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

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IMPORTANCE Childhood lead exposure has been linked to disrupted brain development, but long-term consequences for structural brain integrity are unknown.

OBJECTIVE To test the hypothesis that childhood lead exposure is associated with magnetic resonance imaging (MRI) measurements of lower structural integrity of the brain in midlife.

DESIGN, SETTING, AND PARTICIPANTS The Dunedin Study followed a population-representative 1972-1973 birth cohort in New Zealand (N = 564 analytic sample) to age 45 years (until April 2019).

EXPOSURES Childhood blood lead levels measured at age 11 years.

MAIN OUTCOMES AND MEASURES Structural brain integrity at age 45 years assessed via MRI (primary outcomes): gray matter (cortical thickness, surface area, hippocampal volume), white matter (white matter hyperintensities, fractional anisotropy [theoretical range, 0 {diffusion is perfectly isotropic} to 100 {diffusion is perfectly anisotropic}]), and the Brain Age Gap Estimation (BrainAGE), a composite index of the gap between chronological age and a machine learning algorithm–estimated brain age (0 indicates a brain age equivalent to chronological age; positive and negative values represent an older and younger brain age, respectively). Cognitive function at age 45 years was assessed objectively via the Wechsler Adult Intelligence Scale IV (IQ range, 40-160, standardized to a mean of 100 [SD, 15]) and subjectively via informant and self-reports (*z*-score units; scale mean, 0 [SD, 1]).

RESULTS Of 1037 original participants, 997 were alive at age 45 years, of whom 564 (57%) had received lead testing at age 11 years (302 [54%] male) (median follow-up, 34 [interquartile range, 33.7-34.7] years). Mean blood lead level at age 11 years was 10.99 (SD, 4.63) μg/dL. After adjusting for covariates, each 5-μg/dL higher childhood blood lead level was significantly associated with 1.19-cm^2 smaller cortical surface area (95% CI, −2.35 to −0.02 cm^2; $P = .05$), 0.10-cm^3 smaller hippocampal volume (95% CI, −0.17 to −0.03 cm^3; $P = .006$), lower global fractional anisotropy ($b = −0.12$; 95% CI, −0.24 to −0.01; $P = .04$), and a BrainAGE index 0.77 years older (95% CI, 0.02-1.51 years; $P = .05$) at age 45 years. There were no statistically significant associations between blood lead level and log-transformed white matter hyperintensity volume ($b = 0.05$ log mm^3; 95% CI, −0.02 to 0.13 log mm^3; $P = .17$) or mean cortical thickness ($b = −0.004$ mm; 95% CI, −0.012 to 0.004 mm; $P = .39$). Each 5-μg/dL higher childhood blood lead level was significantly associated with a 2.07-point lower IQ score at age 45 years (95% CI, −3.39 to −0.74; $P = .002$) and a 0.12-point higher score on informant-rated cognitive problems (95% CI, 0.01-0.23; $P = .03$). There was no statistically significant association between childhood blood lead levels and self-reported cognitive problems ($b = −0.02$ points; 95% CI, −0.10 to 0.07; $P = .68$).

CONCLUSIONS AND RELEVANCE In this longitudinal cohort study with a median 34-year follow-up, higher childhood blood lead level was associated with differences in some MRI measures of brain structure that suggested lower structural brain integrity in midlife. Because of the large number of statistical comparisons, some findings may represent type I error.

Supplemental content

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Many adults born during the peak use of lead in gasoline (1960s-1980s) were exposed to lead, a neurotoxicant, as children.[1,2] Lead disrupts brain development.[3] Lead-exposed children consequently develop lower intellectual abilities, fine motor skills, and emotion regulation capacity.[4-6] Although the long-term consequences of early-life exposure remain unclear, childhood lead exposure in a population-representative birth cohort, the Dunedin Study, was previously associated with IQ deficits at age 38 years, representing a decline from childhood.[7] Cognitive decline across many years is a risk factor for degenerative brain disease, including dementia.[8-10] However, it is unclear if childhood lead exposure is directly associated with adult neurodegeneration.[11,12]

The Dunedin Study was used to test the hypothesis that childhood lead exposure is associated with differences in magnetic resonance imaging (MRI) measurements of structural integrity of the brain in midlife that could be suggestive of greater risk of neurodegenerative diseases in later adulthood (lower cortical thickness, surface area, hippocampal volume, and fractional anisotropy; greater white matter hyperintensity volume; older brain age). Because studies of brain structure are strengthened by evidence of functional differences, the hypotheses that lead-related brain structural differences are accompanied by differences in cognitive performance suggestive of decline or early functional impairment were also tested. As previously reported,[13] Dunedin Study childhood blood lead levels matched those of other developed-nation cohorts tested contemporaneously. Unlike other cohorts, however,[1] there was no social patterning of lead exposure in the Dunedin Study cohort; as previously reported,[7] participants showed similarly elevated lead levels across socioeconomic strata, providing a unique context for testing the consequences of lead exposure without potential socioeconomic confounding. It was hypothesized that adults with greater childhood blood lead levels would demonstrate lower brain integrity, as indicated by MRI measurements, and that associations between lead exposure and brain integrity would be accompanied by poorer cognitive function.

Key Points

Question Is childhood lead exposure associated with differences in magnetic resonance imaging (MRI) measurements of the integrity of brain structure in midlife?

