Low-Level Fetal Lead Exposure Effect on Neurobehavioral Development in Early Infancy

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ABSTRACT. A prospective method was used in this study to assess the effects of fetal lead exposure on neurodevelopmental status in 3- and 6-month old infants. At their first prenatal medical appointments, 305 lower socioeconomic status women residing in predesignated lead-hazardous areas of Cincinnati were recruited. Lead was measured in whole blood in both the mother and fetal-placental unit (prenatal and cord) and the neonate (ten days and 3 months). All blood lead levels were less than 30 μg/dL. Infant development was assessed with the Bayley scales at 3 and 6 months of age. Multiple regression analyses which treated perinatal health factors such as birth weight and gestation as confounders indicated an independent, inverse relationship between both prenatal and neonatal blood lead levels and performance on the Bayley Mental Developmental Index at both ages. Male infants and infants from the poorest families appeared to be especially sensitive to these psychoteratogenic influences. Further study using a structural equations approach indicated that neurobehavioral deficits were partly mediated by lead-related reductions in birth weight and gestation. *Pediatrics* 1987;80:721–730; *lead, fetal development, behavior, sex differences, teratology.*

ABBREVIATIONS. MDI, Mental Developmental Index; HOME, Home Observation for Measurement of the Environment; PDI, Psychomotor Developmental Index.

It has long been recognized that lead at high doses is an abortifacient and potential teratogen.[1-3] Lead is known to cross the human placenta and accrue in fetal tissues during gestation.[4] Congenital lead poisoning has been previously reported in neonates of women working in the lead industry and in association with the consumption of non-commercially produced spirits.[5] Reports of congenital lead poisoning in infants from third-world countries, where lead is still widely used in pottery and cosmetics, continue to appear.[6]

Today, the primary concern of pediatricians and epidemiologists is on levels of fetal lead exposure that do not normally result in miscarriage or obvious neonatal pathologic conditions. There is a growing body of data from several longitudinal studies that indicate that lower level in utero lead exposure may be related to deficits in both fetal growth and postnatal behavioral development. For example, Bellinger and his colleagues[7-9] in Boston found that umbilical cord blood Pb levels of less than 25 μg/dL were independently associated with small deficits in Bayley Mental Developmental Index (MDI) at 6, 12, and 24 months of age. In other longitudinal studies in Cincinnati and Port Pirie, Australia, low level fetal lead exposure has been associated with lower birth weight,[10,11] and shorter gestation.[11,12] Needleman and his colleagues[13] evaluated the relationship between prenatal exposure to lead and minor congenital anomalies in 4,354 births in Boston. Umbilical cord blood lead level was found to be associated, in a dose-related manner, with an increased risk for minor anomalies.

In this paper, we present the first results of a major longitudinal study of the effects of chronic low to moderate lead exposure on child development.[14] It was hypothesized that prenatal exposure to lead, as indexed by maternal, umbilical cord, and neonatal blood lead levels, would be related to sensorimotor developmental deficits when infants were 3 and 6 months of age. It was also hypothesized that lead exposure would interact with other peri-

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natal risk factors such as race, sex, and social class; those fetuses at higher risk because of genetic or social factors would later display a greater lead-related behavioral deficit. Finally, it was hypothesized that neurobehavioral deficits would be partly a function of the negative effect of prenatal lead exposure on fetal growth (birth weight) and physical maturation (gestational age as determined by examination of the neonate).

METHODS

Subjects

The final follow-up study sample consisted of 305 mothers, recruited between 1979 and 1984, residing in predesignated lead-hazardous areas of Cincinnati. This geographical area has a history of having a relatively large number of children with lead poisoning according to city health department data. Results of other studies on the Cincinnati cohort have shown that lead from paint, dust, and generally poor housing stock is the major contributor to body burden.[15] Informed consent for participation in the study was obtained at prenatal recruitment and again at delivery to obtain permission for infant follow-up. Women known to be addicted to drugs, alcoholic, or diabetic or those with proven neurologic disorders, psychoses, or mental retardation were excluded from prenatal recruitment. Excluded from prenatal recruitment on these bases were 487 women, and 23 refused to participate (ie, have their blood sampled for lead). The age of enrolled mothers at delivery was 22.7 ± 4.5 years (mean ± SD); 87% of the mothers were single, and 86% were on public assistance. Vital descriptive statistics on mothers and infants in the study are given in Table 1.

