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The effect of confounding variables in studies of lead exposure and IQ

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ABSTRACT

Methods proposed to address confounding variables frequently do not adequately distinguish confounding from covariation. A confounder is a variable that correlates both with the outcome and the major exposure variable. Accurate treatment of confounding is crucial to low dose extrapolation of the effects of chemical exposures based on epidemiology studies. This study explores the limitations of current regression models in extrapolation to the low dose region of the dose-response curve due to the existence of unrecognized and uncontrolled confounding, using epidemiological data for lead. Based on the reported data in analyses by Lanphear and colleagues and Crump and colleagues, and drawing on other studies, Wilson and Wilson considered maternal IQ, HOME score, SES, parental education, birthweight, smoking, and race as characteristic variables which may have interaction effects. This analysis identifies confounding variables based on the seven longitudinal cohorts in analyses conducted by Lanphear and colleagues and by Crump and colleagues and confirms maternal IQ, HOME score, maternal education and maternal marital status at birth are "Highly Likely" confounders, while race is a "Likely" confounder. The cohort data were reanalyzed using the methods presented by Crump and colleagues while also considering the interaction among the identified confounding variables. This analysis determined that confounders influence IQ estimates in a quantifiable way that may exceed or at least obscure previously-reported effects of blood lead on IQ with blood lead levels below 5 μg/dL; however, limitations in the datasets make predictions of the low dose dose-response analysis questionable.

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Introduction

Epidemiological studies are frequently used to identify likely associations between an exposure and an outcome. Taking these assessments to the next step of asserting causality is much more difficult. For example, the association could be spurious if confounding factors are not adequately accounted for. In some cases, associations have been found to be due to reverse causality, that is, the outcome is found to have affected the measure of exposure. For associations that have been well established via multiple studies, attempts are sometimes made to derive dose-response relationships for low exposure conditions. Such low dose extrapolation is even more fraught with uncertainty due to confounding.

In regression analyses of epidemiological data, there can be confusion regarding which variables are covariates and which are confounders (Gurka 2018). For this analysis we are using the following definitions: a covariate is a variable that correlates with the outcome independent of the major exposure variable, whereas a confounder is a variable that correlates both with the outcome and with the major exposure variable. (Figure 1). Multivariate regression can include both covariates and confounders as independent variables to

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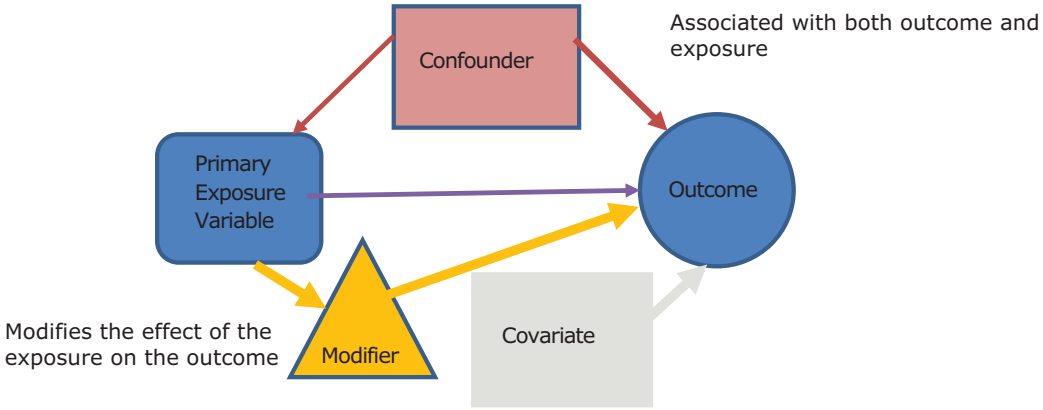

Figure 1. Relationships between variables and outcomes.

"correct" for the effect of these variables. In the case of confounders, including the confounder as an independent variable only accounts for the differences in variance and will not account for its effect on the outcome. An interaction term between the confounder and the outcome must be included in the regression model to account for this effect, which is similar to the way a modifier is considered in regression modeling (Gurka 2018). The difference would be that for a confounder, both the independent confounder and the interaction between the confounder and the primary exposure parameter should be included in the model. In the case of the modifier only, the interaction term is necessary.

High doses of some environmental chemicals such as lead and methylmercury have clearly been associated with adverse effects on neurological function in children (Agency for Toxic Substances and Disease Registry 2013, 2019; Antunes Dos Santos et al. 2016; Caito and Aschner 2017; Jackson 2018). In such studies, careful control for confounding factors has been shown to be critical because the effects of confounders are often stronger than the effects of the exposure of interest in the low-to-moderate dose region (Trask and Kosofsky 2000; Mink et al. 2004).

This is true for lead where covariates and confounders related to parental IQ and social factors account for over 50% of the variance in cognitive stability as compared to only 1–2% variance due to lead exposure (Bellinger and Dietrich 1994; Kaufman 2001). Concerns have been raised about the impact of confounding on low dose extrapolation of the effects of lead exposure on intellectual function (Wilson and Wilson 2016). The effect of lead on intelligence quotient in children has been the subject of numerous studies (Koller et al. 2004), with more recent studies concluding there are deficits associated with blood lead concentrations below 10 μg/dL (Lanphear et al. 2005, 2019; Rothenberg and Rothenberg 2005; National Toxicology Program 2012; Budtz-Jørgensen et al. 2013; Crump et al. 2013; Pan et al. 2018; Rocha and Trujillo 2019). Some of these studies have also included dose-response assessments in an attempt to quantify the decrements at various blood lead levels (BPbs), but factors affecting the low dose dose-response is still an area of active study (e.g. Desrochers-Couture et al. 2018) and questions remain about how to accurately characterize the associations (Health Canada 2013; Wilson and Wilson 2016). Confounding presents a greater threat to the validity of low dose extrapolation because the effects of lead at the lowest doses are more likely to be weaker than the effects of the confounders.