Findings In this longitudinal prospective cohort study of 564 New Zealand children followed up to midlife, greater lead exposure in childhood was significantly associated with differences in MRI measurements of brain structure at age 45 years, including smaller cortical surface area, smaller hippocampal volume, lower global fractional anisotropy, and an older estimated brain age.

Meaning Higher childhood blood lead level was associated with differences in MRI measurements of brain structure that suggested lower structural brain integrity in midlife.

Methods

Study Design and Population

The project premise and analysis plan were preregistered and are stored on Google at https://tinyurl.com/y9v2tesf and Open Science at https://osf.io/pwzv8. Reported analyses were checked for reproducibility by an independent data analyst, who recreated the code by working from the manuscript and then applied it to a fresh data set.

Participants were members of the Dunedin Study. The full cohort comprises all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible based on residence in the province and who participated in the first assessment at age 3 years. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island.[14] On adult health, the cohort matches the New Zealand National Health and Nutrition Survey on key indicators (eg, body mass index, smoking, visits to a physician)[14] and the New Zealand Census of citizens of the same age on educational attainment.[15] The cohort is primarily White (as self-described using fixed categories, assessed to determine population representativeness of cohort). Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years, with the most recent data collection completed in April 2019, at age 45 years. Written informed consent was obtained at each assessment, from parents during childhood visits and from participants in adulthood. Study protocols were approved by the institutional ethical review boards of the participating universities. Archived childhood blood lead data were linked to MRI measures of structural brain integrity and measures of cognitive performance collected at age 45 years.

Measures

Childhood Blood Lead Levels

Approximately 30 mL of venous blood was collected at age 11 years. Whole blood samples were analyzed through graphite furnace atomic absorption spectrophotometry. Blood lead is reported in micrograms per deciliter (1 µg/dL = 0.0483 µmol/L). Details on the method of blood collection, storage, and analysis have been previously described.[13] Study informants, participants, researchers, and staff at midlife follow-up were blinded to archival blood lead levels.[16]

Outcomes

Brain Measures | At age 45 years, participants completed a neuroimaging protocol including assessment of brain structure with T1-weighted, fluid-attenuated inversion recovery and diffusion-weighted sequences using a Siemens Skyra 3T scanner (Siemens Healthcare) equipped with a 64-channel head and neck coil. High-resolution structural images were used to generate estimates of primary study outcomes in 3 domains (eTable 1 in the Supplement): (1) gray matter (mean cortical thickness, total cortical surface area, and, because of its importance to memory function and dementia,[17] bilateral hippocampal volume); (2) white matter (volume of white matter hyperintensities [WMH] and global fractional anisotropy [theoretical range, 0 {diffusion is perfectly isotropic} to 100 {diffusion is perfectly anisotropic}]); and (3) 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 (a 0 BrainAGE index indicates a brain age that is equivalent to chronological age; positive and negative values represent an older and younger brain age, respectively).[18,19]

Follow-up tests assessing regional specificity in the relationship between childhood lead exposure and midlife structural brain integrity included secondary MRI outcomes of gray matter (thickness and surface area of 360 cortical regions and subcortical gray matter volume in 12 nuclei) and white matter (fractional anisotropy of 44 tracts). See the eAppendix in the Supplement for further details.

Cognitive Measures | Cognitive health was measured at age 45 years using objective tests of cognitive performance (the Wechsler Adult Intelligence Scale IV [WAIS-IV] full-scale IQ; potential range, 40-160, standardized to a mean of 100 [SD, 15]). In addition, subjective reports of everyday cognitive functioning were provided by study participants and by informants nominated by each study participant as someone who knew them well. Both participants and informants rated whether the study participant experienced specific memory and attention problems over the past year. The ratings provided by study participants and informants were each standardized within the full cohort to *z*-score units (mean of 0 [SD, 1]) (eTable 1 in the Supplement).

Statistical Analysis

First, descriptive statistics were generated for the whole cohort and separately for participants with and without blood lead data; differences between those with and without data were examined using *t* tests.

Second, associations between childhood blood lead levels and brain imaging outcomes were tested using ordinary least-squares regression. Each outcome was examined using (1) a sex-adjusted baseline model in which the outcome was regressed on childhood blood lead levels and sex to account for known sex differences in lead metabolism and brain morphology and (2) a fully adjusted model in which the outcome was regressed on childhood blood lead levels and sex, maternal IQ (assessed via the Science Research Associates verbal test[20] administered to study mothers when participants were 3 years old) and childhood socioeconomic status (defined as the mean of the highest occupational status of either parent across study assessments from participants' birth through age 15 years, assessed via the Elley-Irving scale[21] assigning parental occupations into 1 of 6 status groups [6 = professional; 1 = unskilled laborer]). Following these primary tests, prespecified exploratory models were built using the same approach to test for regional specificity in the association between childhood blood lead level and adult brain structure, focusing on the secondary brain outcomes: parcel-wise cortical thickness and surface area, subcortical gray matter volume, and tract-specific fractional anisotropy. Measure-wide significance thresholds were derived for each measure type by applying a false discovery rate correction to the nominal α of .05, adjusting for number of cortical regions (360 each for cortical thickness and surface area), subcortical volumes (12), and white matter tracts (44) tested. Post hoc sensitivity tests were also conducted adjusting all primary and secondary tests for measures of adult health known to be associated with MRI measures of brain integrity and cognitive performance measures: alcohol use, tobacco smoking, and hypertension, taken at the assessment at age 45 years. Details on these measures are provided in eTable 3 in the Supplement.

