LOW DOSE LEAD DOSE-RESPONSE

ASSESSING INFLUENCE OF CONFOUNDING VARIABLES

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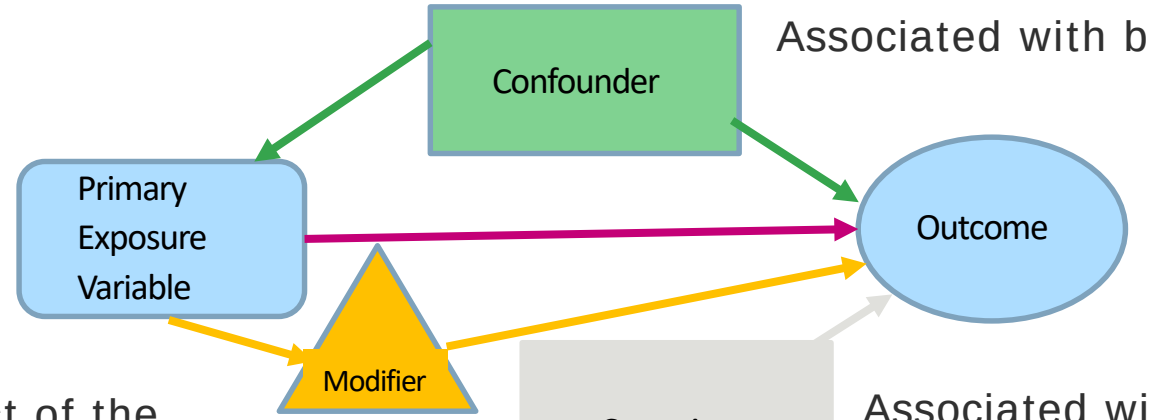
CONSIDERATION OF CONFOUNDERS IN DOSE-RESPONSE MODELING

- When using epidemiological data in dose-response modeling, especially when extrapolating to the low-dose region of the dose-response curve, confounding variables need to be identified and used in the modeling
- **Covariates and confounders are often confused**
  - A covariate is a variable that correlates with the outcome independent of the major exposure variable
  - A confounder is a variable that correlates both with the outcome and with the major exposure variable

- **Wilson and Wilson (2016)** report that uncontrolled confounding may be contributing to over estimation of the lead effect. *"Confounding occurs when the measured association between an exposure variable and an outcome is distorted by an effect of a third variable (called a confounding variable or confounder)"*

CONFOUNDERS, COVARIATES AND MODERATORS



Associated with both outcome and exposure

Modifies the effect of the exposure on the outcome

Associated with outcome but not exposure

- Regression includes both covariates and confounders as independent variables to “correct” for the effect of these variables
- Confounder included as an independent variable accounts for differences in variance; **NOT** effect of the confounder on the exposure. Interaction term between the confounder and the exposure must be included.
- Modifiers also included as an interaction term between confounder and exposure but not as an independent variable

WILSON AND WILSON (2016)

- "*many prospective, cross-sectional and pooled studies claiming to have adjusted for confounding when they have only addressed the covariance effects of the confounders on child IQ*".
- Covariance effect of confounders such as maternal IQ, HOME score, SES and parental education account for 11–27%, 7–48%, 5–16% and 2–12 % of the variance in child IQ

- Blood lead levels (BPb) generally accounts for only a few percent of the variance in child IQ
- Some or all of that may be caused by the interaction effect of a confounder on BPb

METHODS TO ACCOUNT FOR CONFOUNDERS, COVARIATES AND MODERATORS

- Design of Study
  - Restriction to only people with the same level of confounding factor
  - Matching groups for comparisons
  - Randomization
- Controlling in Analysis
  - Stratification of analysis
    - Requires continuous variables to be categorized
    - Inability to control simultaneously for multiple confounding variables
  - Multiple regression
    - Including covariates and confounders as independent variables, and both confounders and modifiers as interaction terms with the exposure parameter (e.g. confounder × exposure parameter)
    - Allows for simultaneous control of multiple covariate, confounding and modifier variables