One publication that has been influential in the setting of an association between measures of intelligence and low lead exposure is the pooled-analysis conducted by Lanphear et al. (2005). Wilson and Wilson (2016) explored limitations of the regression models used in that pooled-analysis to extrapolate to the low dose region of the dose-response curve due to the existence of unrecognized and uncontrolled confounding. Wilson and Wilson (2016) indicated that "while the effects of higher levels of lead exposure are not disputed, overestimation of health effects at low lead exposure has significant implications for policy-makers trying to protect public health through cost-effective regulations." Even with only limited access to the Lanphear cohort data in publications (Lanphear et al. 2005; Crump et al. 2013), Wilson and Wilson (2016) identified several potential confounders which may have interaction effects, including maternal IQ, Home Observation for Measurement of the Environment (HOME) score, socioeconomic status (SES), parental education, birthweight, smoking, and race.

Our work with the full database of cohort data used by Lanphear et al. (2005) and Crump et al. (2013) in this paper presents a method to identify the confounding variables and a reanalysis of the data using the interaction terms identified. Our analysis follows the methods presented in Crump et al. (2013) while also considering the interaction among the identified confounding variables and the BPb variables. This analysis, which is an expansion of the original regression method shows that the interactions of these variables with the blood lead levels have a significant effect on the predictions in the low dose range of the dose-response analysis.

Materials and methods

Seven longitudinal studies (Table 1) make up the cohort database that has been used in pooled-analyses to evaluate the association between BPb concentrations in children and the measure of their intelligence (Lanphear et al. 2005;

Rothenberg and Rothenberg 2005; Crump et al. 2013). Each of these seven studies followed a cohort of children from birth and measured levels of lead in their blood at certain defined times. From time to time their intellectual development was measured along with other variables that might affect or correlate with that development. The reader is referred to Lanphear et al. (2005) and Crump et al. (2013) for the details of the cohort data.

Using the IQ test values and blood lead values selected in Crump et al. (2013), the other characteristic variables (Table 2) reported in the cohort studies were examined to determine if any of the variables could potentially confound the results reported in Lanphear et al. (2005) or Crump et al. (2013). Several of the characteristic variables (HOME score, maternal education, maternal IQ, maternal alcohol use, and maternal smoking) have been defined as site-specific due to being defined or measured in different ways in different studies by Crump et al. (2013), and these site-specific variables were used as part of the analyses. In addition, the combined versions of these variables (not site-specific) which were relied upon by Lanphear et al. were also used to explore this issue. The exposure variables considered in the analysis (Table 3) are those described in Crump et al. (2013), which closely correspond to those used by Lanphear et al. (2005) with some minor changes in the calculations. The exposure variables included calculations of the blood lead levels for the concurrent time to the IQ test, average over lifetime, early childhood (average up to 24 months), at 24 months, and overall peak as well as the natural log transformations of each. All were considered but only the concurrent lead (clead) and the natural log of concurrent lead (lnc) are presented in this paper, both for brevity and due to the determination by Crump et al. (2013) that "concurrent BPb was found statistically to provide the best description of the data" and because both Lanphear and Crump found that the exposure response is non-linear.

Once the confounders were identified, the interaction terms that describe the confounding were added to the other covariates in analyzing the data.

Table 1. Longitudinal cohort studies.

Location	Reference
Boston, Massachusetts	Bellinger et al. (1992)
Cincinnati, Ohio	Dietrich et al. (1993)
Cleveland, Ohio	Ernhart et al. (1989)
Mexico City, Mexico	Schnaas et al. (2000)
Port Pirie, Australia	Baghurst et al. (1992)
Rochester, New York	Canfield et al. (2003)
Yugoslavia	Wasserman et al. (1997)

Identifying confounders

Both a correlation analysis and a linear regression method were used to determine which of the characteristic variables could be considered to be confounders. Empirical identification was done considering the observed relationships between the exposure, outcome, and potential confounders using significance criteria (p-values less than or equal to 0.05) and change in estimate (CIE) values of greater than or equal to 10% (Lee and Burstyn 2016).

Correlation analyses

Correlation analyses were conducted to identify which of the characteristic variables (Table 2) were significantly correlated with both the reported IQ of the children and the BPb concentrations (the exposure variables of Table 3). A significant correlation with both the IQ and BPb concentration provides an indication that the characteristic variable has an effect on both the final outcome (IQ) and the expected cause of the final outcome (BPb). Spearman, Pearson or point biserial correlation (Tate 1954) procedures provided in SAS V. 9.4 and a SAS macro for the point biserial correlation (SAS 2007) were used to evaluate this, with Pearson correlation used for those variables identified as having continuous results (e.g. birth weight, gestational age, HOME score, mother's age, maternal education, and maternal IQ), while Spearman's correlation was used for those having ordinal categorical results (e.g. birth order) and point biserial correlation was used for the remaining categorical variables (e.g. marital status, race, and sex). Among the site-specific variables, some reported continuous and some categorical responses for alcohol and

Table 3. Outcome and exposure variables.

Variable name	Description
iq	Child's IQ level
clead	Concurrent lead (concentration measured closest to IQ test)
lnc	Natural log (ln) of concurrent lead variable (clead)

Table 2. Characteristic variables reported in cohort studies.

Variable name	Description	Type (possible values)
bo	Birth order	Continuous (1–9)
bwgt	Birth weight	Continuous
gage	Gestational age	Continuous
home	HOME score with fewest missing	Continuous – site specific
mage	Mother's age	Continuous
marital	Marital status at delivery	Categorical (unmarried – 0; married – 1)
medu	Maternal education	Continuous (8–17) – site specific
momiq	Maternal IQ	Continuous – site specific
race	Ethnicity	Categorical (non-white – 0; white – 1)
sex	Gender of child	Categorical (male – 1; female – 2)
site_alc	Alcohol use during pregnancy	Categorical (Y/N for Cincinnati, Mexico, Rochester, and Yugoslavia); continuous (all other locations) – site specific
site_cigs	Tobacco use during pregnancy	Categorical (Y/N for Yugoslavia); – site specific continuous no. of cigs/day (all other locations)

tobacco use during pregnancy (Table 2). In these cases, the Pearson or Spearman correlations were used where appropriate for each of the individual locations. Statistical significance was determined for both Pearson and Spearman correlations using a *t*-statistic determined from the correlation coefficient by the SAS Proc Corr procedure and a correlation was deemed statistically significant if it had a *p*-value of 0.05 or less.

