Moderation Analysis of Calcium Levels on the Effect of Environmental Mixtures on Child Neurodevelopment

Malika Top, Data Science Major Capstone '24

BACKGROUND

- Exposure to mixed toxic metals like lead (Pb), arsenic (As), and manganese (Mn) has been proven to have negative effects on fetal and child development. A study by Valeri et al. in 2017 looked at the joint effect of prenatal exposure to these metals, given the realities of multiple exposures at a time, on neurodevelopment scores at 20-40 months of age in a cohort study in Bangladesh.
- Based on existing literature on reductive effects of calcium supplementation on blood lead levels in pregnant women (Ettinger et al., 2009), this project performs a moderative analysis on calcium **to see whether calcium (Ca) levels impact the degree to which metal exposure has an impact on cognitive score.**

DATA

- The subset of data used (n=351 mother-child pairs) comes from a prospective cohort study conducted in the Sirajdikhan and Pabna district of Bangladesh
- Variables of study: umbilical cord blood levels for Pb, As, and Mn (exposure), child neurodevelopment score as calculated from Bayley Scales of Infant and ToddlerDevelopment™ (outcome), and child's calcium level at time of follow-up visit
- Included covariates to adjust for confounding: age visit, sex, education of the mother, education of the spouse, protein intake, smoke environment, the daily intake of cups of water, and the sum of HOME scores (influence of socioeconomic status on the evaluation of the home environment)

METHODS

Traditional Multivariable Linear Regression Analysis:

$$Y_i = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 X{*}Z + \varepsilon_i$$

where Y_i is a vector of cognitive score outcomes, β_0 is the intercept when metal exposure and calcium level equal 0, X is the matrix of combined metal exposures, Z is the proposed moderator variable, there is an interaction between X and Z, and ε is a vector representing the random error term, following a normal distribution.

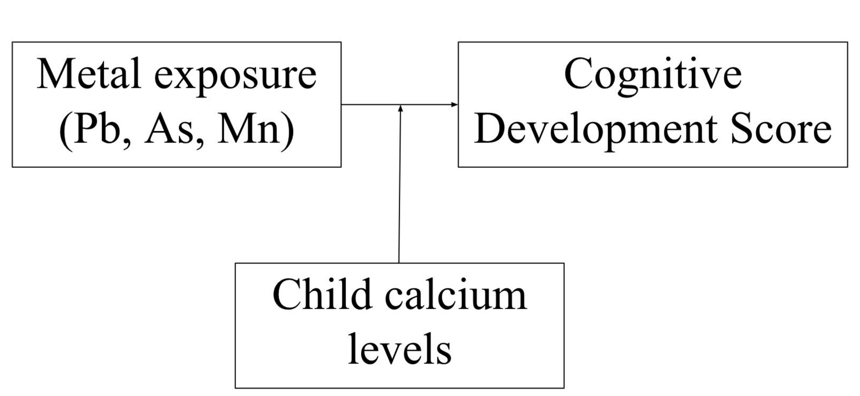

Fig. 1 A model proposing the moderating effect of Ca on the relationship between metal exposure and CS