Infants of less than 35 weeks' gestation, and/or 1,500 g birth weight were excluded from postnatal recruitment. Furthermore, recruited infants must have had an Apgar score of 6 or greater at five minutes and have no serious medical condition such as Down syndrome, phenylketonuria, or significant congenital anomaly. Excluded from postnatal recruitment based on these criteria were 76 neonates, and 129 families refused the 5-year postnatal follow-up. Study infants had a mean birth weight of 3,134.6 g (SD 462.8) and mean gestational age by physical examination[16] of 39.5 weeks (SD 1.7). Examinations for gestational age were conducted by University Hospital residents who were trained by J. L. Ballard, MD, the author of the protocol. Interexaminer reliability studies were not conducted for the purpose of the present study. However, the Ballard gestation estimate appeared to have excellent predictive validity given the strong and highly significant associations with mental and motor developmental outcomes at 3 and 6 months of age.

TABLE 1. Descriptive Statistics on Study Sample

Variable	Mean	SD	Low	High
Maternal age (yr)	22.7	4.5	15	39
Social class*	17.2	5.4	8	50
Home Observation for Measurement of the Environment[24] score†	31.5	4.7	17	42
No. of children in home	2.6	1.5	1	6
% unmarried	87.0			
Birth wt (g)	3,134.6	462.8	1,814	4,400
Gestational age (wk)‡	39.5	1.7	35	43
5-min Apgar score	8.9	0.4	7	9
% black	84.9			
% girls	49.8			

* Hollingshead Four-Factor Index of Social Status.[23]
† Scores of 30 or less are considered poor.
‡ As assessed by standardized physical examination of the neonate.[16]

Descriptive statistics on mothers and infants who were excluded from the study by prenatal/postnatal criteria or refusal to participate are given in Table 2. A comparison of Tables 1 and 2 show that study dyads and excluded dyads were similar in terms of such key sociodemographic variables as maternal age, marital status, and gravidity. As one would expect, excluded neonates had lower birth weights, gestational ages, and Apgar scores. There was also a higher tendency for white and/or married families to refuse study participation.

Assessment of Potential Confounders and Covariates

Undue lead exposure is known to covary with a number of social and biologic risks that may mimic, obscure, or otherwise interact with the effects of toxicant exposure on child development.[17-20] Therefore, a substantial amount of medical and social background data were collected on all subjects. The candidate confounders and covariates that were selected a priori based upon their theoretical and/or known empirical association with both the target independent variable (fetal lead exposure) and/or target dependent variable (3- and 6-month neurodevelopmental status) are listed in Fig 1.

Obstetrical history and pertinent perinatal data were recorded from the mother's and neonate's charts. These data were then coded using the Littman-Parmelee Obstetrical and Postnatal Complications Scales.[21] A Composite Index of Tobacco and Alcohol Consumption, taken from the Problem Oriented, Perinatal Risk Assessment System[22] was also used. The Composite Index of Tobacco and Alcohol Consumption variable was dichotomously

TABLE 2. Descriptive Statistics on Mothers and Infants Excluded From Study

Variable/Group	Maternal Exclusions	Neonatal Exclusions	Refusals	Abortions	Stillbirths
No.	487	76	152	43	10
% black	71	80	64	76	67
% unmarried	79	79	62	79	100
Maternal age (mean yr ± SD)	21.7 ± 5.9	22.9 ± 5.8	22.4 ± 4.1	23.2 ± 5.8	19.9 ± 5.1
Gravidity (mean No. ± SD)	1.7 ± 1.9	2.1 ± 2.0	1.7 ± 1.6	1.4 ± 1.4	0.9 ± 1.2
Birth wt (mean g ± SD)	3,097 ± 572	2,204 ± 892	3,237 ± 497	161 ± 04	1,246 ± 799
5-min Apgar score (mean ± SD)	8.7 ± 0.9	7.5 ± 2.5	8.8 ± 0.6		
Gestational age by examination[16] (mean wk ± SD)	38.9 ± 2.7	34.9 ± 4.6	39.4 ± 1.7	15.6 ± 0.5	29.0 ± 6.6

Perinatal Variables
- Birth wt
- Gestational age by examination
- Obstetrical Complications Scale
- Postnatal Complications Scale
- Composite Index of Tobacco and Alcohol Consumption
- No. of cigarettes smoked per day
- Maternal age at birth of child
- Gravidity
- Parity
- Maternal total iron-binding capacity
- Race of child
- Sex of child

Socioheredity Variables
- Socioeconomic status
- Developmental Stimulation (Home Observation for Measurement of the Environment Scale)
- No. of children in the home

Fig 1. Candidate confounders and/or covariates.

coded with a value of "1" indicating use of tobacco and/or alcohol during pregnancy. Use of these substances during the prenatal period was reported by 58% of study mothers. Information was also gathered through prenatal interview on the average number of cigarettes smoked per day during pregnancy. Most smoking women (98%) reported consumption of one pack (20 cigarettes) or none per day. Forty-seven percent of the cohort were nonsmokers. There was no evidence of alcoholism or drug-addiction during any of the sample pregnancies.