Regression modeling

A second analysis was conducted using the multi-linear regression procedure SAS PROC GLM to identify confounding variables. Using PROC GLM, the effect on the association between a given exposure variable and the outcome (IQ) was examined when an additional independent variable was added to the regression. For example, in the initial regression model using a child's IQ (iq) and the natural log of concurrent lead (lnc), $iq = b_0 + b_1 \times lnc$, b_0 is the variable representing the intercept, and b_1 is the estimated regression coefficient quantifying the association between iq and lnc, the regression coefficient. The b_1, was compared to an alternate regression coefficient, $\hat{b}_1$, estimated when a second characteristic variable was included in the model, for example, $iq = b_0 + \hat{b}_1 \times lnc + b_2 \times bwgt$ where the second characteristic variable is the birthweight (bwgt). If the percent change between the b_1 and $\hat{b}_1$ estimates was greater than ±10%, then the second characteristic variable is considered to be a confounder. Note that those characteristic variables considered to be site-specific are evaluated by combining the site variable (location) with the characteristic variable, for example, $iq = b_0 + \hat{b}_1 \times lnc + b_2 \times site \times home$.

Estimating the effect of identified confounders on the dose-response modeling

After the confounders were identified, a backward stepwise multiple regression on IQ was performed similar to that reported in Crump et al. (2013) but with the addition of the interaction terms and using the thirteen original variables identified by Lanphear et al. (2005) in the stepwise procedure (Site, HOME score, maternal education, maternal IQ, birth weight, maternal alcohol use, maternal smoking habit, maternal marital status, birth order, gender, race, mother's age, and gestational age). The selection for entry into the regression was a significance of 0.10 and for staying in the regression, the significance level was 0.15. Confounders were included by using both the base variable and the interaction term and were grouped so that they left the model together (e.g. the terms for the HOME score and the interaction of the HOME score with the BPb value – Home and Clead × Home).

The association of the BPb with IQ was examined using two specific linear regression models developed using the confounders. The first is a linear model using the site-specific confounders of HOME score, and maternal education level (years of schooling), and IQ. The second uses the same confounders but does not make them site-specific. This provides an easier to use a version of the model where the effect of changes in blood lead and the confounders can be seen.

Results

Identification of confounders

As described in both Lanphear et al. (2005) and Crump et al. (2013), the concurrent blood lead value (clead, or lnc: natural log of concurrent lead) was identified as the most statistically descriptive of the exposure-response variables. The *p*-values resulting from our correlation evaluation are presented in Supplemental Table S-1 for the child's IQ and in Supplemental Tables S-2a and S-2b for the concurrent lead and the natural log of the concurrent lead measures, respectively.

The variables HOME score (home), marital status (marital), mother's education (medu), and mother's IQ (momiq) were identified as potential confounders due to their significant correlation with both the child's IQ (as shown in Supplemental Table S-1) and natural log of concurrent lead (lnc) and concurrent lead concentrations (as shown in Supplemental Tables S-2a and b) for at least four of the seven sites. When using regression modeling (see Supplemental Tables S-3) to evaluate the possible confounders, the characteristic variables ethnicity (race), HOME score (home), marital status (marital), mother's education (medu), and mother's IQ (momiq), were identified as confounders based on having β estimate differences greater than 10 percent.

Table 4 provides a summary of the confounder identification determined by covariate analysis, regression analysis, and overall, and uses a designation of "Highly Likely" to indicate that the characteristic variable was identified as a potential confounder in both the correlation and regression

Table 4. Identified confounders by regression and correlations.

Description	Potential identified by correlation	Potential confounders identified by regression	Final selection of confounders
Birth order	No	No	No
Birth weight	No	No	No
Gestational age	No	No	No
HOME score	Yes	Yes	Highly Likely
Mother's age	No	No	No
Marital status at delivery	Yes	Yes	Highly Likely
Maternal education	Yes	Yes	Highly Likely
Maternal IQ	Yes	Yes	Highly Likely
Ethnicity	No	Yes	Likely
Gender of child	No	No	No
Alcohol use during pregnancy	No	No	No
Tobacco use during pregnancy	No	No	No

Gray highlight indicates variable has been identified as Likely or Highly Likely to be confounders.

analyses. A child's ethnicity was deemed to only be a "Likely" confounder since it was not selected by both correlation and regression; as a consequence, it was not included further as a confounder in this analysis.

Identification of dose-response model

The backward stepwise multiple regression on IQ was conducted using the 13 original variables with the addition of the interaction terms for those variables identified as significant confounders (i.e. "Highly Likely" in Table 4). The variable for "site" plus the twelve variables listed in Table 4 are included at the start of the model development process to select the variables that are significant contributors to the estimate of the child's IQ. The four variables that were considered to be "Highly Likely" confounders based on the analysis reported in Table 4 were included in the model as both a single variable and an interaction term (e.g. momiq and momiq × BPb) with both terms considered together when determining if they should remain in the model. The backward selection process in SAS Proc GLM was used to determine that the variables that are significant contributors to the estimate of a child's IQ were site, birth bodyweight, mother's IQ, mother's education level, mother's tobacco use, HOME score, and gender. The two characteristic variables removed in the backward selection process (mother's marital status at delivery and mother's alcohol use) did not have a significant contribution to the variation in IQ when used in conjunction with the rest of the characterization variables. The backward selection process selected three confounders (mother's IQ, mother's education level, and HOME score) for inclusion in the final model.

Interaction effects between confounders

Using both the linear and non-linear models with concurrent lead values, an estimate of the amount of change in the child's IQ can be calculated for each of the sites based on the average values for the confounder variables (HOME score, mother's education, and mother's IQ) at that site which were included in the final model. Table 5 shows the range of values for the different confounders and reported children's IQ by sites. Note that the highest average child IQs reported by site were at a location with the highest mother's IQ and maternal education level (Boston), and the lowest occurred at the locations with the lower HOME scores, education levels, and maternal IQs (Cincinnati, Cleveland, Rochester, and Yugoslavia).