MEASUREMENT DIFFERENCES

- Different IQ tests
  - Wechsler Intelligence Scale for Children VIII, and Children Revised
  - Wechsler Preschool and Primary Scales of Intelligence Full Scale IQ, and Full Scale IQ - Revised
  - McCarthy General Cognitive Index, and Scales of Children's Abilities
  - Stanford–Binet Intelligence Scale,
- Different methods of taking blood (venous, capillary)
- Different times of blood collection and IQ tests
- Different labs with different tests for measuring blood lead concentrations

CASE STUDY: LEAD

- **Widely studied chemical, cconcerns related to neurological effects in humans**

- **Effects on IQ in children**
  - USEPA Air Quality Criteria Document for Lead (USEPA, 2006) states:
    - *‘‘the most compelling evidence for effects at blood Pb concentrations (BPb) <10 mg/dL, as well as a nonlinear relationship between blood Pb levels and IQ, comes from the international pooled analysis of seven prospective cohort studies (n=1333) by Lanphear et al. (2005)”*
  - USEPA National Ambient Air Quality Standards for Lead (USEPA, 2008)
    - Based on Lanphear et al. (2005) and others, noted IQ loss in the health effects for children and set a standard of 0.15 $\mu g/m^3$ (as a 3-month average in total suspended particles)
    - Standard of 0.15 $\mu g/m^3$ retained in 2016 without revision

LANPHEAR ET AL. (2005)

- An international pooled study of epidemiological data
  - Port Pirie, Australia (Baghurst et al. 1992)
  - Boston, Massachusetts, USA (Bellinger et al. 1992)
  - Rochester, New York, USA (Canfield et al. 2003)
  - Cleveland , Ohio (Ernhart et al. 1989)
  - Cincinnati, Ohio, USA (Dietrich et al. 1993)
  - Mexico City, Mexico (Schnass et al. 2000)
  - Kosovo (Mitrovica and Pristina), Yugoslavia (Wasserman et al. 1997)
- Blood data not taken at consistent time points
  - Cord blood (Boston, Cleveland, Mexico City, Port Pirie, and Yugoslavia)
  - Through age 5 years at various time intervals for all 7 sites (57 months for Boston)
  - Additional data between 5 and 7 years (Cincinnati, Mexico City, Port Pirie, Rochester, and Yugoslavia)
  - Last data at 10 years (Boston) and 12 years (Port Pirie)
- Home Scores taken between 6 months and 48 months

COVARIATES CONSIDERED

- Site identifier
- HOME Inventory
    - Reflects the quality and quantity of emotional and cognitive stimulation in the home environment and is defined differently for children of different ages (Caldwell & Bradley, 1984).
- Child's sex, birth weight, gestational age, and birth order
- Maternal education, IQ, age, marital status at child's birth, prenatal smoking status, prenatal alcohol use
- Ethnicity – only provided as white or non-white

Site specific parameter

- Data values for these parameter were measured differently for different sites, e.g. home scores, prenatal smoking and prenatal alcohol use
- Each of these were considered in the regressions as 7 specific parameters – one for each site

LANPHEAR ET AL. (2005)

CONCLUSIONS

- Evidence of lead-related intellectual deficits among children with peak blood lead levels < 7.5 µg/dL.
- No evidence of a threshold.
- Overall decline of 6.2 IQ points (95% CI, 3.8–8.6) for an increase in blood lead levels from < 1 to 10 µg/dL.
- Concurrent blood lead levels or average lifetime estimates of lead exposure were stronger intellectual deficits than peak or early childhood blood lead concentration.
- Existing data indicate that there is no evidence of a threshold for the adverse consequences of lead exposure

LIMITATIONS

- Limitations of the tools used to measure important covariates.
- The HOME Inventory was not conducted at the same age for children in all of the sites, and the HOME Inventory and IQ tests have not been validated in all cultural or ethnic communities.
- Omission of unmeasured variables may produce residual confounding.
- Unique limitations in each cohort that raise questions about the validity and generalizability of their findings.

