin cutoff value of ≤ 12 ng/mL (*3,44,45,46*). A secondary analysis used

Table 1. Loadings and eigenvalues for two environmental lead factors derived from principal components analysis of environmental exposure measures.[a]

Components	Factor pattern Factor 1	Factor 2
Ln – Soil lead (µg/g)	0.75	–0.10
Ln – Indoor paint lead (µg/g)	0.58	–0.32
Ln – Outdoor paint lead (µg/g)	0.72	–0.08
Ln – Dust lead level (µg/g)	0.63	–0.49
Ln – Dust lead loading[b] (µg/m^2)	0.30	0.83
House age (years)	0.79	–0.31
Eigenvalues	2.52	1.14

Ln, natural logarithm.
[a]Calculated with SAS Proc Factor, minimum eigenvalue = 1, no rotation (*49,50*). [b]Lead loading = mass of lead per area of floor sampled for house dust, micrograms per square meter.

Table 2. Distribution of demographic characteristics and geometric mean blood lead and ferritin levels by demographic strata.

Covariate	Distribution of total sample n = 382 (%)	Blood lead GM (µg/dL) (± 1 SD)	Ferritin GM[a] (ng/mL) (± 1 SD)
Overall	381 (100)[b]	4.9 (2.5–9.5)	19.1 (8.1–45.1)
Age (years)			
1	59 (15)	5.4 (2.6–11.2)	13.3 (5.3–33.4)
2	82 (22)	4.8 (2.6–9.0)	17.6 (7.5–41.7)
3	102 (27)	5.0 (2.5–9.9)	19.7 (8.2–47.0)
4	74 (19)	4.5 (2.5–7.9)	24.2 (11.8–49.9)
5	64 (17)	4.8 (2.3–20.0)	19.9 (8.4-47.0)
Ethnicity			
Black	95 (25)	5.8 (3.3–10.0)	20.9 (9.2–47.5)
Hispanic	152 (40)	4.4 (2.2–8.6)	16.8 (6.6–42.5)
Asian	68 (18)	5.8 (2.9–11.6)	20.3 (8.4–48.9)
Other[c]	64 (17)	4.1 (2.0–8.4)	22.2 (11.8–41.7)
Sex			
Female	194 (51)	5.1 (2.5–10.3)	16.9 (7.3–39.3)
Male	187 (49)	4.6 (2.5–8.7)	21.5 (9.1–50.9)
SES			
Low	202 (53)	5.4 (2.9–10.1)	18.5 (7.5–46.1)
Medium	116 (30)	4.7 (2.3–9.6)	18.2 (8.1–40.9)
High	63 (17)	3.8 (2.1–7.1)	22.9 (10.8–46.1)
Reported use of vitamins with iron			
Yes	65 (17)	3.8 (2.0–7.2)	17.6 (7.8–39.6)
No	316 (83)	5.1 (2.6–9.9)	19.5 (8.2–46.5)
Time spent in school/day care			
Yes	105 (28)	4.3 (2.3–8.2)	20.7 (9.5–45.2)
No	276 (72)	5.1 (2.9–9.9)	18.5 (7.7–44.7)

GM, geometric mean.
[a]Thirty-five missing ferritin measurements; distribution of reduced samples is very similar to total distribution. [b]One missing blood lead measurement. [c]Predominantly white.

other measures of iron status—Hct, Hgb, and MCV. The age-specific cutoff values to define low iron status were < 33–34% for Hct, < 11–11.2 g/dL for Hgb (*47*), and < 67–73 fL for MCV (*15,48*).

Statistical analyses. We performed all statistical analyses using SAS PC software (*49,50*). Measures of blood and environmental lead and ferritin were log-transformed (*40*).

Initial analyses used simple linear regression and scatter plots to investigate the associations among ferritin, blood lead, and covariates. We then developed multiple linear regression models to assess associations between ferritin and the dependent variable, blood lead, while accounting for potential confounders that affect blood lead and/or iron status measures [age, sex, ethnicity, socioeconomic status (SES), and reported use of vitamins with iron] (*1,14, 15,45*) or were significant in the bivariate analysis. For example, bivariate analyses suggested that attendance in day care or school protected against lead exposure, perhaps because children who spent more time away from their homes may receive less exposure from home contamination. Thus, we controlled for this variable in the regression model.

We performed the above analyses using both a continuous measure of ferritin and a dichotomous measure (≤ 12 or >12 ng/mL). We also examined other measures of iron status (Hgb, Hct, MCV), both individually and as a composite measure, where iron deficiency was assigned if ferritin, Hgb, Hct, or MCV was low (as defined above). Hgb, Hct, and MCV, all later signs of iron deficiency (*13,44*), were not consistently related to blood lead. The results for ferritin and the composite measure of iron status were consistently related to blood lead; of these, ferritin was the best predictor of blood lead. Therefore we report results only for ferritin.

The next steps involved determining whether ferritin status modified the relationship between environmental lead and blood lead. We assigned each child to a high, medium, or low contaminated environment based on a composite measure of contamination. This measure was derived from a principal components analysis (minimum eigenvalue criteria = 1.0) that reduced the six correlated environmental variables (r = 0.15–0.65, p-value = 0.01 or less) (soil, indoor or outdoor paint, dust lead, lead loading, and housing age) to two independent environmental factors.