Table 6 shows the site-specific regression model results for BPb and the blood lead-associated variables identified as confounders. This table contains the parameter specific β values which provide the strength of the association between each parameter and the child's IQ. To calculate the model-estimated change in IQ for a specific site, a method similar to that reported in Mink et al. (2004) was used, where the parameter values supplied in Table 6 are combined with the average values for the confounders in Table 5. For example, the change in IQ expected for the linear model for the Boston site if BPb were 1 μg/dL is computed as follows:

$$\begin{aligned}\text{Change in IQ} = \text{BPb} \times \Big(&0.0815 + (-0.0033 \times \text{mother's IQ}) \\ &+ (-0.0634 \times \text{mother's education level}) \\ &+ (0.0203 \times \text{HOME score})\Big)\end{aligned} \tag{1}$$

Using the average values supplied in Table 5 for the Boston site of 122.98 for the mother's IQ, 15.05 for the mother's education level, and 37.02 for the HOME score, the change in IQ for an increase of 1 μg/dL in the BPb is calculated to be a decrease of 0.52 points.

Similarly, the change in IQ for the log-linear model would be:

$$\begin{aligned}\text{Change in IQ} = &\ \text{Ln}(\text{BPb} + 1) \\ &\times \Big(1.1063 + (0.0014 \times \text{mother's IQ}) \\ &+ (0.5428 \times \text{mother's education level}\Big) \\ &+ (-0.3444 \times \text{HOME score})\end{aligned} \tag{2}$$

For this model using the same average values from Table 5 for the mother's IQ, mother's education level, and

Table 5. Summary of confounders and child IQ values by site and overall.

			Average values for each Site						
						Child's IQ reported			
Site	N	Gender	HOME score	Maternal education level	Maternal IQ	Minimum	Mean	Maximum	Concurrent BPb
Boston	67	Male	37.02	15.05	122.98	82	112.5	150	5.976
	67	Female				80	117.1	150	6.364
Cincinnati	113	Male	32.44	11.19	75.20	50	85.4	114	8.927
	108	Female				63	88.7	114	7.831
Cleveland	78	Male	38.07	10.61	73.33	55	85.7	123	15.538
	65	Female				58	90.0	123	15.592
Mexico	70	Male	30.58	11.29	93.87	85	109.6	137	7.393
	72	Female				79	106.7	127	8.632
Port Pirie	149	Male	42.60	10.59	94.38	53	107.2	133	13.496
	173	Female				53	104.7	146	13.829
Rochester	92	Male	26.75	12.20	81.03	55	82.8	146	5.334
	91	Female				56	87.1	124	4.873
Yugoslavia	116	Male	29.97	8.86	87.36	49	74.1	122	23.627
	115	Female				50	74.3	116	18.084
All Sites	1376		34.49	11.12	88.89	49	94.0	150	11.776

Table 6. Model results for blood lead (BPb) and blood lead-associated confounding variables – site-specific.

		Model 1 – linear model		Model 2 – log-linear Ln (BPb +1) model	
Variable	Site	Variable value	Variable for interaction with BPb (confounder × BPb)	Variable value	Variable for interaction with BPb (confounder × ln(BPb + 1))
BPb		0.0815		1.1063	
Mother's IQ	Boston	0.0593	−0.0033	0.0173	0.0014
	Cincinnati	0.2660	0.0033	0.2032	0.0438
	Cleveland	0.1787	0.0014	−0.1360	0.1250
	Mexico	0.3114	0.0018	0.1606	0.0807
	Port Pirie	0.3905	0.0040	0.3791	0.0245
	Rochester	0.5986	−0.0398	0.8287	−0.2701
	Yugoslavia	0.1648	−0.0009	0.2044	−0.0198
Mother's education level	Boston	2.2477	−0.0634	0.8630	0.5428
	Cincinnati	0.3027	−0.1082	1.6417	−1.0877
	Cleveland	−0.0480	0.0734	−0.8020	0.7044
	Mexico	−0.9896	0.1280	−1.5845	0.7699
	Port Pirie	0.5971	−0.0225	2.8773	−0.9897
	Rochester	−0.7781	0.3074	−2.6754	2.0643
	Yugoslavia	0.7935	−0.0118	1.3653	−0.2924
HOME score	Boston	0.7355	0.0203	1.6023	−0.3444
	Cincinnati	0.0923	0.0172	−0.0160	0.1057
	Cleveland	1.3010	−0.0389	2.4643	−0.6414
	Mexico	0.6066	−0.0646	1.4045	−0.6230
	Port Pirie	0.6944	−0.0082	0.2519	0.1116
	Rochester	0.4875	−0.0539	0.8663	−0.4048
	Yugoslavia	0.8175	−0.0010	0.7851	0.0084

Highlighted cells indicate variable values that are statistically significantly different from zero.

Table 7. Estimates of change in IQ associated with BPb = 1 μg/dL.

Site	Model 1 – linear model Mean (95% LCL, 95% UCL)	Model 2 – log-linear model Mean (95% LCL, 95% UCL)
Boston	−0.52 (−0.60, −0.45)	−2.29 (−2.81, −1.77)
Cincinnati	−0.32 (−0.36, −0.29)	−3.01 (−3.71, −2.32)
Cleveland	−0.52 (−0.60, −0.44)	−4.63 (−6.34, −2.92)
Mexico	−0.28 (−0.36, −0.20)	−1.16 (−2.30, −0.02)
Port Pirie	−0.13 (−0.16, −0.09)	−1.60 (−2.44, −0.77)
Rochester	−0.84 (−0.90, −0.78)	−4.45 (−5.02, −3.88)
Yugoslavia	−0.13 (−0.14, −0.12)	−2.05 (−2.34, −1.77)

LCL: lower confidence limit; UCL: upper confidence limit; μg/dL: microgram per deciliter.