CRUMP ET AL. (2013) REANALYSIS

- Used the same data as Lanphear et al. (2005) with minor corrections/changes
  - Corrections - Lanphear Boston BPb values were transformed to LN(BPB + 1) to use by untransformed incorrectly as BPb = EXP(LN(BPB +1)) +1
  - Changes
    - Used weighted lifetime averages instead of unweighted as done by Lanphear et al.
    - Added an early childhood (0-24 months) weighted average BPb to analysis
    - Incorporated as much of the available measure BPb data in averages instead of using only those where the majority of sites had a measurement
    - Used 57 month IQ measurement for Boston (McCarthy) instead of 120 month (Wechsler Performance) – both used BPb from 57 months
    - For 10 children in Mexico without 84-month IQ values, the 78 or 72-month IQ was substituted

CRUMP ET AL. (2013)

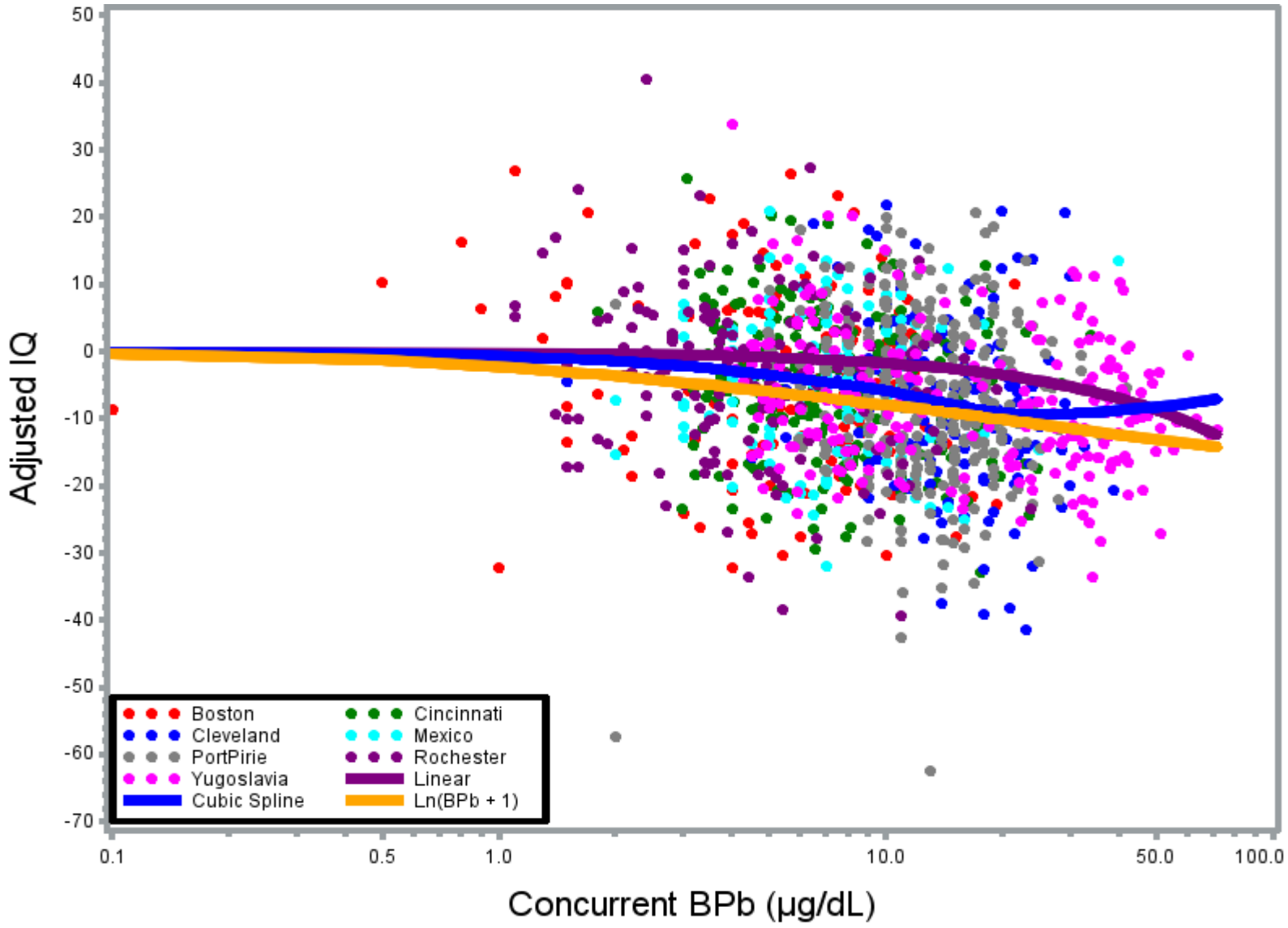
CONCLUSIONS

- Relationship between BPb and IQ was non-linear
- Concurrent BPb provided the best statistical description of the exposure-response
- Statistical evidence for an association of BPb with IQ at peak BPb exposures below 7 mg/dL (and as low as concurrent BPb of 5 mg/dL).

LIMITATIONS

- None of our statistical tests were corrected for multiple comparisons
- All are based on the assumption that our final model is the true model.

GRAPH OF MODELS FROM CRUMP ET AL. (2015) ANALYSIS



Note: Adjusted values derived from spline model fit.

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CONFOUNDERS – HOW TO IDENTIFY

NOT CONSIDERED BY LANPHEAR ET AL. (2005) OR CRUMP ET AL. (2013)

- Correlation analysis
  - Does a correlation exist between a covariate and both the BPb and IQ?
  - What levels of correlation should be considered significant or is it sufficient to use significance p-values?
- Regression Analysis
  - Does addition of the covariate to a regression of IQ = intercept + β × BPb affect the BPb parameter β by a significant amount?
  - What should be considered a significant amount? (10% - used in this case study)

POTENTIAL CONFOUNDERS IDENTIFIED

Correlation Analysis	Regression Analysis
Home Inventory score*	Home Inventory score*
Mother's age	
Martial status at delivery	Martial status at delivery
Mother's education level*	Mother's education level*
Maternal IQ*	Maternal IQ*
Tobacco use during pregnancy	
	Ethnicity

