eAppendix
Description of models of predicted rate of change.

Blood manganese levels do not have a single "normal" value throughout life. The limited amount of research on population means suggests that values change with different life stages. Pregnancy and early childhood appear to be periods when blood manganese levels change rapidly: maternal blood manganese levels peak during pregnancy, and infant blood levels are highest early in life[30,31] with subsequent declines.[32-34] We therefore explored whether the rate of change in blood manganese between 12 and 24 months of age might be associated with neurodevelopment score or change in neurodevelopment score. The difference between two time points may be a noisy estimate of the blood manganese trend in each child due to measurement error as well as day-to-day fluctuations in actual manganese concentrations. To address this, we fit mixed models of repeated blood manganese measures with time as a predictor and random slopes for each individual. Predicted rate of change in manganese for each individual, determined by adding the random individual effect to the fixed effect of time, was subsequently used as the exposure variable in models predicting neurodevelopment score. This approach may have greater predictive validity of exposure and, thus, increased sensitivity, as demonstrated by McCracken et al.,[35] compared with calculating an absolute difference between concentrations at 12 and 24 months of age for each individual. We used similar mixed models to calculate a predicted change in neurodevelopment score between 12 and 24 months and between 24 and 36 months of age, and used this term as the outcome variable.

The average change in blood manganese between 12 and 24 months of age was a decrease of 5.7 μg/l (SD 4.5, range: 21.4 μg/l decrease – 15.0 μg/l increase). Children with greater declines

in manganese from 12 to 24 months had slightly higher Mental Development Index scores, though effect estimates were small and imprecise. For Psychomotor Development Index, no consistent associations were observed. In models of change in manganese predicting change in Bayley scores, effect estimates were close to zero. Overall, the rate of change in manganese did not appear to be associated with neurodevelopment.

References

30. Spencer A. Whole blood manganese levels in pregnancy and the neonate. *Nutrition*. 1999;15:731–734.

31. Tholin K, Palm R, Hallmans G, Sandstrom B. Manganese status during pregnancy. *Ann N Y Acad Sci*. 1993;678:359 –360.

32. Chan AW, Minski MJ, Lim L, Lai JC. Changes in brain regional manganese and magnesium levels during postnatal development: modulations by chronic manganese administration. *Metab Brain Dis*. 1992;
7:21–33.

33. Collipp PJ, Chen SY, Maitinsky S. Manganese in infant formulas and learning disability. *Ann Nutr Metab*. 1983;27:488–494.

34. Takeda A, Ishiwatari S, Okada S. Manganese uptake into rat brain during development and aging. *J Neurosci Res*. 1999;56:93–98.

35. McCracken JP, Schwartz J, Bruce N, Mittleman M, Ryan LM, Smith KR. Combining individual- and group-level exposure information: child carbon monoxide in the Guatemala woodstove randomized control trial. *Epidemiology*. 2009;20:127–136.