Third, associations between childhood blood lead levels and cognitive outcomes were estimated using ordinary least-squares regression following the same approach as step 2, with sex-adjusted and fully adjusted models. Following these models, the objective cognitive test outcome (WAIS-IV full-scale IQ) was subjected to 2 separate additional adjustments. (1) Significant lead-related brain outcomes at age 45 years identified in step 2 were adjusted to determine whether lead-IQ associations were occurring among the same individuals as lead-brain associations, using the Clogg test[22] to determine statistically significant effect size attenuation. (2) Cognitive test performance measured in childhood prior to lead testing (via the Wechsler Intelligence Scale for Children-Revised mean of age 7 and 9 years full-scale IQ; 99% and 95% of children assessed within 2 months of their birthday at each age, respectively) (eTable 1 in the Supplement) was adjusted to determine whether lead-IQ associations at age 45 years reflected longitudinal decline from childhood to midlife, using a residualized model of cognitive change.[23] As post hoc sensitivity analyses, tests of cognitive decline were also run using change scores and mixed-effects regression.

Lead level was analyzed as a continuous measure. Statistical effect sizes are presented in clinically meaningful 5-μg/dL units, approximately 1 SD in the cohort and a multiple of the historical international "level of concern" (10 μg/dL), as well as the current reference value (5 μg/dL). Mean primary outcomes for participants above the historical level of concern were also compared with those at or below it (≤10 μg/dL). Only participants who had complete data on all covariates for each outcome were included in each model; no data were imputed. With an overall analytic sample of N = 564, primary analyses were potentially sensitive to statistical effect sizes as low as a Cohen f^2 = 0.02 at 80% power. The threshold for statistical significance was a 2-tailed P = .05. Cognitive outcomes were analyzed using Stata version 16.1 (StataCorp), brain outcomes using R version 3.4.4 (R Foundation). All primary and secondary outcomes and analyses were prespecified. Because of the potential for type I error due to multiple comparisons of the large number of primary and secondary outcomes, study findings should be interpreted as exploratory.

Results

Of 1037 original cohort members (93% White), 997 were still alive at age 45 years, 564 (57%) of whom had received blood

Table 1. Participant Demographics, MRI Brain Outcome Measures, and Cognitive Measures (N = 564)

Characteristics and measures	Value
Sex, No. (%)	
Female	262 (46.5)
Male	302 (53.5)
Childhood blood lead level, mean (SD), µg/dL	10.99 (4.63)
Maternal verbal IQ, mean (SD) [scale, 0-80][a]	40.35 (14.17)
Childhood socioeconomic status, mean (SD) [scale, 1-6]	3.80 (1.12)
Cortical thickness, mean (SD), mm[b]	2.55 (0.09)
Cortical surface area, mean (SD), cm^{2}[c]	186.47 (16.38)
Hippocampal volume, mean (SD), cm^{3}[d]	8.67 (0.83)
White matter hyperintensity volume, mean (SD), log mm^{3}[e]	6.52 (0.79)
Fractional anisotropy, mean (SD)[f]	42.56 (1.20)
BrainAGE index, mean (SD)[g]	−0.19 (7.89)
WAIS-IV full-scale IQ at age 45 y, mean (SD)[h]	101.00 (14.80)
Cognitive problems, mean (SD), *z* score	
Informant-reported[i]	0.00 (1.02)
Self-reported[j]	−0.07 (0.89)

Abbreviation: MRI, magnetic resonance imaging.

[a] Maternal verbal IQ was assessed with the Thurstone scale.

[b] Mean cortical thickness across the cortex was measured using FreeSurfer version 5.3. Local measures of regional cortical thickness were investigated in follow-up analyses using the HCP-MPP1.0 parcellation (eFigure 2 in the Supplement).

[c] Total surface area across the cortex was measured using FreeSurfer version 5.3. Local measures of regional surface area were investigated in follow-up analyses using the HCP-MPP1.0 parcellation (eFigure 2 in the Supplement).

[d] Total volume of the bilateral hippocampus, a region of the brain important for learning and memory, was measured using FreeSurfer's automated segmentation (ASEG) algorithm.

[e] Total volume of white matter hyperintensities was measured using the "unidentified bright objects" algorithm. White matter hyperintensities are bright spots on a T2-weighted MRI scan that are a sign of deterioration of white matter. The variable was log-transformed to produce an approximately normal distribution.

[f] Fractional anisotropy of white matter tracts. Fractional anisotropy is a unitless measure of the tendency for water molecules to diffuse along tracts instead of randomly. Higher values indicate restricted diffusion and are considered an MRI sign of greater white matter integrity. Fractional anisotropy was scaled from 0 (diffusion is perfectly isotropic) to 100 (diffusion is perfectly anisotropic). Measured using the FMRIB Software Library diffusion toolbox. Local measures of tract-wise fractional anisotropy were investigated in follow-up analyses for each tract in the Johns Hopkins University white matter atlas.