* Site-specific values

ADDING CONFOUNDERS INTO REGRESSION EQUATIONS

- Regression with covariates
  - IQ = site + BPb + covariates (where site serves as the intercept)
  - IQ = p1_i × site + β × BPb + p2 × bwgt + p3_i × site × momiq + p4_i × site × medu +p5_i × site × site_cigs + p6_i × site × site_alc + p7_i × site × home + p8 × bo
- Regression with covariates and confounders
  - IQ = site + BPb + covariates + confounders + BPb × (confounders)
  - IQ = p1_i × site + β × BPb + p2 × bwgt + p3_i × site × momiq + p4_i × site × medu +p5_i × site × site_cigs + p6_i × site × site_alc + p7_i × site × home + p8 × bo + BPb × (p9_i × site × home + p10_i × site × medu +p11_i × site × momiq)
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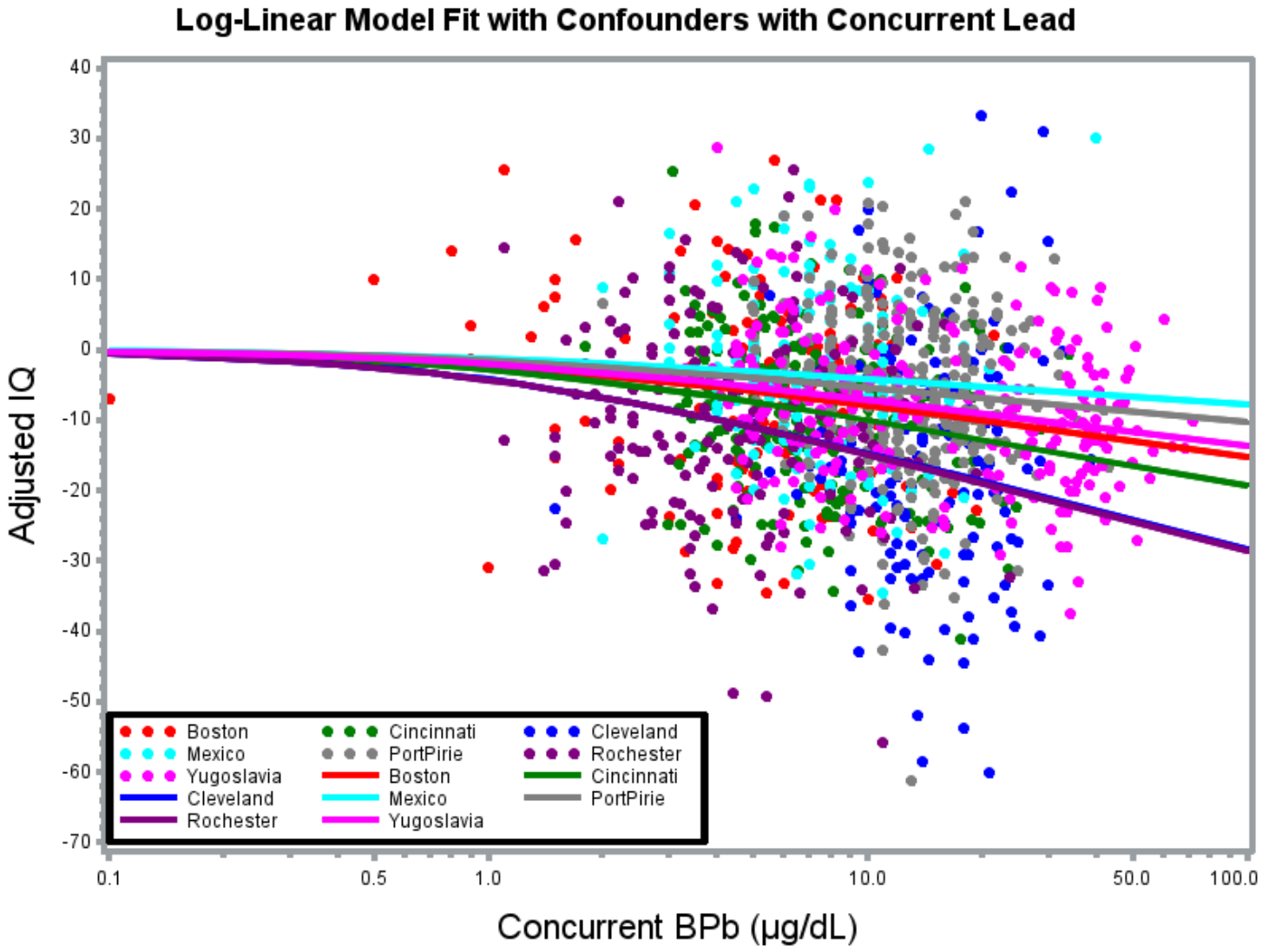
PRELIMINARY MODEL:
CONFOUNDER ADJUSTED, SITE SPECIFIC LOG-LINEAR MODELS



Adjusted values derived from log-linear model fit.

Cleveland and Rochester models overlay each other.