The socioeconomic status of the infant's family was assessed at 3 months postpartum with the Hollingshead[23] four-Factor Index of Social Status. The mean socioeconomic status score for study mothers or families was 17.2 (SD 5.4), reflecting the preponderance of single-parent, low-income households. As scheduled in the Cincinnati protocol, the quality of the infant's domestic environment was assessed with the Home Observation for Measurement of the Environment (HOME) at 6 and 12 months (B. M. Caldwell and R. H. Bradley, unpublished data, 1978). The HOME combines interviewer's questions with direct observations to yield subscale and total HOME scores. In general, results of the HOME measure the parent's responsiveness and personal involvement with her infant and the extent to which the physical environment is stimulating and safe. To procure a more stable and reliable measure of first-year environmental quality, the mean of the 6- and 12-month HOME scores was calculated for each infant and tested as a potential developmental covariate and/or confounder in regression models with lead variables.

All candidate covariables were pretested for their confounding potential in a "disease-primary trait" covariance matrix using a higher than standard P value ($\leq .10$) as criterion for initial inclusion in regression models with lead.[25] Any covariable associated with either blood lead level, behavioral development, or both was included in subsequent regression analyses.

Assessment of Lead Exposure and Neurobehavioral Development

A critical task of any study of this kind is the accurate and reliable assessment of lead level in physiologic compartments. The microanalytical laboratory at the University of Cincinnati, Department of Environmental Health, participates in several quality control programs for the measurement of lead in whole blood. The performance of this laboratory has been uniformly superior throughout the course of the current study.[11,26]

Maternal blood samples were collected by venipuncture at the first prenatal clinic visit. Of these samples, 50% were collected in the first trimester, and 49% and 1% were collected in the second and third trimesters, respectively. The difference in mean blood lead level by trimester of pregnancy was not statistically significant ($F = .27$, $P = .76$). Therefore, it was not deemed necessary to analyze these sets of blood lead data separately. Cord blood samples were collected at delivery, and newborn infant samples were collected postnatally at ten days (corrected for gestational age) and 3 months of age. Blood was drawn from infants by venipuncture, heel stick, or finger stick depending upon the

physical characteristics of the infant. Contamination of blood samples drawn by a method other than venipuncture was not a problem because of thorough presampling cleansing procedures and the controlled clinical conditions under which phlebotomy took place. Studies comparing the results of finger stick and venipuncture methods in our laboratory have shown no appreciable differences between the two methods when these strict practices are adhered to. Indeed, finger stick samples yielded slightly lower blood lead values, which is opposite to what one would expect if contamination were a problem. Prenatal (maternal) blood measurements were conducted by Environmental Sciences Associates (ESA) using an ESA model 2014 Anodic Stripping Voltammeter with strip chart recording. Cord and postnatal blood samples were analyzed at the University of Cincinnati using an ESA model 3010 Anodic Stripping Voltammeter. To increase precision of measurement, the instrument's digital readout was abandoned in favor of peak height determination using a strip chart recorder. We routinely conduct split-sample analyses comparing the 3010 results from our own laboratory with the 2014 ESA results. The Pearson r correlation between these two methods has never been less than +.97.

All blood lead values were corrected to an average hematocrit for developmental age, because the concentration of erythrocytes will affect the level of lead measured in whole blood. For some analyses, blood lead values were transformed to their natural logarithm. Duplicate statistical analyses were undertaken to determine whether such transformations affected the final regression models or statistical significance of lead exposure variables. In all cases, the final regression models examining the effects of fetal lead exposure on behavioral development remained the same whether blood lead was expressed in micrograms per deciliter or natural log units.

Statistics on blood lead variables are shown in Table 3. Mothers had an arithmetic mean prenatal blood lead value of 8.0 μg/dL (SD = 3.7) and mean umbilical cord blood lead value of 6.3 μg/dL (SD = 4.5). Newborns had arithmetic mean blood lead values of 4.6 μg/dL (SD = 2.8) at ten days of life and 5.9 μg/dL (SD = 3.4) at 3 months of age. Three-month blood lead was considered in this study as another index of fetal exposure, although extrauterine sources of lead in diet, water, and atmosphere cannot be entirely discounted.

The intercorrelations among fetal lead exposure variables are shown in Table 4. Most correlations between lead exposure variables were low to moderate. This was probably due, in part, to the long periods of time between assessments (eg, maternal and umbilical cord samples) and the fact that blood was taken from different pools (ie, maternal and neonatal).

In observational studies, data are often missing on one or more key independent or dependent variables. This proved to be the case for fetal lead exposure variables. Of the 305 subjects in the sample, 266 prenatal, 96 cord, and 302 newborn blood lead values were available for analyses. Prenatal blood lead levels were usually missing because of the inability to obtain a sample at the time of recruitment. Furthermore, only high quality cord blood lead samples were considered suitable for analysis; those with clots or microclots were not assessed. Newborn blood lead assessments were missing as a result of a missed postnatal appointment or the inability to obtain a sample because of the physical characteristics of the infant. Nevertheless, analysis of variance showed that subjects with missing prenatal, cord, or newborn blood lead measurements did not significantly differ ($P \leq .10$) from the rest of the sample on study covariates or indices of behavioral development.