[g] The Brain Age Gap Estimation (BrainAGE) index is a composite neuroimaging biomarker of age-related brain structure, which estimates aging-related variance in diverse brains structures from cross-sectional brain measures. The BrainAGE index is estimated by training machine-learning algorithms to predict chronological age from structural MRI data collected in large samples of individuals across a broad age range. Using a publicly available algorithm, the BrainAGE index was estimated from surface area, cortical thickness, and subcortical volume data to produce a brain age gap estimate, which is the difference between an individual's predicted age based on MRI data and their chronological age. Positive BrainAGE values suggest that the brain is morphologically "older" than an individual's chronological age would predict.

[h] Objective cognitive performance was assessed using the Wechsler Adult Intelligence Scale IV (WAIS-IV; potential score range, 40-160; standardized in the full cohort to a mean of 100 [SD, 15]) at age 45 years to produce the overall full-scale IQ. Higher scores indicate greater cognitive performance.

[i] Subjective everyday cognitive function was reported by individuals who knew the participants well. These informants were mailed questionnaires and asked to complete a checklist indicating whether the study participant had problems with memory or attention over the past year. Memory and attention problem scales (correlated at $r = 0.66$; $P < .001$) were combined by taking the mean of the 2 scores to produce a composite informant-reported cognitive problems scale standardized in the full cohort to a mean of 0 (SD, 1).

[j] Subjective everyday cognitive function was also assessed by participant self-report. Study personnel administered a standardized interview about participants' memory and attention over the prior year. Memory and attention problem scales (correlated at $r = 0.56$; $P < .001$) were combined by taking the mean of the 2 scores to produce a composite self-reported cognitive problems scale standardized in the full cohort to a mean of 0 (SD, 1).

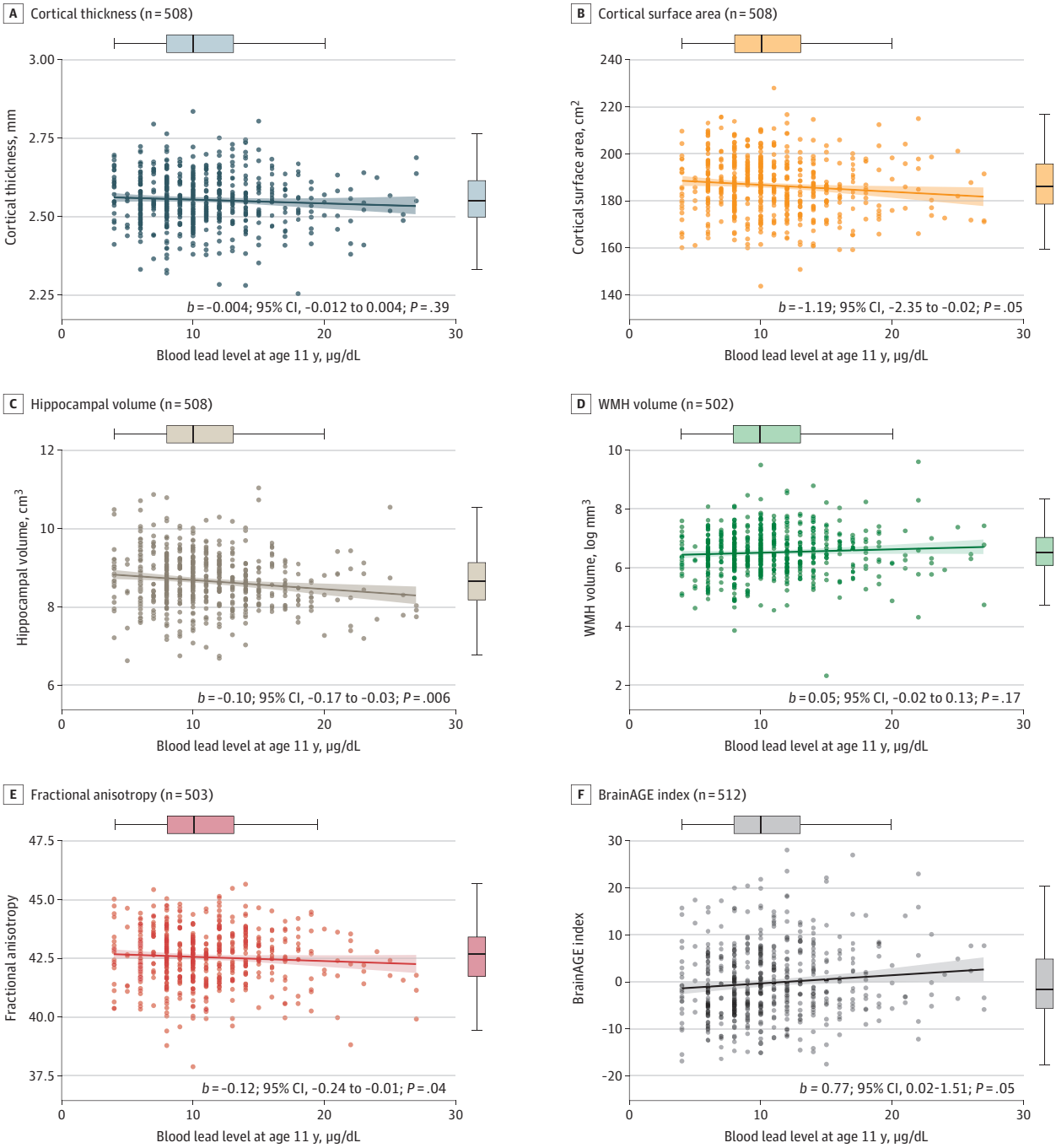
lead testing at age 11 years (302 [54%] male) (**Table 1**). (The remaining children at age 11 years did not consent to give blood or were assessed at school, where blood could not be drawn.) Ninety-four percent of participants were assessed within 2 months of their birthday, 98% within 4 months. Participants alive at age 45 years with (n = 564) and without (n = 433) childhood blood lead data did not differ to a statistically significant extent in terms of their mothers' IQs or their social class origins (eTable 2 in the Supplement).