Table 1 presents the loadings for the variables in each factor. The first factor, Environmental Lead Factor 1, summarizes the largest share of the environmental data (eigenvalue = 2.52) and is primarily a general summary of the environmental lead variables. The second, Environmental Lead Factor 2, (eigenvalue = 1.4) is weighted most heavily by lead loading (the mass of lead per area of floor sample for house dust, micrograms per square meter) and reflects an effect of house dust lead loading that is independent from the overall household lead levels. We calculated contamination scores for each child by multiplying the loadings for each factor by the values of the associated variables and summing. We then assigned tertiles of these scores to high, medium, and low environmental contamination categories for each child.

Next, we conducted simple bivariate analyses to examine trends in blood lead levels between children with low ferritin and normal ferritin levels overall and within each level of environmental lead contamination. Results are presented for individual ethnic groups, all ethnic groups combined, and non-Asians combined. The bivariate analysis confirmed that Asians had a distinctly different relationship between blood lead levels and iron status at each level of environmental contamination. Our final model was run with and without Asians. Final results are presented for non-Asians only.

Finally, we developed a multivariate regression model with the dependent variable blood lead; the independent variables consisted of the covariates, main effects of iron status and environmental category, and an interaction term of these last two variables. We used this model to compute adjusted (least squares) mean blood lead levels for children with low and normal ferritin levels. This strategy allowed us to compare mean blood lead levels within and between environmental lead categories while adjusting for covariates, including age, sex, ethnicity, SES, reported use of vitamins with iron, and whether or not a child spent time in school or day care.

Results

Table 2 presents the study population distribution and blood lead and ferritin levels stratified by major covariates considered in the analysis. Overall, blood lead levels were similar to levels in the U.S. population as a whole at that time (geometric mean = 4.9 µg/dL; maximum = 23 µg/dL). However, 14% of the children exceeded 10 µg/dL, the CDC level of concern. No trends with age were apparent. Blacks and Asians had higher lead levels than Hispanics and whites. Female children also had slightly higher blood lead. Higher SES, reported use of vitamins with iron, and time spent in school or day care were associated with lower lead levels.

The average ferritin level was 19.1 ng/mL (Table 2), with 24% of children having ferritin levels < 12 ng/mL. As expected, ferritin tended to increase with age. Ferritin level was somewhat lower among Hispanics, female children, those with low SES, and those who did not attend school or day care. Paradoxically, ferritin was slightly higher among children with no reported use of vitamins.

Environmental measurements demonstrate significant lead hazards in the homes of many participating children (Table 3). Seventeen percent of soil lead levels were > 500 µg/g, a level associated with significant childhood exposure (*1,2,51*). Exterior paint lead levels were several times higher than interior paint, with 23% and 63% of interior and exterior paint samples, respectively, exceeding 5,000 µg/g, the current Department of Housing and Urban Development action level for abatement (*52*). Seventy-six percent of homes were built before 1950, after which paint lead levels started to decline (*53,54*). The six environmental variables were significantly correlated (r = 0.15–0.65; p-value = 0.01).

Table 4 presents unadjusted geometric mean blood lead levels for children with low ferritin and normal ferritin levels in all ethnic groups. For the population as a whole, the mean blood lead level is slightly higher (by 1 µg/dL) for children with low ferritin levels. This pattern persists within all ethnic groups, except for Asians, where children with normal ferritin levels appear to have higher blood lead levels. Excluding Asian children from the total population increases the difference in blood lead levels between children with low ferritin and those with normal ferritin levels to 1.8 µg/dL.

After adjusting for the potential covariates (ethnicity, sex, age, SES, use of vitamins, and whether or not the child has spent time in school or day care), the geometric mean

Table 3. Descriptive statistics for environmental measurements of lead and housing age.[a]

Medium	No. of homes sampled[b]	No. of children in homes with samples	Mean	± 1 SD	Maximum
Soil	227	375	234[c] µg/g	104–529	2,664
Indoor paint	222	367	1,412[c] µg/g	207–9,611	201,014
Outdoor paint	219	360	8,430[c] µg/g	949–74,892	320,834
Dust concentration	188	312	180[c] µg/g	79–411	3,105
Lead loading	188	312	24[c] µg/g	5–105	886
Housing age	232	361	52[d] (years)	31–73	100

[a]Data from Sutton et al. (*40*). [b]Total number of homes in study: 232. [c]Geometric mean +1 SD. [d]Arithmetic mean ±1 SD.

blood lead levels for non-Asian children with low ferritin and those with normal ferritin were 5.7 and 4.0 µg/dL, respectively (t = 4.0, p-value < 0.01). Including Asian children in the model reduced the magnitude of the difference to 1.0 µg/dL (t = 2.4, p-value = 0.02).