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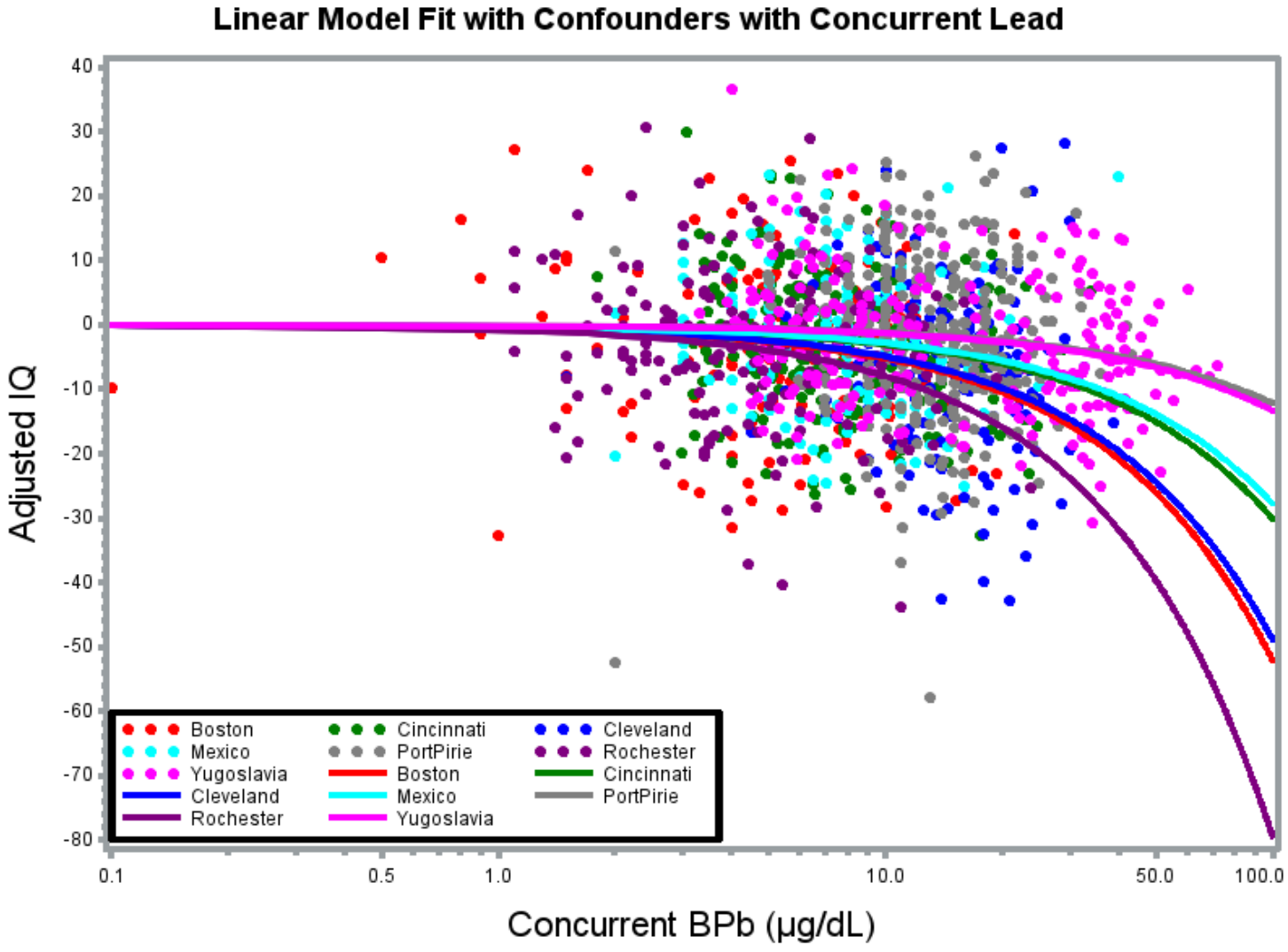
PRELIMINARY MODEL:
CONFOUNDER ADJUSTED, SITE SPECIFIC LINEAR MODELS



Adjusted values derived from linear model fit.

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QUESTIONS

- Do you think our two pronged approach for identifying confounders is sufficient? If not, what other tests would you recommend.
- Adding confounders to regression analysis makes interpretation of results more difficult due to the addition of the effect of blood lead multiplied by other variables (confounders), which can sometimes be site specific. Do you think that this is a problem or is it more appropriate to have a range of possible changes in the dependent variable (IQ for this case) based on a set value of the blood lead variable (e.g. 2.5 µg/dL) and a range of possibly site specific values for the confounders?
- Are you aware of any other studies that have applied this approach to address the effects of confounding (vs. covariation)? If so, what lessons might we learn from those studies?