Childhood blood lead levels ranged from 4 to 31 µg/dL (mean, 10.99 [SD, 4.63] µg/dL); 258 participants (46%; 156 [60%] male) had blood lead levels above the historical international level of concern of 10 µg/dL and 530 (94%; 287 [54%] male) had levels above the current reference value of 5 µg/dL.[24] Girls had lower lead levels than boys (mean, 10.42 µg/dL among girls [n = 262] and 11.48 µg/dL among boys [n = 302]; difference, −1.06; 95% CI, −1.82 to −0.30; $P = .007$). There was no significant socioeconomic gradient in lead exposure (Pearson $r = -0.01$ between blood lead level and family socioeconomic status; $P = .86$)[7]; children with high blood lead levels belonged to all socioeconomic groups (eFigure 1 in the Supplement).

Brain Measures

Five hundred eight participants (90% of the analytic sample) had data available for all covariates and gray matter measures. Mean cortical thickness was 2.6 (SD, 0.1) mm, mean total cortical surface area was 186.5 (SD, 16.4) cm^{2}, and mean bilateral hippocampal volume was 8.7 (SD, 0.8) cm^{3}. A total of 502 or 503 participants (89%) had data for white matter

Figure 1. Association of Childhood Blood Lead Level With MRI Measurements of Midlife Structural Brain Integrity



BrainAGE indicates Brain Age Gap Estimation; WMH, white matter hyperintensities. Each panel presents a scatterplot of the association between childhood blood lead levels and magnetic resonance imaging (MRI) brain outcome measures at age 45 years, with regression lines and their 95% confidence intervals (shaded areas). Box plots show the distribution of lead levels and brain outcomes; the box borders and midline represent the 25th, 50th, and 75th percentiles, with whiskers extending to the furthest observation within 1.5 interquartile ranges of the 25th and 75th percentiles. All graphs are adjusted for sex. Statistical effect estimates depict unit change in the outcomes for each 5-µg/dL higher level of blood lead in childhood. Reported *b* values are adjusted for sex, maternal IQ, and childhood socioeconomic status.

measures. Mean WMH volume was 6.5 (SD, 0.8) log mm^3 and mean global fractional anisotropy (scale, 0-100) was 42.6 (SD, 1.2). Five hundred twelve participants (91%) had data for the BrainAGE index, with a mean index of −0.2 (SD, 7.9) years.

Across multiple measures, higher childhood blood lead levels were associated with differences in MRI measurements of structural brain integrity in midlife (**Figure 1**) (**Table 2**). After adjustment for covariates, each 5-µg/dL higher childhood blood

Table 2. Associations Between Childhood Blood Lead Level and Brain and Cognitive Outcomes at Age 45 Years[a]

Outcomes	No. of participants	Sex-adjusted model		Fully adjusted model	
		b (95% CI)	*P* value	*b* (95% CI)	*P* value
Brain outcomes					
Gray matter integrity					
Cortical thickness, mm	508	−0.004 (−0.012 to 0.004)	.29	−0.004 (−0.012 to 0.004)	.39
Cortical surface area, cm^2	508	−1.40 (−2.57 to −0.23)	.02	−1.19 (−2.35 to −0.02)	.05
Hippocampal volume, cm^3	508	−0.10 (−0.17 to −0.03)	.003	−0.10 (−0.17 to −0.03)	.006
White matter integrity					
White matter hyperintensities, log mm^3	502	0.06 (−0.02 to 0.13)	.13	0.05 (−0.02 to 0.13)	.17
Fractional anisotropy (scale, 0-100)	503	−0.12 (−0.23 to −0.00)	.05	−0.12 (−0.24 to −0.01)	.04
BrainAGE index	512	0.79 (0.05 to 1.54)	.04	0.77 (0.02 to 1.51)	.05
Cognitive outcomes					
WAIS-IV full-scale IQ (objective cognitive performance)	528	−2.34 (−3.84 to −0.84)	.002	−2.07 (−3.39 to −0.74)	.002
Subjective cognitive function					
Informant-reported cognitive problems	511	0.12 (0.02 to 0.23)	.02	0.12 (0.01 to 0.23)	.03
Self-reported cognitive problems	524	−0.01 (−0.09 to 0.07)	.77	−0.02 (−0.10 to 0.07)	.68