DATA / STATISTICAL ANALYSIS

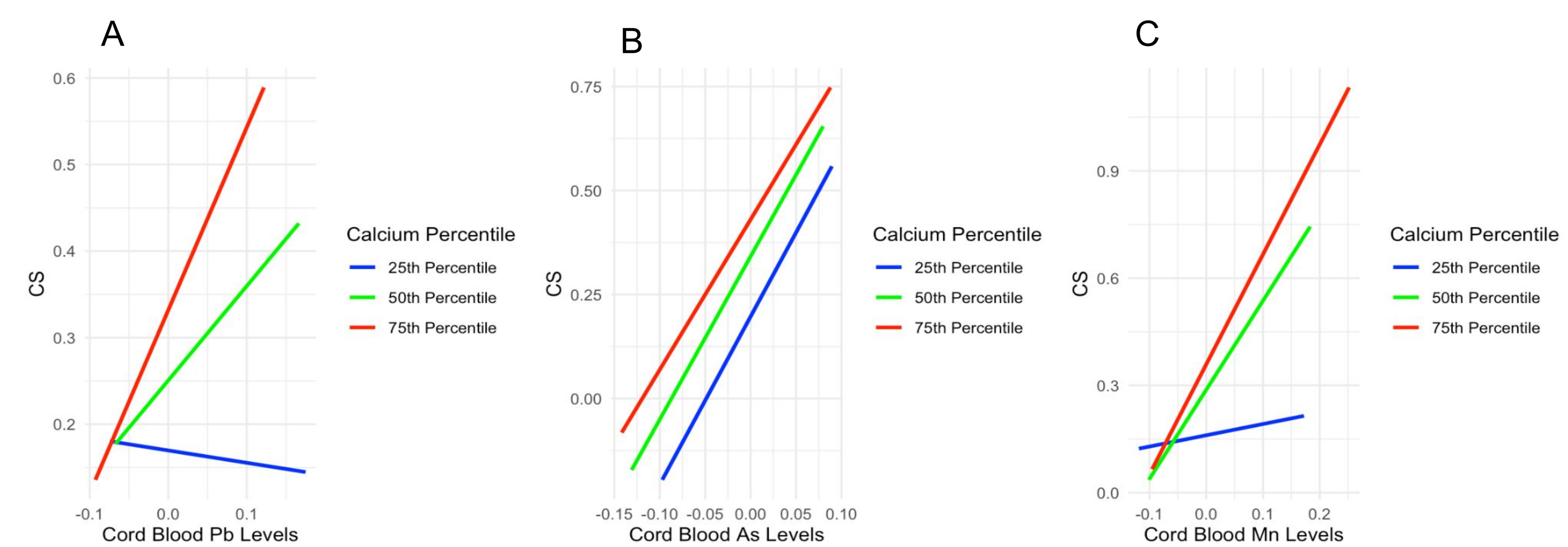

Fig. 2 Relationship between (A) Pb, B) As, (C) Mn and CS at 25th, 50th, and 75th percentiles of calcium levels.

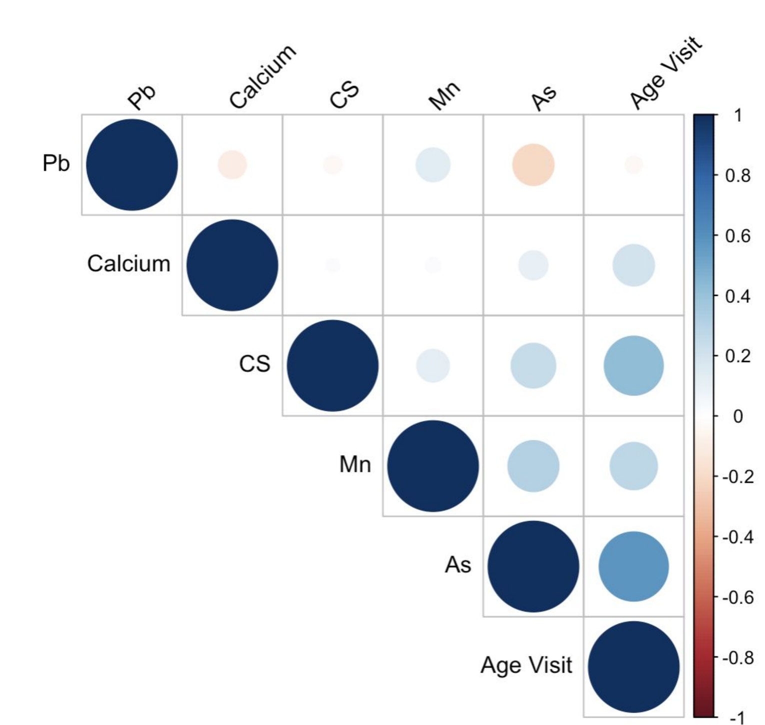

Fig. 3 Correlation matrix between metal exposures, calcium level, child's age at visit, and CS.

Table 1: Interaction Model regression results

	Model A	Model B
Intercept	−1.2362*	−1.1859*
Pb	−0.1852	−0.2265*
As	−0.0774	−0.0032
Mn	0.0405	−0.0381
Ca	−0.0654	−0.0159
Age Visit	4.9759***	8.2653***
Sex	0.5207	0.6542
Education	−2.7529	−2.6057
Spouse Education	2.8083	2.7535
Protein	0.0119	−0.0081
HOME Score	12.7095	12.2899*
Smoking	0.6246	0.6563
Water Cups	3.7279	3.2164
Pb*Z	−0.0836	−0.1488
As*Z	0.1175	0.2831*
Mn*Z	−0.2048	−0.3575*
Z*Age Visit		5.5927**
R^2	0.2401	0.2553
Adj. R^2	0.206	0.2196
F-statistic	7.055	7.155

$^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$

Fig. 4 Regression output comparing Model A (interaction between Ca and metal mixture) with Model B (interactions from A and interaction between Ca and age visit).