HOME score, the calculated decrease in the child's IQ for Boston is 2.29 points.

The results of the linear and log-linear computations, including the upper and lower confidence limits, for each site are presented in Table 7. The average estimated value for the change in IQ associated with a BPb of 1 μg/dL for the average child (i.e. at the average value for the confounders) ranges from −0.84 to −0.13 IQ points for the linear model and to −4.63 to −1.16 points for the log-linear model.

Impact of confounders on IQ

To see the impact of the confounders on changes in IQ, Table 8 shows the effect of adjusting each confounder down from the average (presented in Table 5) by one point and Table 9 shows the effect of adjusting each confounder up by one point from the average when the BPb is at 1 μg/dL. The effect of decreasing the confounders on the linear model's estimates was to change the estimated decline in IQ from a range of −0.84 to −0.13 to −1.4 to −0.3 because of lowered mother's IQ, −2.71 to 0.58 due to lowered mother's education level, and −1.78 to −0.28 for lowered HOME score. Similarly, the log-linear model predicts larger changes in the child's IQ when the mother's IQ (−5.09 to −1.38), mother's education level (−4.31 to −0.11), or HOME score (−6.65 to −1.16) are used in the equation at 1 point below the average values with a BPb of 1 μg/dL. Conversely, the range of predicted values when the confounders are increased by one point over the average changes for the linear model to mother's IQ (−0.47 to 0.27), mother's education level (−1.31 to 1.66), or HOME score (−0.41 to 0.74) shows that a single point of increase over the average will override the effect of BPb of 1 μg/dL at some of these sites. Since the values of standard IQ have a standard deviation of 15 points, a change of 1 point would be considered not statistically different from the average. It is apparent that the uncertainty in all the average confounder values (mother's IQ, mother's education levels and Home scores) would also introduce uncertainty in the model-predicted changes to IQ associated with BPb levels. The log-linear model does not show as much change in IQ with changes in the confounders but does change from the initial range with only the BPb of 1 μg/dL (−4.63 to −1.16) to ranges of (−4.68 to −0.94) for mother's IQ, (−5.69 to 0.59) for mother's education level, and (−3.86 to −0.92) for HOME scores increased one point above averages.

Supplemental Tables S-4 and S-5 show a more complete version of Tables 8 and 9 with BPb values ranging from 0 to 10 and changes in the confounders of mother's IQ, mother's education level, and HOME score varying from a decrease of up to 10 to an increase of up to 10.

Similar tables are provided for the results of using non-site-specific variables for the confounders with parameter values in Table 10, the results of changes in BPb only in Table 11, and the estimated effect on IQ when the BPb is 1 μg/dL and the confounding variable is adjusted either up or down one point (Table 12) from the overall average reported in

Table 8. Estimates of change in IQ associated with BPb = 1 μg/dL and decrease from the average in the other confounders of 1 point each[a].

Confounder	Site	Model 1 – linear model Mean (95% LCL, 95% UCL)	Model 2 – log-linear model Mean (95% LCL, 95% UCL)
Mother's IQ	Boston	−0.58 (−0.65, −0.51)	−2.31 (−2.81, −1.80)
	Cincinnati	−0.59 (−0.63, −0.55)	−3.25 (−3.95, −2.54)
	Cleveland	−0.70 (−0.77, −0.63)	−4.58 (−6.22, −2.94)
	Mexico	−0.59 (−0.66, −0.52)	−1.38 (−2.51, −0.24)
	Port Pirie	−0.52 (−0.56, −0.48)	−2.00 (−2.85, −1.15)
	Rochester	−1.40 (−1.46, −1.34)	−5.09 (−5.65, −4.53)
	Yugoslavia	−0.30 (−0.31, −0.29)	−2.24 (−2.53, −1.95)
Mother's education level	Boston	−2.71 (−2.72, −2.69)	−3.53 (−3.31, −3.74)
	Cincinnati	−0.52 (−0.59, −0.44)	−3.90 (−3.54, −4.25)
	Cleveland	−0.54 (−0.62, −0.47)	−4.31 (−2.71, −5.91)
	Mexico	0.58 (0.58, 0.59)	−0.11 (−1.08, 0.86)
	Port Pirie	−0.70 (−0.86, −0.54)	−3.79 (−3.95, −3.64)
	Rochester	−0.37 (−0.38, −0.36)	−3.20 (−3.68, −2.72)
	Yugoslavia	−0.91 (−0.93, −0.90)	−3.22 (−3.42, −3.01)
HOME score	Boston	−1.28 (−1.36, −1.20)	−3.65 (−4.22, −3.09)
	Cincinnati	−0.43 (−0.46, −0.41)	−3.07 (−3.73, −2.40)
	Cleveland	−1.78 (−1.85, −1.71)	−6.65 (−8.35, −4.95)
	Mexico	−0.28 (−0.36, −0.20)	−1.16 (−2.30, −0.02)
	Port Pirie	−0.81 (−0.83, −0.80)	−1.93 (−2.66, −1.21)
	Rochester	−1.27 (−1.32, −1.23)	−5.03 (−5.58, −4.49)
	Yugoslavia	−0.95 (−0.96, −0.94)	−2.84 (−3.13, −2.56)

[a]The effect of increasing the blood lead level while also decreasing the confounder (mother's IQ, mother's education level or Home score) by one point.

Table 9. Estimates of change in IQ associated with BPb = 1 μg/dL and increases from the averages in the other confounders of 1 point each[a].