[a] Covariates in the fully adjusted model were sex, maternal IQ, and childhood socioeconomic status. Means for the brain magnetic resonance imaging measurements were as follows: cortical surface area, 185.47 (SD, 16.35) cm^2; cortical thickness, 2.56 (SD, 0.09) mm; hippocampal volume, 8.65 (SD, 0.85) cm^3; white matter hyperintensities, 6.52 (SD, 0.80) log mm^3; fractional anisotropy, 42.53 (SD, 1.23); and Brain Age Gap Estimation (BrainAGE) index, 0 (SD, 8.01). Full-scale IQ is scaled to a mean of 100 (SD, 15) and cognitive problems to a mean of 0 (SD, 1). Only participants who had complete data on all covariates for each outcome were included in each model. Beta values in this table represent the unit change in the outcome variable per 5-µg/dL increase in childhood blood lead level. See footnotes to Table 1 for descriptions of the outcome measures.

lead level was associated with a 1.19-cm^2 smaller total cortical surface area (95% CI, −2.35 to −0.02 cm^2; *P* = .05; β = −0.07) and a 0.10-cm^3 smaller mean hippocampal gray matter volume (95% CI, −0.17 to −0.03 cm^3; *P* = .006; β = −0.11). There was no statistically significant association between blood lead level and mean cortical thickness (*b* = −0.004 mm; 95% CI, −0.012 to 0.004 mm; *P* = .39; β = −0.04). Each 5-µg/dL higher childhood blood lead level was associated with 0.12 lower global fractional anisotropy (95% CI, −0.24 to −0.01; *P* = .04; β = −0.10). There was no statistically significant association between blood lead level and log-transformed WMH volume (*b* = 0.05 log mm^3; 95% CI, −0.02 to 0.13 log mm^3; *P* = .17; β = 0.07). In addition, each 5-µg/dL higher childhood blood lead level was associated with a 0.77 years older BrainAGE index (95% CI, 0.02-1.51; *P* = .05; β = 0.09); despite being the same age at midlife assessment, 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 (95% CI, 0.14-2.90; *P* = .03) than those at or below the blood lead concern level in childhood after adjustment for covariates (adjusted mean BrainAGE index above the concern level, 0.56; adjusted mean BrainAGE index below the concern level, −0.96). Additional adjustment for measures at age 45 years of alcohol use, tobacco smoking, and hypertension did not change the results (eTable 3 in the Supplement).

Prespecified secondary analyses of the associations between childhood blood lead level and regional MRI measures of gray and white matter integrity suggested no regional specificity in the association (eFigure 2 in the Supplement). Analyses revealed that blood lead levels had mixed associations with cortical thickness (negative association in 246 of 360 parcels) and more consistent associations with smaller surface area (negative association in 339 of 360 parcels) and lower fractional anisotropy (negative association in 38 of 44 tracts) (eTable 4 in the Supplement). Likewise, the association with smaller hippocampal volume was also observed for other subcortical structures (negative association in 12 of 12 nuclei) (eTable 5 in the Supplement). Although regional associations were not significant at an α level accounting for multiple comparisons (from 12 to 360 tests), association sizes were consistent with those reported from the primary global outcomes.

Cognitive Measures

Five hundred twenty-eight participants (94%) had data available for all covariates and the WAIS-IV full-scale IQ cognitive performance measure (mean, 101 [SD, 14.9] points), 511 participants (91%) had data on informant-reported subjective cognitive function (mean, 0.0 [SD, 1.0] points), and 524 participants (93%) had data on self-reported subjective cognitive function (mean, −0.1 [SD, 0.9] points).

Participants with higher blood lead levels at age 11 years scored lower than peers on IQ testing at age 45 years (Table 2). After adjusting for covariates, each 5-µg/dL higher childhood blood lead level was associated with an additional 2.07-point lower score (95% CI, −3.39 to −0.74; *P* = .002; β = −0.14) on the full-scale IQ. Lead-related cognitive deficits tended to occur among the same individuals who demonstrated lead-related brain differences. Statistical adjustment of the lead-IQ association using the lead-related brain measures (cortical surface area, hippocampal volume, fractional anisotropy, and BrainAGE index) resulted in a moderate, statistically significant association attenuation (27.3% attenuation; adjusted *b* = −1.48 points; 95% CI, −2.89 to −0.07; Clogg test of attenuation[22] *t* = −9.88; *P* < .001). In a residualized-change

model of IQ decline,[23] lead-related IQ deficits at age 45 years represented a decline in performance from childhood (b = −1.97 points after adjustment for covariates and childhood IQ; 95% CI, −2.92 to −1.03; P < .001; β = −0.12) (**Figure 2**). Modeling longitudinal cognitive change through change scores or mixed-effects regression accounting for attrition and age at assessment did not change the results (eTable 6 in the Supplement). 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 (95% CI, 2.03-5.31; P < .001).

Adults with higher blood lead levels at age 11 years also scored worse than cohort peers on the informant-reported scale assessing cognitive problems (Table 2). After adjusting for covariates, each 5-µg/dL higher childhood blood lead level was associated with an additional 0.12-point higher score (95% CI, 0.01-0.23; P = .03; β = 0.11) for informant-reported cognitive problems. However, there was no statistically significant association between childhood blood lead levels and participants' self-reports of cognitive problems (b = −0.02 points; 95% CI, −0.10 to 0.07; P = .68; β = −0.02).

Discussion

In this longitudinal cohort study, higher blood lead levels during childhood were associated with smaller cortical surface area, smaller hippocampal gray matter volume, lower global fractional anisotropy, and older BrainAGE index measured on brain MRI in adults during midlife. Higher childhood blood lead levels were not associated with thinner cortices or greater WMH burden on brain MRI during midlife.