Figure 1 presents the adjusted geometric mean blood lead levels by ferritin status within low, medium, and high lead contamination categories for environmental lead factors (ELF) 1 and 2. We have not included Asian children in these adjusted analyses. Lead levels in children increase with the environmental measures of contamination, as shown in Figure 1. Children with low ferritin levels, regardless of the level of environmental contamination, have higher lead levels than do those with normal ferritin levels. The difference in blood lead levels between those with low and normal ferritin increases as the level of environmental contamination increases. (The mean difference in blood lead levels within each low, medium, and high contamination category for ELF1 = 0.7, 1.9, 3.2 µg/dL, and for ELF2 = 1.7, 0.8, and 2.9 µg/dL, respectively.) The results for both environmental factors are similar. The highest blood lead levels and the largest difference in mean blood lead levels between children with normal and low ferritin are seen in the highest contamination category (3 µg/dL).

Including Asian children in the model tended to reduce the significance and magnitude of the difference in means within each environmental category (about 1 µg/dL) but did not alter the overall pattern. For example, the difference in mean blood lead between low and normal iron-status children in highly contaminated environments was 2.8 µg/dL for ELF1 when Asians were included (p-value = 0.02), but 3.2 µg/dL when Asians were excluded (p-value = 0.01). Excluding the children with estimated environmental data also did not change the results. Finally, because more than one child may have come from the same household, we randomly selected one child from each household to assess possible bias introduced by the lack of independence. Although the statistical significance of some comparisons was reduced because of the smaller sample size, the overall results were not changed (data not shown).

Discussion

Overall, we found that children with iron deficiency, as measured by low ferritin level, had higher blood lead levels than children with normal iron levels. This relationship persisted after we stratified by the level of environmental contamination measured in their homes, with the largest difference in blood lead between iron-deficient and iron-replete children living in the most contaminated environments. These results suggest that inadequate iron status may amplify the effect of lead contamination in the environment by increasing absorption and possibly retention of lead in the body and/or increasing hand-to-mouth or pica behavior and thus lead ingestion (*28,29*).

Our finding is consistent with several studies that have reported higher proportions of children with elevated blood lead among those with low iron levels (*15,16, 34–36*). Yip and Dallman (*15*) found that the correlation of iron deficiency and blood lead was strongest among the youngest children (1–2 years), weaker in older children, and not significant in adults. This lack of correlation between iron and blood lead in older children (10–18 years) was also reported by Hershko et al. (*37*). The age distribution in our study is limited to young children, who are at highest risk for lead exposure, so our results cannot be generalized to findings for older children.

The relationship of iron status and blood lead varied within ethnic groups in this population, with Asian children having an apparently paradoxical association of sufficient iron status and higher blood lead. We have no clear explanation for this unexpected finding. We have speculated about the possibility of lead-contaminated foods or cooking utensils linking both iron and lead ingestion, but no data are available. The Asian participants in our study were primarily of Southeast Asian origin. It is possible that genetic polymorphisms for δ-aminolevulinic acid dehydratase (ALAD) alleles (*55–58*), or other differences in lead binding proteins could affect blood lead independently of iron status. It is also possible that this finding was caused by chance alone. Additional research is needed to explain intraethnic patterns of lead exposure and iron status.

Our results may be affected by misclassification of iron status or environmental lead exposure. Although low ferritin status is sufficient evidence of iron deficiency (*44*), normal ferritin status does not necessarily indicate iron sufficiency because ferritin is an acute-phase reactant and may be elevated by infection or inflammatory disease (*44*). Thus, some iron deficient children may have been misclassified as iron-replete on the basis of ferritin level, which would bias our results toward the null hypothesis. Similarly, the characterization of environmental lead exposure may have been misclassified because we could not consider a child's behavioral interaction with his or her environment within a given environmental contamination category. The presence of a lead hazard in the home is a necessary but not a sufficient prerequisite for exposure to lead. Children's exposures may vary widely depending on behavior. We also did not consider dietary sources of lead exposure other than possible use of imported pottery and home remedies.

Several factors limit the generalizability of our findings. As a cross-sectional study, it is impossible to determine the temporal pattern of exposure, iron deficiency, and blood lead, so we cannot infer causal relationships between these factors. Additionally, it is possible that iron deficiency is correlated with calcium deficiency, which may also enhance lead

Table 4. Unadjusted blood lead levels by ethnicity and ferritin status.[a]

Ferritin status	Geometric mean blood lead (µg/dL)					
	Black	Hispanic	Asian	Other[b]	Total	Total without Asians
Low ferritin	6.6	5.5	4.6	7.7	5.6	6.0
± 1 SD	4.1–10.6	2.9–10.4	1.9–10.8	3.8–15.5	2.8–11.0	3.3–11.0
n	15	38	17	8	78	61
Normal ferritin	5.3	3.8	6.7	3.8	4.6	4.2
± 1 SD	3.1–9.2	2.0–7.2	3.6–12.3	1.9–7.5	2.4–8.8	2.2–8.0
n	63	93	41	44	241	200

[a]Normal ferritin status: ferritin > 12 ng/mL; low ferritin status: ferritin ≤ 12 ng/mL. [b]Predominantly white.