Confounder	Site	Model 1 – linear model Mean (95% LCL, 95% UCL)	Model 2 – log-linear model Mean (95% LCL, 95% UCL)
Mother's IQ	Boston	−0.47 (−0.55, −0.39)	−2.27 (−2.79, −1.75)
	Cincinnati	−0.06 (−0.09, −0.02)	−2.78 (−3.45, −2.11)
	Cleveland	−0.34 (−0.42, −0.26)	−4.68 (−6.44, −2.92)
	Mexico	0.04 (−0.05, 0.12)	−0.94 (−2.09, 0.20)
	Port Pirie	0.27 (0.24, 0.30)	−1.21 (−2.01, −0.41)
	Rochester	−0.28 (−0.34, −0.22)	−3.81 (−4.37, −3.24)
	Yugoslavia	0.03 (0.03, 0.04)	−1.86 (−2.14, −1.59)
Mother's education level	Boston	1.66 (1.66, 1.67)	−1.05 (−1.49, −0.60)
	Cincinnati	−0.13 (−0.14, −0.12)	−2.12 (−2.65, −1.60)
	Cleveland	−0.49 (−0.55, −0.44)	−4.94 (−5.73, −4.15)
	Mexico	−1.14 (−1.22, −1.05)	−2.21 (−3.33, −1.09)
	Port Pirie	0.45 (0.39, 0.51)	0.59 (0.48, 0.69)
	Rochester	−1.31 (−1.32, −1.30)	−5.69 (−6.16, −5.22)
	Yugoslavia	0.65 (0.65, 0.65)	−0.89 (−1.15, −0.63)
HOME score	Boston	0.23 (0.20, 0.26)	−0.92 (−1.33, −0.52)
	Cincinnati	−0.22 (−0.25, −0.18)	−2.95 (−3.65, −2.26)
	Cleveland	0.74 (0.68, 0.81)	−2.61 (−4.25, −0.97)
	Mexico	−0.28 (−0.36, −0.20)	−1.16 (−2.30, −0.02)
	Port Pirie	0.56 (0.53, 0.59)	−1.27 (−2.12, −0.42)
	Rochester	−0.41 (−0.47, −0.34)	−3.86 (−4.44, −3.29)
	Yugoslavia	0.68 (0.68, 0.68)	−1.26 (−1.52, −1.00)

[a]The effect of increasing the blood lead level while also increasing the confounder (mother's IQ, mother's education level or HOME score) by one point.
LCL: lower confidence limit; UCL: upper confidence limit; μg/dL: microgram per deciliter.

Table 10. Model results for blood lead (BPb) and blood lead-associated variables – non-site specific.

	Model 3 – linear model		Model 4 – log-linear Ln (BPb + 1) model	
Variable	Variable value	Variable for interaction with BPb (confounder × BPb)	Variable value	Variable for interaction with BPb (confounder × ln(BPb + 1))
BPb	−0.1247		−4.945	
Mother's IQ	0.296	−0.00087	0.283	−0.0003
Mother's education level	0.517	−0.00704	0.3967	−0.0051
HOME score	0.4745	0.0023	0.3789	0.0437

Table 5. Since the model estimates reported in Tables 10–12 are based on a model that does not contain site-specific variables, the overall average values for the confounders (Table 5) are used. This model is easier to apply and can be used to give a single estimate instead of a range across the sites when confounders are used. Table 11 shows the estimate for the change in IQ based on four different levels of BPb. For 1 μg/dL BPb, the estimate for change in IQ is −0.203 for the

linear model and −2.36 for the log-linear model when the confounders are set at an average (both indicate a decrease in the child's IQ). However, if the confounders are increased by one point above average (Table 12), there is an estimated increase in the child's IQ of 0.092, 0.307, and 0.274 points based on larger than average mother's IQ, mother's education level, and HOME score, respectively, for the linear model but still a decrease in child's IQ of 2.08, 1.96, and 1.95 IQ points for the log-linear model.

Using the models to predict the amount of change in IQ with differing levels of BPb and changes in the confounders, Supplemental Table S-4 shows that for the linear non-site-specific model, the changes occur in a logical manner. Negative changes in the confounders (e.g. lower mother's IQ, education level, and HOME score) result in negative changes to the IQ even without BPb and with BPb those effects are magnified. However, the log-linear non-site-specific model, predicts that only an increase of 10 in the mother's IQ, or 7–10 years in the mother's education level were able to offset even 1 μg/dL in the BPb. The site-specific table (Supplemental Table S-5) is even more problematic as it not only shows the range of possible values, but the Cleveland, Mexico, and Rochester sites show a negative relationship between increases in the mother's education level and IQ even in the absence of BPb for both the linear and log-linear models. In addition, the log-linear model shows a negative relationship between IQ and increasing HOME score for Cincinnati and mother's IQ for Cleveland. Such relationships are not logical, suggesting that the log-linear model is not providing a reliable indication of the influence of confounding variables on predicted IQ. Note that both the linear and log-linear models show a negative relationship between IQ and increasing mother's education level for Cleveland, Mexico City, and Rochester indicating that mother's education levels may have been poorly defined across sites. Table 13 provides goodness of fit information for all 4 models reported in this analysis.

Table 11. Estimates of change in IQ associated with specified BPb and confounders at the average, non-site specific models.

BPb μg/dL	Model 3 – linear model Mean (95% LCL, 95% UCL)	Model 4 – log-linear model Mean (95% LCL, 95% UCL)
1	−0.203 (−0.205, −0.201)	−2.36 (−2.45, −2.28)
2.5	−0.507 (−0.512, −0.503)	−4.27 (−4.40, −4.14)
5	−1.015 (−1.022, −1.008)	−6.11 (−6.26, −5.96)
10	−2.030 (−2.036, −2.024)	−8.18 (−8.33, −8.03)

LCL: lower confidence limit; UCL: upper confidence limit; μg/dL: microgram per deciliter.

Comparison to Crump and colleagues' and Lanphear and colleagues' Results

Estimates of a child's IQ deficit due to exposure to a blood lead concentration of 10 μg/dL are presented in Table 14 for

Table 12. Estimates of change in IQ associated with BPb = 1 μg/dL and decreases or increases in the other confounders of 1 point each from the average[a].

