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ARTICLE: Association of Childhood Lead Exposure With MRI Measurements of Structural Brain Integrity in Midlife

A research team led by Aaron Reuben, Maxwell L. Elliott, Avshalom Caspi, and Terrie E. Moffitt at Duke University reports that, more than three decades after they were found to have elevated blood-lead levels as children, a group of middle-aged adults were found to have small but significant differences in brain structure that corresponded to their dose of lead exposure in early life. These findings are based on a study that followed a birth cohort of 1,000 children, born in one city in New Zealand in the early 1970s and followed to midlife. In 1983, 565 of the children were tested for lead. Because of high lead-in-gasoline levels in New Zealand at the time, childhood lead exposure was widespread and the degree of lead exposure was not related to a child's socioeconomic status in this cohort. This study suggests that childhood lead exposure may have long-term ramifications for brain integrity and cognitive ability. Early life lead exposure may be a risk factor for brain aging and neurodegenerative disease.

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FINDINGS:

We conducted our study in a 1972-1973 New Zealand birth cohort. During the 1970's and 1980s New Zealand had some of the highest lead-in-gasoline levels in the developed world and cohort children with elevated lead levels were found at all socioeconomic levels, rich or poor.

(1) Study members with greater lead exposure in childhood tended to display differences in MRI measures of brain structure at midlife indicative of lower brain integrity.
    a. For each 5µg/dL increase in childhood blood-lead level there was a 1.19-cm^2 smaller total cortical surface area, a 0.10-cm^3 smaller mean hippocampal gray matter volume, a 0.12 lower global fractional anisotropy, and a a 0.77 years older BrainAGE index at age 45 years.
    b. Participants with childhood blood lead levels above the historical international level of concern (>10 µg/dL) exhibited a mean BrainAGE index 1.52 years older than those at or below the blood lead concern level in childhood.
(2) Differences in brain structure were accompanied by lower midlife cognitive ability, reflecting decline from childhood.

a. For each 5µg/dL increase in childhood blood-lead level there was a 2.07 lower IQ score at age 45 years.
a. Participants with childhood blood lead levels above the historical international level of concern (>10 µg/dL) exhibited a mean decline of 2.62 IQ points from childhood to age 45 years. In contrast, those at or below the concern level exhibited a mean increase of 1.05 IQ points from childhood to adulthood, a significant difference of 3.67 IQ points.

(3) By age 45, Study members with greater lead exposure in childhood tended to display modest problems in everday cognitive function, noticeable to others though not to themselves.
    a. For each 5µg/dL increase in childhood blood-lead level there was a 0.12-point higher score for informant-reported cognitive problems.

WHY ARE THESE FINDINGS IMPORTANT?

(1) We have found that children exposed to lead show slightly poorer brain integrity decades later, with commensurate, albiet modest, deficits in cognitive performance and everyday cognitive functioning.
(2) Our MRI brain measures are only from one time-point in midlife, but the midlife cognitive test deficits we report represent decline since childhood testing, and this suggests brain integrity differences have been declining during adulthood.
(3) These lasting effects suggest that effective public-policy responses to community lead exposure events may need a long-term strategy.
(4) The global population of aging individuals exposed to high levels of lead in childhood during the era of leaded-gasoline may be at risk for accelerated brain aging and cognitive decline later in life.
(5) Millions of children around the world are still exposed to high levels of lead. This may have consequenecs for brain health and cognitive ability at the population-level for decades to come.

LIMITATIONS:

(1) Although mean blood-lead levels in this New Zealand cohort were comparable to other developed-city cohorts born in the early 1970's, the lead levels in the Dunedin cohort were nearly entirely above the current blood-lead reference value for clinical attention today (94% of participants had blood lead above 5µg/dL). This study's results may not, therefore, be informative about the long-term consequences of very low lead exposures (i.e., those below 7.5µg/dL).
(2) We only had one measure of childhood lead exposure, blood-lead levels measured at age 11 years.Other research suggests, however, that our measure provided a reasonable approximation of lifetime lead-exposure in our cohort up to that point.
(3) Our cohort, born in the 1970s, likely experienced on-going lead exposure during their childhood. Our findings may not be indicative of the consequences of acute, short-term lead exposure.
(4) Our research is based on only one cohort in one part of the world.

SUPPORTING DETAILS:

PARTICIPANTS: Participants were members of the Dunedin Multidisciplinary Health and Development Study, an investigation of the health and behavior of a representative cohort of 1037 consecutive births between April 1972 and March 1973 in Dunedin, New Zealand. This birth cohort's families represented the full range of socioeconomic status in the general population. Follow-ups have been carried out at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently 45, when 95% of the living cohort members took part.

DOCUMENTARY FILM: We invite you to view a documentary about the Dunedin Study, called "Predict My Future: The Science of Us," available via Curiosity Stream (https://app.curiositystream.com/video/1268).

MEASURING CHILDHOOD BLOOD-LEAD LEVELS: Our measure of childhood lead exposure was blood-lead level assessed at age 11 years. Approximately 30 ml of venous blood was drawn from each 11-year-old who participated in the assessment carried out at the Research Unit and who freely agreed to give blood.

MEASURING BRAIN STRUCTURE: Brain structure was measured at age 45 years using a neuroimaging protocol with T1-weighted, fluid-attenuatedi nversion recovery and diffusion-weighted sequences. High-resolution structural images were used to generate estimates of primary study outcomes in the domains of grey matter, white matter, and the Brain Age Gap Estimation (BrainAGE), a composite index of aging related brain structure differences, calculated as the gap between each study member's chronological age at imaging and their MRI-predicted age, estimated using a machine learning algorithm originally trained in large independent cohorts to predict chronological age from MRI data across a broad age range.

MEASURING COGNITIVE PERFORMANCE: Cognitive performance was assessed at age 45 years using the Wechsler Adult Intelligence Scale –IV (WAIS-IV). Cognitive performance was also assessed in childhood, using the Wechsler Intelligence Scale for Children-Revised (WISC-R) at ages 7 and 9 years (prior to blood-lead evaluation). Change in IQ from childhood to adulthood was calculated by subtracting childhood IQ scores from adult IQ scores.

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