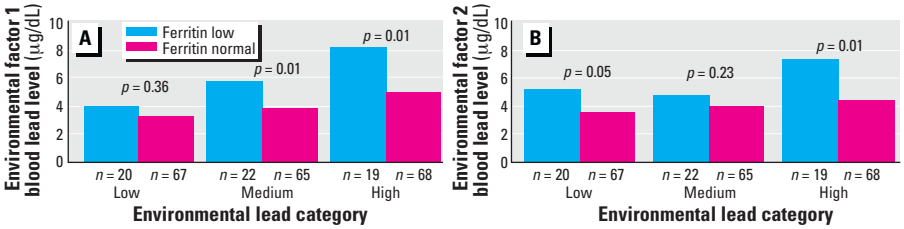

Figure 1. Adjusted geometric mean blood lead levels by ferritin status and environmental lead category: (*A*) Environmental Factor 1; (*B*) Environmental Factor 2. R^2 for full model = 0.23; n = 261 (excludes Asians); p-values for difference of means; ferritin low ≤ 12 ng/mL; ferritin normal > 12 ng/mL. Values adjusted for ethnicity, sex, age, SES, reported use of vitamins with iron, and whether or not the child spent time in school or day care.

absorption (*59–61*). However, the evidence for an inverse relationship between blood lead and calcium intake in the normal physiologic range is uncertain (*62*). Several studies suggest that ingestion of calcium inhibits lead uptake (*35,38,39,59–64*), but the role of chronic calcium deficiency has not been fully elucidated (*62*). Studies of calcium intake and blood lead themselves may be confounded by sociodemographic factors and failure to account for proximate exposure sources.

In summary, we found that iron-deficient children averaged 1–2 μg/dL higher blood lead than children with adequate iron status, with as high as a 3 μg/dL difference for children in the most contaminated environments. By directly controlling for environmental contamination we avoided confounding by the simultaneous presence of sociodemographic lead exposure-risk factors. Because population blood lead levels are log-normally distributed (*10*), small average reductions in lead levels would significantly reduce the proportion of children exceeding 10 μg/dL, the CDC level of concern. Thus, improving iron status in children could, if confirmed, help achieve important public health objectives of reducing blood lead levels below this threshold, particularly for children living in difficult-to-reach contaminated environments. Both iron deficiency and lead exposure disproportionately affect minority, poor, and urban children (*10*). Because iron deficiency has independent effects on cognitive functioning in children that are similar to those of lead poisoning (*1,8,27,65,66*), there should be important prophylactic benefits for children's health and development if organized intensive iron deficiency screening, nutritional counseling, and supplementation were implemented in areas where children are at high risk of both conditions (*67*). Because the relationship between nutritional factors and blood lead is likely to be a complex interaction of nutritional status, individual diurnal and secular nutrient intake patterns, meal frequency, behavior, caregiver ability, and environmental contamination, additional research is urgently needed to validate current hypotheses and quantify the specific benefits of sufficient iron status while accounting for calcium and other major nutrient cations. Because of uncertainties about the benefits of nutritional factors in reducing blood lead (*62*), improved nutritional status must be complemented with removal of lead from children's environments.

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Violence: An Unrecognized Environmental Exposure that May Contribute to Greater Asthma Morbidity in High Risk Inner-City Populations

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In the United States, rising trends in asthma prevalence and severity, which disproportionately impact minorities and the urban poor, have not been fully explained by traditional physical environmental risk factors. Exigencies of inner-city living can increase psychosocial risk factors (e.g., stress) that confer increased asthma morbidity. In the United States, chronic exposure to violence is a unique stressor existing in many high-risk urban neighborhoods. In this paper, we describe a series of cases that exemplify a temporal association between exposure to violence and the precipitation of asthma exacerbations in four urban pediatric patients. In the first three cases, the nature of the exposure is characterized by the proximity to violence, which ranged from direct victimization (through either the threat of physical assault or actual assault) to learning of the death of a peer. The fourth case characterizes a scenario in which a child was exposed to severe parental conflict (i.e., domestic violence) in the hospital setting. Increasingly, studies have begun to explore the effect of living in a violent environment, with a chronic pervasive atmosphere of fear and the perceived or real threat of violence, on health outcomes in population-based studies. Violence exposure may contribute to environmental demands that tax both the individual and the communities in which they live to impact the inner-city asthma burden. At the individual level, intervention strategies aimed to reduce violence exposure, to reduce stress, or to counsel victims or witnesses to violence may be complementary to more traditional asthma treatment in these populations. Change in policies that address the social, economic, and political factors that contribute to crime and violence in urban America may have broader impact. ***Key words*****: asthma, case series, inner-city, stress, violence.** ***Environ Health Perspect*** **109:1085–1089 (2001). [Online _____]**
http://ehpnet1.niehs.nih.gov/docs/2001/109p1089-1089wright/abstract.html

Case Presentation

We present three cases encountered in the Boston City Hospital Pediatric Allergy–Immunology–Respiratory Clinic and a fourth case seen as an inpatient at Boston City Hospital in which exposure to violence seemed to be the asthma symptom precipitant.