Behavioral development was assessed when the infants were 3 and 6 months of age with the MDI and Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development.[27] The Bayley scales at 3 and 6 months provide differential indicators of the infant's neurodevelopmental status and reflect attentiveness and responsiveness to stimuli, motor abilities in the manipulation of objects, and postural control. The Bayley scales were administered in the morning at an inner-city health clinic by one of three professionally trained psychometricians. Care was taken to ensure that the infant was not noticeably ill, fatigued, hungry, or receiving medication when examined. Intertester

TABLE 3. Descriptive Statistics on Fetal Lead Exposure Variables*

Blood Lead Variable	No.	Mean	SD	Low	High
Prenatal (maternal)	266	8.0	3.7	1	27
Umbilical cord	96	6.3	4.5	1	28
Newborn (10 d)	302	4.6	2.8	1	22
Newborn (3 mo)	302	5.9	3.4	1	22

* Results are expressed as micrograms per deciliter of whole blood.

TABLE 4. Intercorrelations Among Fetal Lead Exposure Variables*

	Cord Blood Lead	10-d Blood Lead	3-mo Blood Lead
Prenatal blood lead	0.42†	0.30†	0.38†
Cord blood lead		0.38†	0.32†
10-d blood lead			0.54†

* Pearson r.
† $P \leq .001$.

reliability was assessed several times throughout the study and averaged .96 (Pearson r) for the Bayley MDI and PDI. This research protocol was reviewed and approved by the Committee on Human Research of the University of Cincinnati College of Medicine.

Data Analyses

The data analytic procedures used in this study were designed to achieve the best possible compromise between the conflicting goals of reducing the probability of type I error (ie, false-positive lead effect) and type II error (ie, false-negative [no] lead effect). The analytic strategy involves a priori specification of potential developmental confounders and covariates, pretesting covariables for confounding potential ($P \leq .10$), backward elimination of nonsignificant covariates and confounders through multiple regression analyses to a trimmed regression model, and, finally, the testing of potential dynamic interactions among lead exposures, biologic outcomes, and behavioral performance through structural equation analyses. Multiple regression analyses allow for the evaluation of the contribution of toxicant exposure to development, independent of covariables. Structural equation analyses go further to allow the testing of causal pathways wherein lead indirectly affects neurobehavioral status through its effect on covariables such as birth weight, gestation, or other perinatal factors.

RESULTS

Multiple Regression Analyses

No significant effects of fetal lead exposure on Bayley PDI were found after adjustment for covariates. However, blood indices of in utero lead exposure were consistently related to Bayley MDI at 3 and 6 months of age. The covariate-adjusted parameter estimates for fetal lead exposure variables on 3-month Bayley MDI are given in Table 5. Variables other than blood lead which were retained in the final models as statistically significant predictors of Bayley MDI were birth weight, gestation, maternal age, child race, child sex, and socioeconomic status.

Both prenatal (maternal) and umbilical cord blood lead values were inversely related to MDI at 3 months. For prenatal blood lead, this effect took the form of a covariate-adjusted reduction of 0.34 MDI points per microgram per deciliter of lead in blood, or 9.2 points across the range of prenatal blood lead values observed in the sample. Each microgram per deciliter increase in umbilical cord blood lead was associated with a covariate-adjusted reduction of 0.60 MDI points, or 16.8 MDI points across the range of cord blood lead values observed in the sample. None of the newborn assessments of blood lead were associated with 3-month MDI after covariate adjustment.

TABLE 5. Covariate-Adjusted Parameter Estimates for Fetal Lead Exposure Variables on 3-Month Bayley Mental Developmental Index*

Blood Source	β	SE	t Value	P Value	Range of Effect
Prenatal (maternal)	−.34	0.17	−1.96	.05	9.2
Umbilical cord	−.60	0.26	−2.30	.02	16.8
Newborn (10 d)	.06	0.22	0.26	.79	
Newborn (3 mo)	−.23	0.18	−1.30	.20	

* Other variables remaining in final models as statistically significant ($P < .05$) covariates included birth weight, gestation, maternal age, child race, child sex, and socioeconomic status. Neither Composite Index of Tobacco and Alcohol Consumption nor quantity of cigarettes smoked per day remained in the models as statistically significant covariates. P value calculated by two-tailed test.