Change in confounder value	Confounder	Model 3 – linear model Mean (95% LCL, 95% UCL)	Model 4 – log-linear model Mean (95% LCL, 95% UCL)
One point below average	Mother's IQ	−0.498 (−0.501, −0.495)	−2.65 (−2.72, −2.57)
	Mother's education level	−0.713 (−0.719, −0.706)	−2.76 (−2.83, −2.70)
	HOME score	−0.680 (−0.684, −0.675)	−2.77 (−2.86, −2.68)
One point above average	Mother's IQ	0.092 (0.085, 0.099)	−2.08 (−2.17, −1.99)
	Mother's education level	0.307 (0.304, 0.310)	−1.96 (−2.04, −1.88)
	HOME score	0.274 (0.272, 0.275)	−1.95 (−2.03, −1.88)

[a]Mother's IQ is 1 point lower or higher than overall average in Table 5.
LCL: lower confidence limit; UCL: upper confidence limit; μg/dL: microgram per deciliter.

Table 13. Fit information for comparison of models.

Model type	Transformation on Concurrent BPb	*n*	Coef. (β) (95% CI)		*p*-Value	R^2
Site-specific variables for maternal IQ, maternal education, HOME score, and maternal tobacco use	linear	1376	0.081	(−0.517, 0.679)	0.7893	0.659
	Ln(BPb + 1)	1376	1.106	(−8.277, 10.489)	0.8171	0.660
Only maternal tobacco use site-specific	linear	1376	−0.125	(−0.545, 0.295)	0.5601	0.635
	Ln(BPb + 1)	1376	−4.945	(−10.547, 0.657)	0.0836	0.638

[a]Adjusted for site, HOME score, birth weight, maternal IQ, maternal education, maternal tobacco use, and gender also for confounders mother's age, mother's education and HOME score.
CI: confidence interval; β: beta coefficient; R^2: R-squared.

Table 14. Estimates of deficit in IQ from exposure to 10 μg/dL from different analyses.

IQ deficits at 10 μg/dL (95% CI)				
Model	This analysis	Crump et al. (2013)[a]	Lanphear et al. (2005)[b]	Lanphear et al. (2019)[c]
Linear	2.03 (2.02, 2.04)	1.7 (0.9, 2.5)		
Log-linear	8.18 (8.03, 8.33)	7.9 (5, 10.9)	6.2 (3.8, 8.6)	6.4 (3.9, 8.8)

[a]As reported in Table 5 of Crump et al. (2013).
[b]Calculated from values reported in Lanphear et al. (2005) in Table 4 adjusted estimated for β for the concurrent model as ($\beta \times$LN(10 + 1)).
[c]Calculated from values reported in Lanphear et al. (2019) in Table 4 adjusted estimated for β for the concurrent model as ($\beta \times$LN(10 + 1)).

this analysis, as well as, the Crump et al. (2013) and Lanphear et al. (2005, 2019) analyses. Each of these represents the mean adjusted changes in the IQ score. The concurrent blood lead model selected by Lanphear et al. (2005, 2019) included the covariates HOME score, birth weight, maternal IQ, and maternal education. The model presented in Crump et al. (2013) was adjusted for site, HOME score, birth weight, maternal IQ, maternal education, maternal alcohol use, maternal tobacco use, and birth order. Our model included the covariates of site, birth bodyweight, mother's tobacco use, and gender, along with the three confounders (mother's IQ, mother's education level, and HOME score).

The estimates of a child's IQ deficit at BPb = 10 μg/dL as determined in this analysis are similar to those in Crump et al. (2013) and Lanphear et al. (2005, 2019) with the IQ deficit and confidence limits within the range of confidence limits specified in the other analyses.

Discussion and conclusion

Pooled and meta-analyses (weighted pooled analysis) of epidemiological studies are increasingly being used to demonstrate low dose adverse effects; however, the strong influence of multiple confounders calls into question the reliability of some of those analyses. In any case where uncontrolled confounding could occur, an expansion of typical regression analyses is needed to examine the effect of adding additional variables on the exposure parameter. Whenever the outcome variable has multiple factors that directly affect the incidence, and some of those factors also influence the exposure variable, such confounding may occur.

This study examines a source of uncertainty that has been inadequately addressed in prior studies using regression models with epidemiological data to extrapolate to the low dose region of the dose-response curve. Existing regression models typically account for covariation with multiple characteristic variables, but often incorrectly describe accounting for such interactions as addressing "confounding." Such regression models do not account for the existence of unrecognized and uncontrolled confounding, where a characteristic variable may distort the measured association between an exposure variable and an outcome.

We specifically examine factors that may have affected the reported dose-response for measures of intelligence and low lead exposures conducted by Lanphear et al. (2005) and Crump et al. (2013), who calculated dose-response relationships for BPb levels less than 10 μg/dL. Our analysis builds on an analysis by Wilson and Wilson (2016) that identified several potential confounders that may have interaction effects.

The initial phase of our study was the development of methods to identify characteristic variables likely to be confounders, and the application of these methods to a dataset used to predict low dose effects of lead exposure in young children. In addition to the correlation analysis used in Wilson and Wilson (2016) to determine confounders, the analyses described here included regression analysis to confirm that the addition of the possible confounder to the regression resulted in at least a 10% change in the β value associated with the BPb (Supplemental Tables S-3). Finally, the possible covariates and confounders were used in a selection regression analysis to determine the parameters used for the analysis.

Based on access to a subset of the data used by Lanphear et al. (2005) and Crump et al. (2013), Wilson and Wilson (2016) considered maternal IQ, HOME score, SES, parental education, birthweight, smoking, and race as characteristic variables which may have interaction effects with the blood lead variable. These variables were defined as possible confounders, which is a term that is used loosely in many publications. Often what is termed a confounder is simply a covariate with a high correlation to the independent variable (e.g. IQ) but with no correlation to the main exposure term (e.g. blood lead levels). Using the full dataset, this analysis confirms that maternal IQ, HOME score, marital status at delivery, and maternal education are "Highly Likely" confounders, while the race is a "Likely" confounder.

Therefore, any analysis of the cohort data to predict low dose effects of lead exposure in young children using the methods presented in Crump et al. (2013) and Lanphear et al. (2005, 2019) should consider the interactions among the confounding variables identified in this analysis, particularly HOME score, mother's education, and mother's IQ as these were identified as potential confounders in both the correlation analysis and regression modeling. The problem of differences in data collected at different sites was accommodated by using site-specific variables as was done in Crump et al. (2013). The method can also be applied to multiple exposure measures as a means of examining exposure duration directly, for example, Crump et al. (2013) included concurrent BPb, peak BPb, BPb at 24 months, mean lifetime weighted BPb, and early (6 months to 24 months) mean weighted BPb as exposure measures.