Case 1. Case 1 is a 12-year-old African-American girl with lifelong asthma who has numerous recognized triggers that include pollen, cold air, and exercise. She had presented several times each year to her neighborhood clinic with acute wheezing that responded to nebulized bronchodilator treatment. On initial evaluation in July 1994, her physical exam was notable for allergic rhinitis. Pulmonary function testing showed a mild obstructive defect primarily affecting the small airways: forced vital capacity (FVC), 94%; forced expiratory volume in 1 sec (FEV_1), 79%; and forced expiratory flow rate over the middle 50% of the FVC volume ($FEF_{25\%–75\%}$), 51%. Oral antihistamines, nasal cromolyn, and inhaled steroids were added to her inhaled bronchodilator therapy. In the subsequent month, amoxicillin was begun for sinusitis, and nasal steroids were added to her treatment regimen. After a period of symptom stability she developed increased wheezing in October 1994. Oral prednisone was begun, resulting in rapid improvement to her baseline by the fifth day which was Halloween. On Halloween night, the patient heard gunshots outside of her home in a housing project and shortly thereafter became aware that one of her peers had been fatally shot. She quickly developed recurrent wheezing, slept poorly that night due to respiratory symptoms, and required an extended course of prednisone to control the recurrent asthma exacerbation. Following recovery from this episode, her asthma stabilized.

Case 2. Case 2 is a 15-year-old Hispanic girl who has had severe asthma since infancy and is now enrolled in a college preparatory course in an urban high school. Her history was remarkable because of her need for assisted ventilation with status asthmaticus at the age of 2 years and subsequent every-other-day prednisone therapy up to the age of 5 years. Her currently recognized asthma triggers include exercise, upper respiratory tract infections, and exposure to dust and pets. Allergy skin testing demonstrated sensitivities to several environmental allergens. She was controlled on theophylline, inhaled serevent, flunisolide, nedocromil, oral antihistamines, and regular peak flow monitoring. Typical pulmonary function test results before and after bronchodilator therapy, respectively, in the Pediatric Allergy–Immunology–Respiratory clinic for this patient were FVC, 68% and 100%, FEV_1, 43% and 69%, and $FEF_{25\%–75\%}$, 17% and 31%. During the fall of 1994 she developed increased wheezing on three occasions, which required pulse doses of prednisone. Each episode began on a Sunday evening before the start of a new school week. Inquiry revealed that, at the end of the previous school year, the girl had been attacked on a subway platform by a group of girls. She was physically attacked and her jewelry and book bag, containing her asthma medications, were stolen. In retrospect, Case 2 reported an acute asthma episode immediately after the assault. The patient later identified the assailants to the police and pressed charges against them. Through the fall, the patient encountered her assailants periodically on the subway. She subsequently experienced an asthma flare after a court appearance where she testified against her attackers; during this court appearance, they verbally threatened her. After the sentencing of the assailants, the patient had no further

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R.J.W. received support from NIH training grant HL07427 and the Medical Foundation Deborah Munroe Noonan Memorial Fund.

Received 24 April 2001; accepted 20 July 2001.

documented acute asthma exacerbations for 15 months corresponding to the period of incarceration of her assailants. Over this time course she stopped taking her medications except for an albuterol inhaler as needed and she did not receive follow-up in the Pediatric Allergy-Immunology-Respiratory Clinic. Following the release of the assailants, she again developed severe symptoms requiring two hospitalizations in a 2-month period.

Case 3. Case 3 is a 9-year-old Caucasian girl with asthma since early infancy. The known triggers include exercise, emotional upsets, and upper respiratory tract infections. Allergy skin testing demonstrated sensitivity to many environmental allergens including *Aspergillus*. Sputum cultures have been repeatedly negative for *Aspergillus*, and measured immunoglobulin E (IgE) is 154. Her asthma was managed on inhaled flunisolide, cromolyn, an albuterol inhaler as needed, nasal cromolyn, and diphenhydramine. During the spring of 1994, frequent asthma exacerbations led to a 3-month course of prednisone. Typical pulmonary function test results were as follows: FVC, 90%; FEV_1, 69%; and $FEF_{25\%–75\%}$, 41%. Intensive allergen control measures in the home, including replacing carpeting with linoleum, installing a dehumidifier, restoring crumbling walls, and fumigation, were associated with success in weaning the patient off prednisone and normalization of her spirometry. In October 1994 her daily wheezing returned. It was subsequently revealed that Case 3 had been assaulted on the school bus by an older boy and had reported the incident to teachers. Thereafter the perpetrator's female cousin began to threaten to stab the patient with sharp scissors while they were riding the school bus. The patient finally refused to board the school bus one day for the ride home and subsequently developed wheezing and respiratory distress requiring emergency treatment.

Case 4. Case 4 is a 3-year-old girl admitted to the pediatric intensive care unit (ICU) with an asthma exacerbation in the setting of a viral illness and an exposure to sprayed pesticide 10 days before the onset of symptoms. The patient's initial oxygen saturation was 77% on room air and 89–95% on a 100% non-rebreather face mask. She did not require intubation. Three days into her hospital course, the patient began to show slow clinical improvement on a medical regimen that included continuous nebulized ventolin treatments, intravenous solumedrol, ipratroprium bromide nebulized treatments, and a continuous terbutaline infusion, which was started on the second hospital day.