The covariate-adjusted parameter estimates for fetal lead exposure variables on 6-month MDI are given in Table 6. As was the case for 3-month MDI, variables other than blood lead which were retained in the final model as statistically significant predictors of Bayley MDI were birth weight, gestation, maternal age, child sex, and socioeconomic status. Prenatal (maternal) and ten-day newborn blood lead levels were both significantly related to reductions in Bayley MDI at 6 months of age. For prenatal blood lead, dose-related deficits in MDI were more pronounced in boys, as indicated by the significant prenatal blood lead by sex interaction. Multiple regression analyses for boys only showed that each microgram per deciliter increase in prenatal blood lead was associated with a covariate-adjusted decrement of 0.84 MDI points ($P \leq .01$), or an overall decrement of 22.7 MDI points across the range of prenatal blood lead observed in the sample.

For newborn (ten-day) blood lead, dose-related deficits in MDI were most pronounced in infants from the poorest families, as indicated by the significant ten-day blood lead by socioeconomic status interaction. Multiple regression analyses for infants with scores less than the median socioeconomic status score showed that each microgram per deciliter increase in ten-day blood lead level was associated with a covariate-adjusted decrement of 0.73 MDI points ($P \leq .03$), or 16.1 MDI points across the range of ten-day blood lead observed in the sample. Umbilical cord and 3-month blood lead values were also inversely related to 6-month MDI

TABLE 6. Covariate-Adjusted Parameter Estimates for Fetal Lead Exposure Variables on 6-Month Bayley Mental Developmental Index*

Blood Source or Interaction	β	SE	t Value	P Value	Range of Effect
Prenatal (maternal)	−0.76	0.34	−2.16	.02	22.7†
Prenatal × child sex	1.27	0.51	2.49	.01	
Umbilical cord	−0.66	0.37	−1.76	.08	
Newborn (10 d)	−3.49	1.29	2.69	.007	16.1‡
Newborn × socioeconomic status	0.18	0.07	2.45	.01	
Newborn (3 mo)	−0.48	0.27	−1.78	.07	

* Other variables remaining in final models as statistically significant ($P < .05$) covariates included birth weight, gestation, maternal age, child race, child sex, and socioeconomic status. Neither Composite Index of Tobacco and Alcohol Consumption nor quantity of cigarettes smoked per day remained in the models as statistically significant covariates. P value calculated by two-tailed test.

† In male infants.

‡ In infants with scores less than the median socioeconomic status score for the sample.

but were not quite statistically significant when using a two-tail test. Nevertheless, the consistency of an apparent adverse neurobehavioral effect across blood lead variables was striking.

Structural Equation Analyses

Multiple regression analyses are severely limited by the fact that they can only evaluate static interactions between toxicant exposure and other factors that can affect neurobehavioral development.[28] Many of the variables considered as potential covariates or confounders may actually be health outcomes of intoxication and thereby mediate later developmental deficits. Perinatal health factors such as birth weight and gestational age are good examples. Previous research with the Cincinnati data base has demonstrated that higher maternal blood lead levels are associated with statistically significant reductions in weight at birth.[10] Rather than considering birth weight or other perinatal health factors as confounders of the blood lead-behavior relationship in multiple regression analyses, such covariables may be more appropriately modeled (both conceptually and statistically) as mediators of later neurobehavioral deficits. Until recently, adequate statistical techniques to estimate such indirect effects in longitudinal studies have not been available. Now, many of the statistical problems inherent in path analysis have been solved by the method known as structural equations.[29,30] This statistical method is typically used to test a set of specific causal hypotheses against a set of observed data (usually a covariance matrix of observed relations among the variables in the models). In the present study, structural equation analyses were used to test the hypothesis that lead-related deficits in infant neurodevelopmental status at 3 and 6 months of age were due, in part, to lead-related lower birth weight and shortened gestational age. Prenatal (maternal) blood lead was modeled in these analyses, because it was most highly correlated with perinatal outcomes in previous work with these data.[10]

The structural analysis was conducted in the following manner. The variables shown in Table 2 were ordered according to the causal relationships hypothesized to exist. Child's race and sex, mother's age, socioeconomic status, Composite Index of Tobacco and Alcohol Consumption, gravidity, and parity were initially included as exogenous (independent) variables in all structural equations. In addition, the static interaction of prenatal blood lead with each of these exogenous variables was initially entertained in each of the structural equation models. The endogenous (dependent) variables included in these models were prenatal blood lead, gestation, birth weight, Obstetrical Complications Scale score, Postnatal Complications Scale score, and, finally, 3- or 6-month MDI and PDI. This list reflects the ordering of posited causal events among these variables (ie, prenatal blood lead is hypothesized to affect each of the endogenous variables that follow, whereas MDI and PDI are assumed to be final outcomes in the model). Furthermore, the variables of birth weight and gestational age were allowed to be noncausally correlated with the Obstetrical and Postnatal Complications Scale scores. Finally, MDI and PDI were treated as independent, final outcomes, and not correlated in a causal manner. Prenatal blood lead was log transformed, because it served as an intermediate endogenous variable and assumptions of normality of distribution needed to be met.