These results are consistent with the limited existing evidence about the associations of early-life lead exposure with brain morphology and function. Large-scale imaging among children evaluated for lead levels has yet to occur; however, a study that included MRI of approximately 10 000 children (mean age, 10 years) found that children with the highest lead exposure risk (based on neighborhood poverty rates and housing age) tended to have smaller cortical gray matter volume, smaller cortical surface area, and worse cognitive test performance.[5] Young adult follow-up among members of the Cincinnati Lead Study, tested for lead exposure prenatally and across the preschool years, likewise identified lead-related differences in multiple regional cortical gray matter volumes (n = 157; mean age, 20.8 years),[25] global fractional anisotropy (n = 91; mean age, 22.9 years),[26] and multiple regional white matter volumes (n = 144; mean age, 26.8 years).[27] As cortical surface area is highly correlated with cortical volume (r ≈ 0.90),[28] the current findings at age 45 years are consistent with and extend these previous results. This study was based on MRI measurements and did not investigate brain tissue directly. However, at the cellular level, these MRI-measured lead-related brain morphology differences may indicate smaller neurons, reduced neurogenesis, reduced dendritic arborization, or changes in neuropil (gray matter differences)[29]; disrupted axonal pruning, mild gliosis, or demyelination (white matter differences); and an overall morphological profile suggestive of older brains.[27]

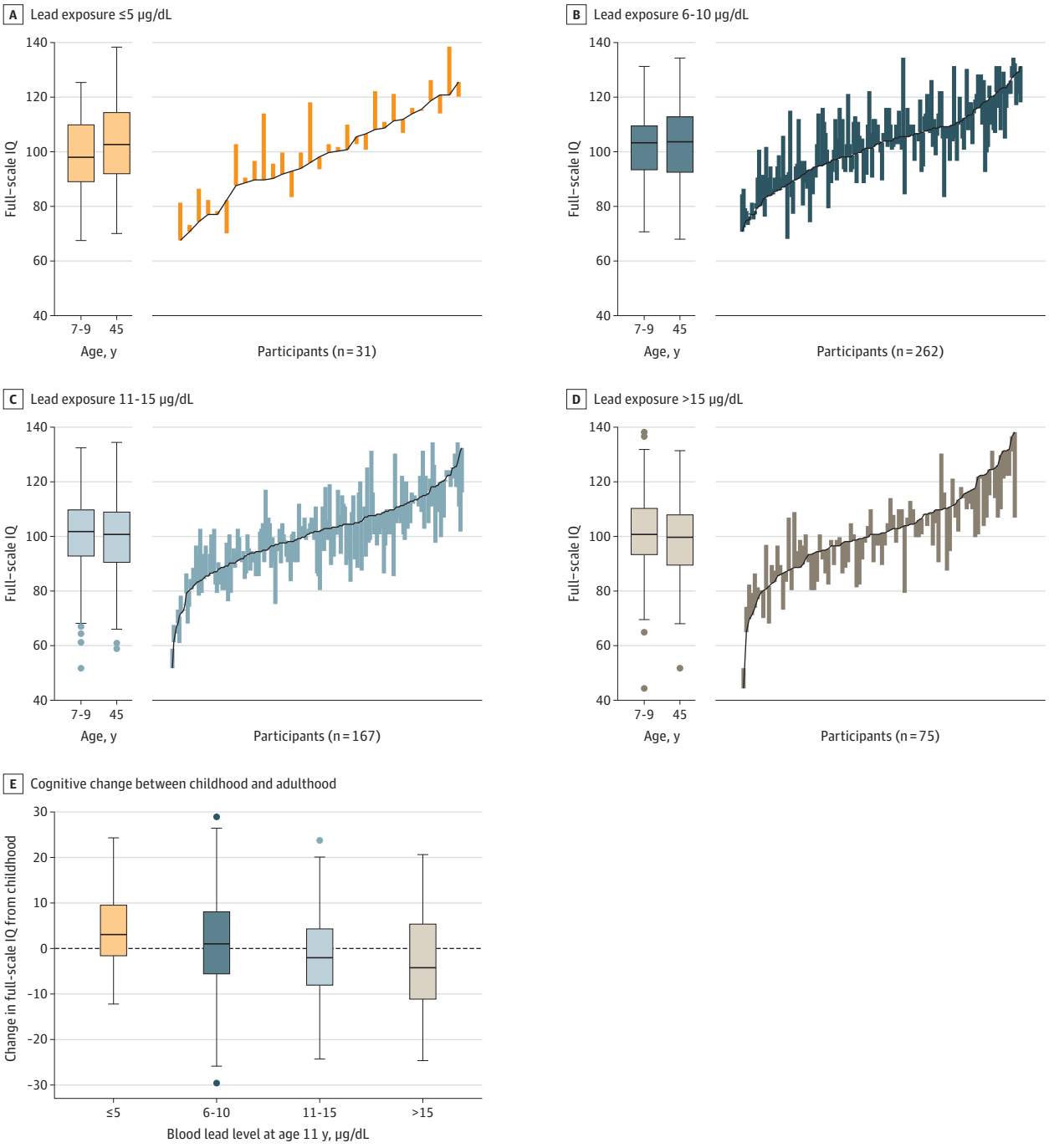
Findings of lead-related associations with cortical surface area, hippocampal volume, fractional anisotropy, and BrainAGE index, but not with cortical thickness or WMH volume, suggest 2 complementary hypotheses. First, lead-related midlife brain integrity differences, as indicated by MRI measurements, may reflect the long-term consequences of early developmental disruption in morphological domains that are characterized by active development throughout the long period of chronic lead exposure experienced by Dunedin Study participants (prenatally through adolescence).[4,16,30] Cortical surface area, hippocampal volume, and white matter microstructural integrity increase across childhood and peak in early adulthood.[31,32] In contrast, cortical thickness peaks by age 2 years, plateaus, and then decreases, reflecting pruning and age-related thinning, while WMH volume tends to be stable across childhood, reflecting the rarity of pediatric white matter lesions.[32,33] Second, this midlife cohort may not be sufficiently aged to detect lead associations with all brain measures. As cortical thinning and WMH volume advance with age,[34,35] differences in these domains may yet emerge. Longitudinal imaging of cohorts with lead testing will allow investigation of these hypotheses.