Case 4's mother stayed with her around the clock. Visits by the patient's father were associated with loud arguments between the parents, which were overheard by the medical staff caring for the patient. On one occasion, a nurse observed the patient's mother slapping the father and then the patient's father pushing and shoving the mother. The health care staff noted that the patient's respiratory rate had increased from 50–60 breaths/min to 80–90 breaths/min during her exposure to these parental encounters. One event documented in the medical record describes the father hitting the mother, causing her to crash into the glass doors of the patient's ICU room. The patient became visibly upset and began screaming. Vital signs documented before the event charted a respiratory rate of 30–34 breaths/min, a heart rate of 145 beats/min, a temperature of 99.4°F, and oxygen saturation of 92% on a 40% face mask. Vital signs documented in the 3–4 hr after the episode showed a clinical decompensation with a respiratory rate of 42–50 breaths/min, a heart rate of 155–180 beats/min, and an initial oxygen saturation of 91% on a 70% face mask. A clinical exam documented decreased air movement and recurrent wheezing associated with the persistent tachypnea and tachycardia.

Discussion

These cases exemplify a temporal association between exposure to violence and the precipitation of asthma exacerbations in four inner-city pediatric patients. Although each patient is vulnerable to a variety of asthma triggers, exposure to violent events seemed to be a common precipitant of asthma symptoms. Notably, Case 2 experienced improvement in her chronic asthma symptoms once the perceived threat of violence was no longer present and deterioration in her respiratory status when that threat reemerged. In Case 4, there was a clear temporal association between witnessing parental conflict and deterioration in the patient's clinical course and vital signs. Because of a raised awareness, we are now inquiring about exposure to violence as an apparent asthma symptom precipitant. Although these cases support a role of exposure to violence and acute exacerbations of established asthma, we should also consider plausible pathways through which living in a violent environment may influence the genesis of asthma.

Asthma is the most common chronic disease of childhood and a leading cause of morbidity in children. In the United States, recent trends of increasing childhood asthma prevalence and morbidity disproportionately affect nonwhite children living in urban areas and children living in poverty (*1–3*). It is not clear that differences in generally known asthma risk factors such as chemical and particulate air pollutants (*4*), environmental and *in utero* tobacco smoke exposure (*5*), viral respiratory infections (*6*), and home allergen exposure (*7*) fully explain these trends. As yet unidentified unique factors may contribute to the higher asthma morbidity and mortality rates seen in inner-city poor minority populations (*8*).

Connections between the health and economic well-being of populations are increasingly seen to be embedded within the larger context of people's lives. It has been proposed that differential exposure to and perception of stress may, in part, explain socioeconomic disparities in health (*9*). Various sociodemographic characteristics (e.g., lower social class, ethnic minority status) may predispose individuals to particular pervasive forms of life stress (*10,11*), and the degree of chronic stress can be significantly influenced by the characteristics of the communities in which people live (*12*). Chronic stress in U.S. urban populations has been conceptualized as neighborhood disadvantage, characterized by the presence of a number of community-level stressors including poverty, unemployment, substandard housing, and high crime/violence rates (*13*). Such physical and social factors can be a source of environmental demands that contribute to stress experienced by populations living in a particular area (*14*).

Studies in minority and lower-income populations have shown a high prevalence of children who encounter violence in the inner city. A prevalence study at Boston City Hospital found that 10% of children had witnessed a knifing or shooting before the age of 6 years; 18% had witnessed shoving, kicking, or punching; and 47% had heard gunshots (*15*). In an inner-city cohort in Chicago, Illinois, investigators found that of children between the ages of 7 and 13, 42% had seen someone shot and 37% had seen someone stabbed (*16*). A survey of urban elementary school children in New Orleans, Louisiana, found that more than 90% had witnessed violent episodes, 70% involving use of weapons (*17*). Although stress is decidedly common and has many causes in our society, the increased prevalence of chronic community violence is a specific and extreme stressor confronting the urban poor.

Violence can be conceptualized as a source of psychological and environmental stress that taxes both the individual and the communities in which they live. Community violence can be considered a pervasive stressor that adds to environmental demands imposed on an already vulnerable population of children and families (*18*). Inner-city populations that experience high rates of exposure to violence are also characterized by high levels of poverty, hopelessness, lack of opportunity, and unemployment (i.e., chronic ongoing stressors). Living in a violent environment is

associated with a chronic pervasive atmosphere of fear and the perceived threat of violence (*19,20*). Children and families living with community violence are likely to view their world and their lives as being out of their control. Facing daily life experiences in an unpredictable or uncontrollable environment predisposes these populations to greater deleterious effects of stress (*21*). Moreover, both the duration and the frequency of experienced stress are important determinants of its impact on health and illness. Variable response to acute challenges (e.g., high frequency of exposure to violence) superimposed on chronic stressors (e.g., other components of neighborhood disadvantage) may have different implications on disease expression (*22*). Events that last a very short time can also have more long-term stress effects through lasting physiologic responses thought to be maintained by recurrent unwanted or "intrusive" thoughts about past events (*23*). Symptoms of post-traumatic stress disorder (PTSD), including flashbacks or recurrent memories of traumatic events, are highly associated with exposure to violence (*24*).