From this initial (fully parameterized) model, nonsignificant paths were removed from the structural equations until all remaining paths were significant at $P \leq .10$ (two-tail test). Maximum likelihood estimates of the remaining parameters in the model were then obtained using the Linear Struc-

tural Relations (LISREL) program of Joreskog and Sorbom.[3] Any nonsignificant ($P > .05$) parameters were removed from the models in a stepwise fashion. An exogenous variable that was not found to be significantly related to any endogenous variable within the structural equation was eliminated from the model. Similarly, an endogenous variable that was not significantly affected by any other variable, and did not significantly affect any other endogenous variable, was eliminated from the model.

This strategy of backward removal of nonsignificant parameters was used, and a final model was derived for both the 3-month and 6-month developmental assessments. The only remaining static interaction term was prenatal blood lead by sex on 6-month Bayley scales outcomes (as was the case in the standard multiple regression analyses).

The final structural model derived from these analyses for 3-month MDI and PDI is shown in Fig 2. As predicted, prenatal blood lead was inversely related to birth weight (−150 g per natural log unit of blood lead), which, in turn, was positively associated with 3-month MDI and PDI. (Log blood lead values ranged from 0 to 3.295837 while antilog values ranged from 0 to 27.) Prenatal blood lead was also inversely associated with gestational age (−0.46 weeks per log unit of blood lead), which, in turn, was also positively associated with Bayley developmental outcomes. Therefore, a portion of lead's adverse effect on behavioral development at 3 months of age was "indirect," through its dynamic interaction with fetal growth and maturational variables. Prenatal blood lead was associated with less optimal Postnatal Complications Scale scores (Fig 2).

In addition to lead, consumption of tobacco and/or alcohol products during pregnancy was related to both higher prenatal blood lead values (as has been found in other studies), lowered birth weight, and, ultimately, lower MDI and PDI through its effect on fetal growth. It is interesting that this effect should be reliable in a sample characterized by a relatively low level of consumption of these products and attests to the general validity of the Composite Index of Tobacco and Alcohol Consumption variable.

The structural equation analyses results for 6-month MDI and PDI are presented in Figure 3. For the most part, the 3- and 6-month models were identical, with the exception of race and mother's

