Elsewhere in *JAMA Network Open*, Li and colleagues report the results of a study that yields important new information on lead toxic effects, an environmental hazard that has been the subject of decades of research and public health controls, yet for which many critical unknowns remain. One of the novel aspects of their work is its focus on the risk to neurodevelopment posed by prenatal lead exposure. As opposed to postnatal (ie, pediatric) lead exposure—which, based on the evidence from hundreds of rigorous investigations around the world, has resulted in a long history of ever-tightening environmental controls, screening of blood lead levels in children, and ever-lower levels of lead in blood that are considered acceptable—there has been relatively little attention to lead exposure in the womb. By conducting this research with both state-of-the-art methods for measuring prenatal and postnatal lead exposure and the advantage of a large sample size, Li et al. have advanced the field, generating results indicating that prenatal lead exposure is adversely associated with cognition, independent of postnatal lead exposure.

From a methodological perspective, it is instructive to note that in this study, lead levels in maternal plasma (as opposed to maternal whole blood) were found to be associated with lower cognition scores among offspring. In so doing, Li et al. have provided further support to earlier research suggesting that maternal plasma lead, which is typically less than 1% to 5% of the level of lead in maternal whole blood, is not in complete equilibrium with the lead bound to red cells. Nevertheless, it is the component of lead in blood that is bioavailable to cross the placenta and therefore has the most influence on fetal lead exposure and resulting neurotoxic effects. However, given the very low concentrations of lead that need to be measured in plasma (typically 10-100 times lower than lead levels in whole blood) as well as the care that is needed to prevent hemolysis during specimen collection and processing (which would contaminate plasma with the >95% of lead in a whole blood sample that is bound to red cells), specialized research protocols need to be followed for both collecting blood and measuring lead that are not typically associated with blood lead level testing done by clinical laboratories.

The second novel aspect of the work by Li et al. is the use of the results from the meta-analysis of previous genomewide association studies (GWAS) conducted by the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium to construct a polygenic risk score (PRS) that they then applied to their analysis to investigate lead-gene interactions. The 58 single nucleotide variants that formed their PRS were significantly associated with the Mental Development Index (MDI) scores of the participants and also seemed to confer heightened susceptibility to lead's association with the scores, with an almost doubling of the risk comparing those in the high- vs low-genetic risk categories. This work complements that of investigations that have leveraged knowledge of common functional genetic variants associated with mechanistic pathways likely underlying lead's neurotoxic effects to test a priori gene-lead interaction hypotheses, such as studies on the modifying effect on lead's impact on children's IQ of the dopamine D2 receptor *DRD2 TaqI A* variant. It also follows on a previous study that used data from 2 environmental birth cohort studies to conduct an alternative type of GWAS investigation that integrated a genomewide gene-lead interaction analysis with results from an in vitro transcriptomic analysis of lead-induced changes in human neural stem cells. In so doing, the investigators identified a particular common gene as a potential modifier of prenatal lead exposure on MDI scores, ie, *SLC1A5*, a gene known to be involved in synaptic function,
neuronal development, and excitotoxicity. As methods (and the appetite) for conducting gene-environmental interaction research involving lead exposure continue to grow, more insights will surely follow that help shed light on the most important mechanisms involved in lead's neurodevelopmental toxic effects, with possible ramifications for treatment as well as prevention.

In terms of implications for public health, it is sobering to note that the lead exposure of the population studied by Li et al was relatively modest, as reflected by blood lead levels of the 2-year-old children. While the geometric mean of 4.39 μg/dL exceeds the current level of concern promulgated by the US Centers for Disease Control of 3.5 μg/dL, it is well below levels associated with any clinical symptoms. Such levels (as well as those that are higher) continue around the world, not only from legacy sources such as old (pre-1975) housing containing lead paint and old lead (pre-1950) and lead-soldered (pre-1975) plumbing that remains in the United States and several other high-resource countries, but especially in low- and middle-income countries where there are ongoing active sources of exposure, particularly from informal lead acid battery recycling and manufacturing, metal mining and processing, electronic waste, and the use of lead as a food adulterant, primarily in spices. In addition, as the authors mentioned in their introduction, for pregnant women, the mobilization of bone lead stores during pregnancy remains of concern. Left unmentioned is that skeletal stores of lead persist for decades, and in women who have had chronic lead exposure, research has clearly shown that the heightened bone resorption that occurs during pregnancy is accompanied by the increased release of bone lead stores, resulting in elevated circulating lead levels even if women are fastidious in avoiding lead exposure during pregnancy itself. Recognition of this phenomenon prompted National Institutes of Health-funded randomized trials of calcium supplementation (1200 mg at bedtime) that, in turn, were shown to reduce bone resorption as well as circulating blood lead levels by approximately 24% among pregnant women who were most adherent to the intervention. This provides additional justification for pregnant women to take calcium supplementation, a recommendation made by the World Health Organization since 2016 as a measure for lowering the risk of preeclampsia.

Overall, many mysteries remain regarding lead's impact on the brain and brain development (as well as other outcomes), despite it being one of the most studied environmental hazards in history. But what is crystal clear is that the highest priority for society as well as public health remains prevention of lead exposure. By showing adverse cognitive impacts on the offspring of mothers due to relatively modest levels of lead exposure that not only are invisible and asymptomatic but likely at least partially a result of mobilization of lead from bone stores accumulated from past exposures, the study by Li et al has underscored the importance of reducing lead exposure for individuals of all ages and throughout the life course. For populations around the world, the implementation of wise policies that are rigorously enforced and surveillance remains the only sensible public health approach to the problem.
Committee of the US Environmental Protection Agency’s Clean Air Scientific Advisory Committee and for testifying as an expert witness in litigation related to lead exposure and toxicity outside the submitted work.

REFERENCES