Psychological stress has been associated with the activation of the hypothalamic–pituitary–adrenal (HPA) axis and disturbed regulation of the HPA system.This may best be understood within McEwen el al.'s concept of allostasis, which refers to the ability of the body to achieve stability through change, such that "the autonomic nervous system, the HPA axis, and cardiovascular, metabolic, and immune systems protect the body by responding to internal and external stress" (*25*). The potential cost of such accommodation is conceptualized as allostatic load, which is the wear and tear from chronic overactivity (or underactivity) of the HPA system. With regard to immune function, during a period of acute stress, increased cortisol and catecholamines promote allostasis by influencing cell trafficking and by modulating cytokines, which fight infection (*26*). In contrast, chronic overactivity (or underactivity) of these same mediators may result in allostatic load (i.e., potential immunosuppressive effects when the mediators are chronically secreted or not turned off). Some optimal level of mediators is needed to maintain a functional balance, and the absence of appropriate levels of gluccocorticoids and catecholamines may allow other immune mediators to overreact and increase the risk of inflammatory disorders (*27*). In this framework, violence can be conceptualized as a psychosocial environmental exposure that can "get into the body" and result in biological changes that may contribute to asthma morbidity.

There is a renewed interest in the links between psychological stimuli and asthma (*28,29*). Exposure to violence as a major life stressor may impact on the pathogenesis of asthma and/or contribute to the morbidity of disease by triggering exacerbations through neuroimmunologic mechanisms. Augmented parasympathetic response has been documented after intense or prolonged stress experiences (*30,31*). Increased parasympathetic tone produces increased smooth muscle tone in the lung and thus may mediate emotionally induced bronchoconstriction in asthma (*32*). Cytokines known to be important in inflammatory diseases like asthma may also serve a role in mediating the acute response to physical and emotional stress. Psychosocial stressors can moderate both humoral and cellular immune function (*33,34*). Stressor-linked alterations in the immune system may predispose to respiratory tract infections (*35,36*), which may trigger acute asthma exacerbations. Stress hormones influence immunoglobulin and cytokine expression and thus may increase a genetically predisposed individual's risk of developing asthma. Current knowledge supports the notion that expression of the asthmatic phenotype, as related to the immune response, is modulated by environmental factors that include viral infection, air pollutants, maternal smoking, breast-feeding, and allergen exposure (*37*). Stress may potentiate the allergic response to allergens by increasing the release of inflammatory mediators and the subsequent cascade of inflammatory events characteristic of chronic asthma. That is, violence as a psychosocial stressor may be an "adjuvant" to the asthmatic inflammatory response. Thus, while stress and emotional distress are generally recognized as factors aggravating asthma symptoms in those with existing disease, they may play a role in the genesis of the disease as well (*29*).

Preliminary empirical evidence suggests that exposure to violence may contribute to the burden of asthma morbidity on the inner-city poor. In a cohort study in Boston, Wright et al. (*38*) retrospectively ascertained lifetime exposure to violence through a parental-report interview questionnaire administered to 416 caregivers and their children who are being followed longitudinally for respiratory health outcomes, including asthma. Preliminary analyses suggest a link between higher lifetime exposure to community violence and an increased risk of asthma and wheeze syndromes and prescription bronchodilator use.

Violence exposure may ameliorate resources needed to manage and cope with chronic asthma. Exposure to community violence (and other determinants of neighborhood disadvantage) may operate through effects on impulse control, risk-taking behavior, and the adoption of coping behaviors such as smoking, thus leading to increased exposure to a known environmental asthma trigger (*39*). Smoking can be conceptualized, at the individual level, as a strategy to cope with negative affect or stress (*40,41*). Neighborhood effects on health behaviors such as smoking have also been demonstrated (*42,43*). For example, evidence from the 1987 General Social Survey (*44*) suggests that stress may be one factor promoting increased prevalence of smoking in African-American communities. Romano et al. (*45*) surveyed 1,137 African-American households and found that the strongest predictor of smoking was a report of high-level stress, represented by a "hassles" index. The "hassles" index was an abbreviated 10-item scale based on items chosen to represent a dimension that community residents involved in the project perceived to be especially relevant. Notably, among the items were neighborhood level factors including being concerned about violence or living in an unsafe area.

Community-level characteristics such as increased prevalence of violence may influence an individual's behavior, resulting in increased exposure to other known environmental risk factors for asthma. Parents in high-violence communities may restrict their children's outdoor activities. In the same Boston pediatric cohort discussed above, parental reports of keeping children indoors primarily because of fear of neighborhood violence was related to increased risk of wheeze and physician's diagnosis of asthma prior to the age of 2 years (*46*). Reasonable hypotheses as to why this association was seen may include the following. The child who is kept indoors may become deconditioned, experiencing shortness of breath with decreasing levels of exertion. An increased sedentary lifestyle may be linked to obesity in children. Recent studies have linked obesity to asthma (*47,48*), and studies suggest that obesity has increased among families living in poverty in the United States (*49*). Also, children who are kept indoors may be exposed for longer periods to indoor aeroallergens and have an increased likelihood of sensitization and allergic symptoms in response to dust mite, pet, roach, and rodent allergens. Parents who are worried about their children's safety in their neighborhood because of crime may keep their children indoors and otherwise restrict their social behavior; thus each child's ability to develop support networks may be compromised (i.e., exposure to violence may lead to diminished stress-buffering factors such as social networks) (*50*). Psychopathology (e.g., PTSD, depression) influenced by life stress and chronic exposure to violence may also prevent the child from forming relationships that are necessary to promote normal social development. Fear of crime fosters a distrust of

others and can contribute to social isolation (*51*). It is clear that violence is related to factors that limit formation of social networks. These additional supports may be especially important to health and well-being in high-risk urban populations faced with cumulative effects of many other ecologic stressors (i.e., poverty, low education, poor housing).