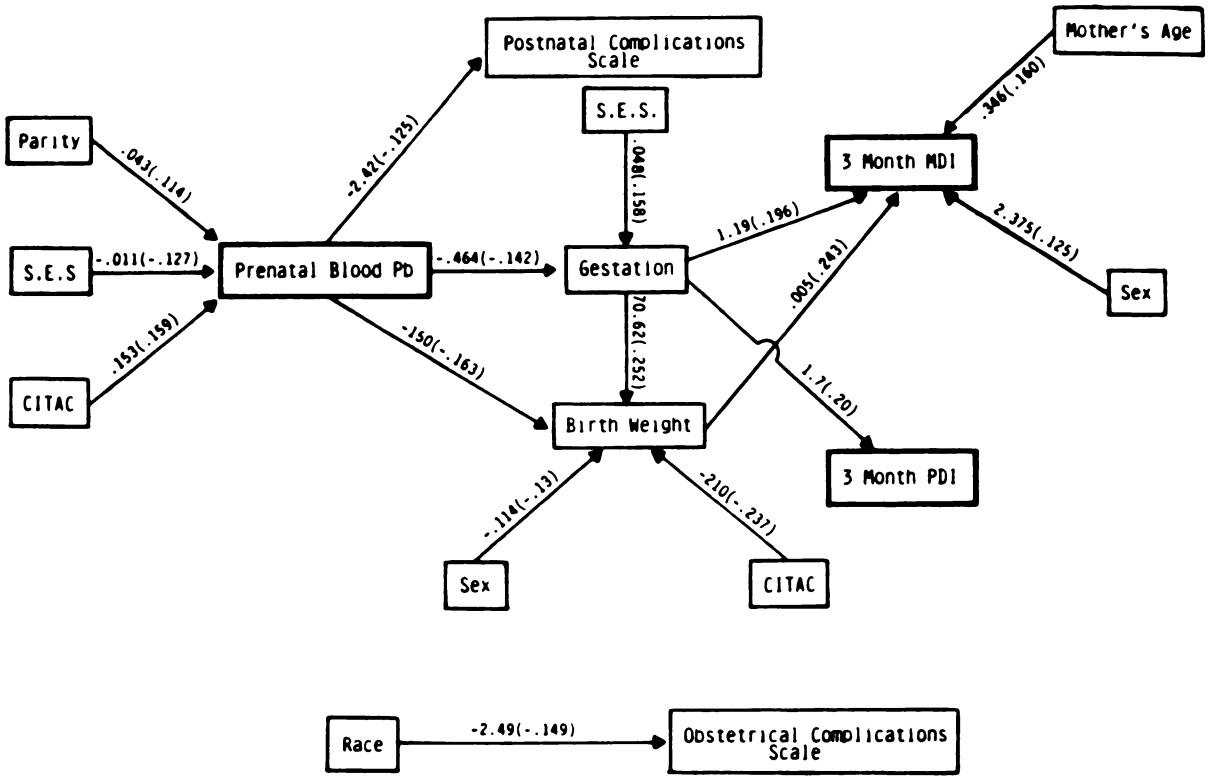

Fig 2. Relationships among prenatal lead (Pb) exposure, perinatal outcomes, and developmental variables as revealed through structural equation analyses for 3-month Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). Unstandardized and (standardized) regression coefficients are shown. Omnibus goodness-of-fit test provided by LISREL[31] program was surveyed at each step of elimination procedure. At no time did approximate χ^2 square value for goodness of fit exceed expectation, indicating that final models so obtained fit the data well. Abbreviations: S.E.S., socioeconomic status; CITAC, Composite Index of Tobacco and Alcohol Consumption.

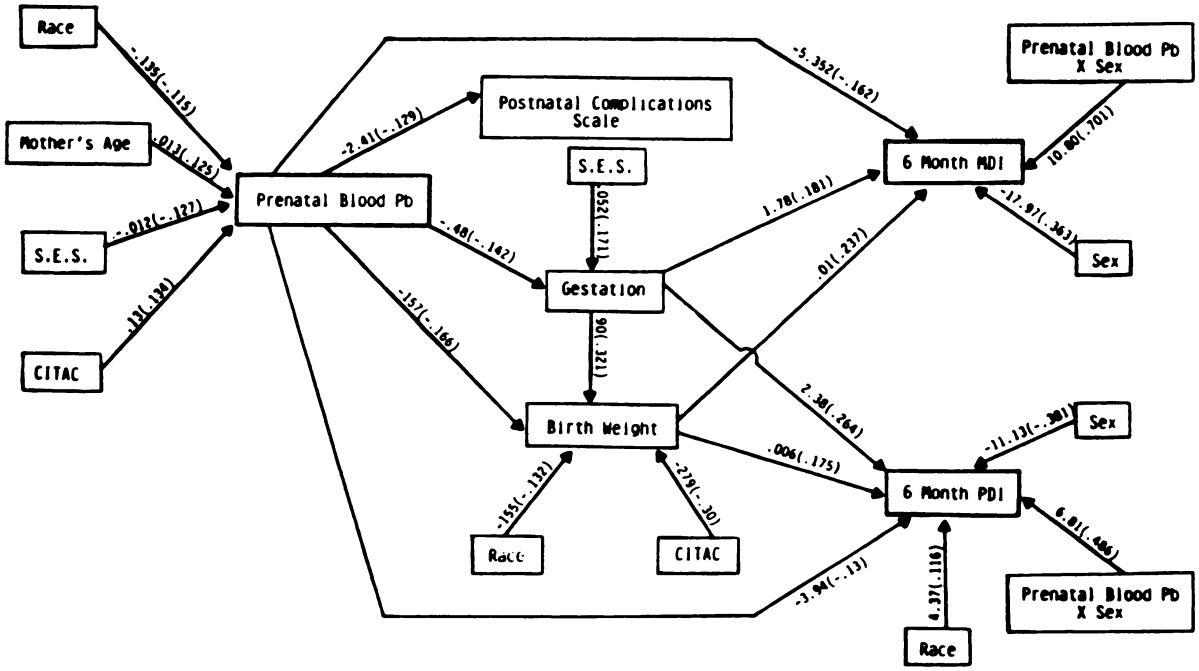

Fig 3. Relationships among prenatal lead (Pb) exposure, perinatal outcomes, and developmental variables as revealed through structural equation analyses for 6-month Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). Unstandardized and (standardized) regression coefficients are shown. Omnibus goodness-of-fit test provided by LISREL[31] program was surveyed at each step of elimination procedure. At no time did approximate χ^2 square value for goodness of fit exceed expectation, indicating that final models so obtained fit the data well. Abbreviations: S.E.S., socioeconomic status; CITAC, Composite Index of Tobacco and Alcohol Consumption.

age predicting prenatal blood lead value in the 6-month model and the aforementioned prenatal blood lead by sex interaction on 6-month Bayley developmental outcomes. Also, the absolute size of the standardized and unstandardized regression coefficients differ to a certain degree because the variables in the models themselves slightly differed and the fact that each model contains some subjects who are unique (ie, a small number of study subjects did not receive a 3-month Bayley assessment and a few did not receive a 6-month Bayley assessment).