Both linear and log-linear models were used in this analysis to be consistent with other analyses (Lanphear et al. 2005; Jusko et al. 2008; Crump et al. 2013). However, it is noted by Wilson and Wilson (2016) that "If the best fit linear regression shows a negative association between IQ and log Blood Lead Levels (BLL), it will always transform to an exponentially declining curve (a supralinear relationship) if plotted against BLL. If that is inconsistent with physiological explanations, the assumption of a linear regression should be reexamined, and effort directed to finding a threshold." There is no doubt that there is a negative relationship between lead and IQ; however, given the relatively small effects of lead on IQ at low doses as compared with other factors affecting IQ, it is difficult to believe that the relationship between very low levels of lead and IQ is as large as would be reflected by these log-linear relationships.

In addition, the negative relationships predicted by the site-specific models between increases in the confounders and IQ are inconsistent with studies of the influence of those variables on IQ. Child IQ has been shown to be strongly affected by the mother's education, mother's IQ, and HOME score in numerous studies (Bradley et al. 1993; Bacharach and Baumeister 1998; Tong et al. 2007; Alati et al. 2008; Eriksen et al. 2013). Tong et al. (2007) reported that a 10-unit

increment in maternal IQ led to increases in cognitive development by 2.9 to 4.8 points, and a 10-unit increment in HOME score led to increases in cognitive development by 4.2 to 9.0 points, after adjustment for confounding factors. Consequently, a model that predicts negative relationships is not providing accurate predictions for these variables.

Note that when the site-specific models are used the β values for the BPb are positive (Table 6) which indicates it is only through the effects in the interaction terms that changes in the BPb decrease the IQ. In contrast, in the non-site-specific model, the β values for the BPb are negative (Table 10) but having a value of a confounder one point or more above average cancels the negative effect of BPb at one μg/dL for the linear model. For the log-linear model, even increases of 10 points in the mother's IQ is insufficient to counteract the effect of more than 1 μg/dL BPb (see Supplemental Table S-4).

A key limitation of this method is related to the data needs. The application of this approach requires access to full data sets, and the studies included must have reported robust exposure data with many characteristic variables. In addition, there must be a large number of subjects with BPb in the concentration ranges of interest for dose-response prediction as there may need to be a number of regression parameters estimated by the regression equations. In this analysis we had access to the full datasets; however, there are relatively few records in the low dose region with blood lead levels below 5 μg/dL. Our analysis was also limited by the fact that the covariates and confounders were not uniformly reported for all of the cohorts (e.g. tobacco and alcohol use during pregnancy and ethnicity). Another limitation is that the only socio-economic factor available was the HOME score. Additional socio-economic variables such as the categorized yearly income used by Jusko et al. (2008) could also prove useful, as would reliable measurement of parental IQ. Considering the large role of parental IQ in child IQ, this is a crucial factor. The IQ of one parent accounts for 17.6% of the variation in the child's IQ, and the IQs of both parents account for 25% of the variation in the child's IQ (Kaufman 2001). Studies of lead and child IQ seldom report father's IQ, but testing both mother's and father's IQ increases the overlap between parent and child IQ by 42% (Kaufman 2001). Taken together, these limitations cause us to conclude that the available datasets do not support a reliable dose-response analysis for effects of blood lead levels less than 5 μg/dL on IQ.

Another concern in the low dose extrapolation is the uncertainty associated with the reliability of the IQ measures for both child and mother. Measures of IQ are not accurate to one point. Uncertainty in the mother's actual IQ could result in a range of predicted child IQs at any given BPb that is larger than the change in IQ brought about by a low increment in BPb. Thus, confounding by the mother's IQ may be magnified by the uncertainty associated with this measure.

Our model does not address the issue of joint confounding by multiple variables. Future development of this model should explore approaches that consider joint confounding. The key confounders identified in this study (mother's education, mother's IQ and HOME score) are not independent of each other, which should be taken into consideration in any analysis of joint confounding.

The approach used in this study to expand typical regression analyses to identify previously overlooked interaction effects could increase the accuracy and reliability of risk calculations based on low-dose dose-response estimates. The methods used to identify the covariates in this approach are general enough that they can be applied to other studies using the study-specific variables when covariates are available and confounding with one or more covariates is expected. Other examples where the measured association between an exposure variable and an outcome at low doses could be distorted by an effect of a third variable include lead exposure and cardiovascular disease (see Cox 2020), fine particulate matter and cardiovascular disease or pulmonary function, and aggravation of asthma by ozone and fine particulate matter.

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Declaration of interest

The authors' affiliations are as shown on the cover page. This work was supported by a contract awarded to Ramboll US Consulting (Ramboll) by the International Lead Association (ILA). The authors independently developed the plan for this study and contacted ILA seeking support to conduct the study. Ramboll is an environmental engineering and consulting firm with some clients in the lead industry. ILA is a not-for-profit trade organization that conducts research on behalf of lead users and producers throughout the world, who provide funding for its operations (https://www.ila-lead.org/). The authors are all employed by Ramboll. Ms. Van Landingham is a Senior Science Advisor with Ramboll and is a consultant on matters related to statistical issues, modeling, computer programming, and data management. Her clients include government agencies and private organizations. Dr. Fuller is a Senior Manager at Ramboll and project management and technical oversight for numerous risk, exposure, and combustion-source assessments at numerous sites in the United States and Brazil. Dr. Schoof is a principal at Ramboll and serves as an expert in the field of environmental lead exposure and lead toxicology. Her clients include both government agencies and private organizations and her projects have included risk assessments for lead-contaminated sites conducted on behalf of responsible parties. Dr. Schoof has also provided expert testimony on lead exposure in legal cases.

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Supplemental material

Supplemental data for this article can be accessed here.

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