Coping with a violent environment may affect compliance with therapy and medical follow-up for asthma. Fong (*52*) discussed the impact of violence on the management of hypertensive urban African Americans, underscoring violence as a perceived barrier to keeping appointments and following prescribed exercise programs. Fear of making a trip across town to a pharmacy or medical facility or adhering to a prescribed walking program as a result of prior victimization or a perceived threat of violence may be a barrier to compliance. This may lead to lapses in use of prophylactic medication, delayed intervention, and consequently greater morbidity. Adolescents who witness violence are more likely to develop a foreshortened sense of the future (*53*) and thus a fatalistic outlook that may undermine their ability to invest in the future by complying with a chronic asthma treatment regimen. Other barriers to adherence to a prescribed asthma regimen may include the lack of a community pharmacy open 24 hr/day. Pharmacies may be reluctant to remain open 24 hr/day in poor communities, especially when violence is a concern. Violence can indirectly affect access to medical care by diverting limited funds away from primary care and specialty clinics, including those caring for asthmatics (*54,55*).

Exposure to violence may affect asthma management when increased family dysfunction impedes development of appropriate coping strategies necessary to facilitate improved quality of care for the asthmatic child. Dysfunctional patterns are common in homes of children with asthma and may be precipitated by anxiety experienced around asthmatic attacks (*56*). Family dysfunction has been related to increased asthma morbidity and mortality (*57,58*). The level of stress in the home of an asthmatic child is likely to increase as parents attempt to balance the child's need for activity and independence with their concerns about avoiding allergen- or exercise-induced symptoms and maintaining adherence to a pharmacologic regimen. Likewise, stress and anxiety may be compounded in families who are also faced with the real or perceived threat of violence or injury in the child's home, neighborhood, or school, which leads to greater dysfunction. Parents who have experienced violence, or whose children have had such experiences, may develop depression or PTSD, which impairs their ability to supervise and respond to their children. This reduction in parenting capacity may undermine an adult's ability to coordinate a child's ongoing asthma care.

Conclusions

Exigencies of inner-city living, such as coping with the high prevalence of exposure to violence, may increase psychosocial risk factors, which in turn may confer increased asthma morbidity on high-risk urban populations. High crime rates, and thus the real or perceived threat of violence, are specific aspects of the inner-city environment that may impact psychologic functioning as well as health-promoting and health care-seeking behaviors of the inhabitants (*59*). More research is needed to examine the public health impact of children and their families living with violence. Systematic exploration of an association between violence (an urban stressor) and asthma throughout childhood may help us to understand the rise in asthma prevalence, severity, and medical care use as well as to further our understanding of its disproportionate occurrence in poor urban children in this country. We present these cases to alert clinicians and researchers to a potential risk factor for increased asthma morbidity that has not previously been recognized.

Increasingly, pediatricians are being asked to manage chronic childhood illness in the context of complicated family and community environments that clearly impact disease management. Pediatricians have long recognized the impact of violence on the health and well-being of children and have been expanding efforts to increase response to exposure to violence as a health care issue in the clinical setting (*60*). The identification of exposure to violence as a trigger of asthma exacerbations may alert health professionals caring for asthmatics in the inner-city setting to inquire about patient's exposure among other known triggers. Secondary intervention strategies designed to reduce exposure to violence or to facilitate positive coping mechanisms for individual patients may obviate the need for more aggressive and costly pharmacologic therapies for asthma with potential side effects. For example, referral to a stress reduction program or to programs that provide counseling for children who have witnessed or experienced violence (*61*) may be helpful. In our experience, it is unlikely that the child's asthma control can be improved unless such psychosocial issues are also addressed.

Primary prevention at the population or neighborhood level should also be considered. Social cohesion and social capital are strongly correlated with rates of violent crime within neighborhoods (*62*). Research suggests that crime is most prevalent in societies that permit large disparities in the material standards of living of its citizens, which in turn are created by broad-scale societal and political factors (*63,64*). Emerging evidence underscores the need for policy makers to pay increased attention to political and economic forces that result in further marginalization of minority populations in the inner city and contribute to the growing income gap between the rich and the poor in this country (*65*). Policies aimed at improvements in life opportunities and living conditions may increase social cohesion and decrease violence in the inner cities. Social cohesion may influence the health behaviors of neighborhood residents by promoting diffusion of health information or increasing the adoption of healthy behaviors through exerting social control over smoking. Improved neighborhood social capital may impact health through increased access to local services and amenities (e.g., safe transportation, pharmacy availability). It is unlikely that the health problems of disadvantaged populations can be solved unless we try to understand the potential role of unique environmental stressors such as violence exposure.

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