To summarize, there is ample evidence in these multiple regression and structural equation analyses of both direct and indirect effects of fetal lead exposure on early neurobehavioral development. Prenatal, umbilical, and newborn blood lead levels were directly related to deficits in Bayley MDI at either 3 months, 6 months, or at both assessments. Boys and infants from the poorest families appeared to be most sensitive to these psychoteratogenic influences. Furthermore, in utero exposure to lead, as indexed by prenatal (maternal) blood lead value, may have exerted additional effects on development through decrements in fetal growth and maturation.

DISCUSSION

Indices of fetal lead exposure were more strongly and consistently related to 3- and 6-month Bayley MDI than PDI. This finding is in accord with previous studies.[7-9] The MDI is also a more reliable and valid subscale at these ages than the PDI.[27] Therefore, it is not surprising that this scale was the most sensitive of developmental outcome variables in the investigation.

At 3 months, both prenatal and umbilical cord blood lead levels were associated with deficits in MDI after covariate adjustment. A caveat may be in order, however, with regard to the cord blood lead results. This finding is based on slightly fewer than one third of the subjects in the study; therefore, it may not be as reliable an effect as that found for other blood lead variables. However, other studies have reported similar relationships between lead in cord blood and neurobehavioral deficits.[7-9]

At 6 months, the results were more complex but still consistent with study hypotheses. Two key perinatal risk factors appeared to be operative in modifying the effects of fetal exposure to lead. First, male infants expressed a much greater 6-month neurobehavioral deficit in response to fetal exposure as assessed by maternal blood lead. This finding is interesting in that several epidemiologic studies have shown that the relative risk of perinatal mortality and morbidity is higher in boys,[32,33] including the risk of poor reproductive outcomes and postnatal development due to fetal exposure to industrial pollutants.[34,35] This "male disadvantage" may be due to slower maturation and integration

of organ systems in boys.[36] Boys also have a higher rate of mental developmental disability in the general population[37,38] and display more profound intellectual deficits as a result of cortical lesions.[39,40] Boys, and perhaps male brains, may be more sensitive to the toxic effects of in utero chemical exposures.

Infants of lower social class families appeared to be more sensitive to the effects of fetal exposure as indexed by newborn (ten-day) blood lead levels. This finding is consistent with previous studies in which a more adverse behavioral effect of lead exposure was shown among the lower social classes.[41,42] Neurobehavioral sequelae as a result of perinatal insult has been shown to be more severe among the lower social classes. It is likely that social class is a collective surrogate for a variety of prenatal stressors that may affect reproductive fitness and make the expression of neurobehavioral deficits more likely in infants from the poorest families.[43,44]

Umbilical cord and 3-month blood lead levels were also inversely associated with 6-month Bayley MDI, although at not quite a statistically significant level when using a two-tailed test. Nevertheless, the consistency of negative relationships across blood lead measures was impressive.

Another noteworthy finding in this study was that early lead-related neurobehavioral deficits were partly mediated through birth weight and gestation. There are a number of studies in which the effects of prenatal lead exposure on obstetrical outcomes were evaluated. Lead has been shown to affect placental metabolism in an in vitro study.[45] There is also evidence that prematurity, lower birth weight, and premature rupture of membranes is associated with maternal blood lead values of 30 μg/dL or greater.[46] Although one recent prospective study has reported a relationship between low-level prenatal lead exposure and premature birth,[12] this is the first study to report an independent, inverse relationship between prenatal blood lead and birth weight at levels of less than 30 μg/dL of whole blood.

The finding of both direct and mediated effects of low-level fetal lead exposure on development suggests that what constitutes safe levels of exposure for children may not be safe for the fetus. It should be stressed that neurobehavioral deficits were related to lead exposures in this study that were well below the "corrective action" level as proposed by the Centers for Disease Control.[47] Indeed, prenatal (maternal) blood lead levels in this sample were well within the range found for US women in their reproductive years as assessed by the National Health and Nutrition Examination Survey.[48] These findings also suggest that in-depth studies of toxicant exposure during the course of pregnancy are essential in defining the "critical period" of exposure for given effects and in understanding the possible mechanisms for these early neurobehavioral deficits. This is by no means a new concept in the field of reproductive toxicology.[49,50] However, because lead is one of several widely distributed toxicants in our environment, the findings of this study deserve the special attention of pediatricians, obstetricians, and public health officials.

Future studies with the Cincinnati cohort will help to determine whether the developmental effects of fetal lead exposure persist into later childhood. By virtue of their geographical location and housing, much of the study cohort is at considerable risk for clinically significant elevations in blood lead levels.[15] It will be important to ascertain how these postnatal exposures affect current behavioral functioning and future intellectual attainment.

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