In this study, children with higher blood lead levels also had, in midlife, lower objectively assessed cognitive performance reflecting decline from childhood and greater rates of everyday cognitive problems.

Collectively, these findings suggest that childhood lead exposure from the era of leaded gasoline may result in lower structural brain integrity as measured by MRI and poorer cognitive function decades later. Although it is too early for neurodegenerative diseases like dementia to emerge in this 45-year-old cohort, in context these findings raise the possibility that childhood lead exposure could represent a risk factor for later-life neurodegenerative disease for 3 reasons. First, although neuroimaging measures were cross-sectional, evidence suggests that individuals with the morphological profile of adults exposed to lead in this study (lower MRI measurements of gray and white matter integrity, older BrainAGE index) may be at higher risk of dementia in old age.[36,37] Second, cognitive deficits were observed as a function of lead exposure with commensurate cognitive decline from childhood to midlife, a known risk factor for dementia.[8-10] Third, mild functional impairments identifiable to others, though not to participants themselves, suggest that clinically meaningful thresholds of diminished cognitive ability may be reached sooner than age 65 years, when neurodegenerative diseases like dementia typically emerge. These 3 hypotheses warrant further investigation.

These findings hold potential implications for public health, research, and clinical practice. For clinicians and policy makers, adults who were exposed to elevated lead levels as children, including the millions exposed during the peak era of leaded gasoline,[30] could be viewed as potentially at risk of neurodegenerative diseases. This hypothesis

Figure 2. Association of Childhood Blood Lead Level With Cognitive Decline From Childhood to Age 45 Years



Change in tested cognitive performance (IQ) from childhood to adulthood (measured on matched scales: Wechsler Intelligence Scale for Children–Revised for childhood IQ and Wechsler Adult Intelligence Scale IV for adult IQ; potential range, 40-160; standardized to a mean of 100 [SD, 15]) for Dunedin Study participants based on their childhood lead exposure. Study participants were split into 4 groups based on severity of lead exposure (1 group for each additional 5-µg/dL blood lead level in childhood). In panels A-D, box plots represent the distribution of full-scale IQ scores at childhood assessments (mean of individual assessments taken at ages 7 and 9 years) and at the adult assessment (age 45 years). On the right side of panels A-D, changes in full-scale IQ are represented as individual bars for each participant. These bars are anchored at the mean childhood IQ assessment score; upward bars represent IQ scores that were higher at age 45 years than in childhood, and downward bars represent IQ scores that were lower at age 45 years than in childhood. Box plots in panel E represent the distributions of cognitive change between childhood and adulthood for each lead exposure group. On average, each 5-µg/dL higher blood lead level in childhood was associated with a 1.97-point decline (95% CI, −2.92 to −1.03; $P < .001$; $\beta = -0.12$) in full-scale IQ by age 45 years. In all panels, box plot borders and midlines represent the 25th, 50th, and 75th percentiles, with whiskers extending to the furthest observation within 1.5 interquartile ranges of the 25th and 75th percentiles. Dots outside the whiskers represent observations greater than 1.5 interquartile ranges of the 25th and 75th percentiles.

warrants investigation. For researchers, these results reinforce the need for increased attention to long-term follow-up in child cohorts assessed for lead exposure, few of whom have been evaluated past young adulthood.[11]

Limitations

This study has several limitations. First, it was observational and cannot establish causation. Second, it investigated only 1 cohort in 1 country and should be replicated elsewhere. Third, it had no measure of cumulative lead exposure (eg, cortical or trabecular bone lead)[38] or of endogenous lead exposure (eg, blood lead levels reflecting lead remobilized from bone).[39] Future studies could disentangle the influence of historical lead exposure from more recent exposure on MRI measurements of brain integrity and neurodegenerative risk. Fourth, hypothesis-driven tests of the 6 primary outcome measures were not corrected for multiple comparisons,[40] raising the possibility of type I error.

Conclusions

In this longitudinal cohort study with a median 34-year follow-up, higher childhood blood lead level was associated with differences in some MRI measures of brain structure that suggested lower structural brain integrity in midlife. Because of the large number of statistical comparisons, some findings may represent type I error.

ARTICLE INFORMATION

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