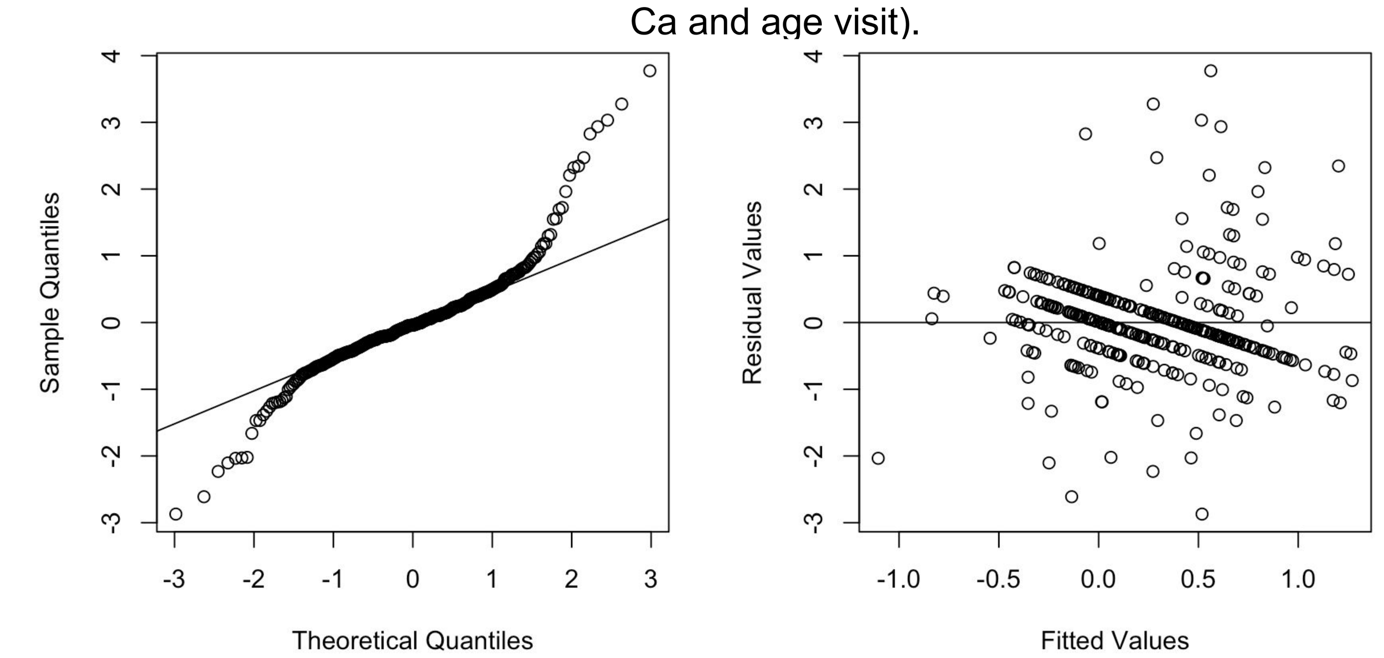

Fig. 5 QQ plot (left) and residuals-vs-fitted values plot (right) to assess normality and homoscedasticity assumptions for Model B

RESULTS

- No evident correlation between Ca and metal exposures nor Ca and cognitive scores
- Only observed negative linear relationship between metal and CS is at 25th percentile of Ca levels for Pb, may indicate that higher amounts of Ca influence the relation between CS and Pb
- Positive relationship between Mn and CS is least extreme at 25th percentile of Ca
- Interaction between Ca and metals in Model A did not yield a statistically significant p-value meaning for this dataset, Ca is not a moderator; however, the child's age and HOME score were significant predictors.
- Model B resulted in significant interaction between As and Ca, and Mn and Ca
- Model B has a marginally higher F-statistic (7.155) and adjusted R^2 (0.22) than Model A's, meaning more variation in CS is explained by the model's independent variables and it has more significant predictors

FUTURE DIRECTIONS

- Lead exposure disproportionately affects lower-income countries with current lead abatement methods being costly, must find alternatives
- Apply a causal mediation analysis on calcium and testing age on the exposure-outcome relationship (Devick et al., 2022)
- Test for the opposite moderative effect by including a matrix of vitamins known to increase toxic metal absorbance like vitamin A and vitamin D.

Limitations:

- These analyses were run only on a subset of the full data, from the Sirajdikhan clinic.
- Heterogenous evidence in the field on associations between calcium and other supplements on cognitive development and health .

REFERENCES

(1) Devick, K. L., Bobb, J. F., Mazumdar, M., Henn, B. C., Bellinger, D. C., Christiani, D. C., Wright, R. O., Williams, P. L., Coull, B. A., & Valeri, L. (2022). Bayesian kernel machine regression–causal mediation analysis. Statistics in Medicine, 41(5), 860–876. https://doi.org/10.1002/sim.9255

(2) Ettinger, A. S., Lamadrid-Figueroa, H., Téllez-Rojo, M. M., Mercado-García, A., Peterson, K. E., Schwartz, J., Hu, H., & Hernández-Avila, M. (2009). Effect of calcium supplementation on blood lead levels in pregnancy: A randomized placebo-controlled trial. Environmental Health Perspectives, 117(1), 26–31. https://doi.org/10.1289/ehp.11868

(3) Valeri, L., Mazumdar, M. M., Bobb, J. F., Claus Henn, B., Rodrigues, E., Sharif, O. I. A., Kile, M. L., Quamruzzaman, Q., Afroz, S., Golam, M., Amarasiriwardena, C., Bellinger, D. C., Christiani, D. C., Coull, B. A., & Wright, R. O. (2017). The joint effect of prenatal exposure to metal mixtures on neurodevelopmental outcomes at 20–40 months of age: Evidence from rural bangladesh. Environmental Health Perspectives, 125(6), 067015. https://doi.org/10.1289/EHP614

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