Concept Paper Template

Provisional Paper Title: Childhood lead exposure and long-term telomere erosion

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Objective of the study:

Millions of adults alive today were exposed to high levels of lead as children. Lead is a persistent environmental pollutant that was once ubiquitous –in gasoline, paints and pipes. Adults now entering midlife were exposed to lead as children during the peak-era of leaded gasoline (mid-1960s through late-1980s). In 1976, 99.8% of American children had blood-lead levels above the current threshold for clinical attention,[1] and the average American's blood-lead level exceeded the current threshold three times over.[2] While lead-exposures declined sharply with the phase-out of lead-in-gasoline, millions worldwide remain at risk.[3]

Lead-exposure may shorten telomere length. Lead is known to harm most organs, and is particularly detrimental to children.[4] Emerging evidence suggests that early-life exposure may shorten telomeres.[5–8] Telomere attrition has consequently been proposed as one potential mechanism linking lead-induced toxicity to long-term harm.[5,9,10] The evidence is limited, however, and findings have been mixed. Three studies in children reported a negative association between BLLs and relative telomere length,[7,8,11] but two reported no association.[12,13] In adults, occupational lead-exposures have been associated with shorter telomeres[6,14] while general-population exposures have not.[5]

Existing evidence has important limitations. First, all studies were cross-sectional, making it impossible to evaluate long-term cumulative harm or gradual telomere erosion across time. Second, these studies were potentially underpowered to detect subtle effects; only two had N>200. Three, no study utilized archival lead-exposure data from the peak lead-exposure era (e.g.,1970s). While today's children usually have low lead-exposures, today's adults generally experienced high exposures as children. There is thus no evidence yet to inform the risk profile owing to childhood exposure for adults now entering later life.

The proposed study will evaluate associations between childhood lead-exposure and telomere length among lead-tested members of the Dunedin Study (N=579). Dunedin represents the only cohort where lead-exposure was unrelated to socioeconomic status.

While archived Dunedin blood-lead and relative leukocyte telomere length (LTL) data have been separately published in this cohort,[15,16] this will be the first study to bring them together. The proposed study would represent the largest comprehensive study of early life lead-exposure and long-term telomere attrition.

Data analysis methods:

AIM 1: Test the hypothesis that children with greater blood-lead level will display shorter LTL than their peers three decades later, at age 38.

Through correlations and multivariate regression we will test the association of childhood blood-lead level with LTL at age 38 in “baseline” models adjusted for sex and “fully adjusted” models adjusted for factors commonly included as confounds in studies of adult LTL or lead, including childhood SES, pack years smoked, BMI, and white blood cell count. If significant lead-LTL associations are found, follow-up tests will determine whether telomere differences co-occur with lead-related outcomes previously identified in the same cohort (e.g., cognitive deficits and decline, psychopathology, differences on MRI measures of brain structural integrity).

AIM 2: Test the hypothesis that children with greater blood-lead level will display greater LTL decline than age-peers across adulthood from age 26 to 38, suggesting an on-going enhanced cellular-aging process unfolding across time.

Through multivariate regression we will test the association of childhood blood-lead level with longitudinal LTL change from age 26-38. Residualized change will be modeled by including age-26-LTL in models regressing age-38-LTL onto lead following the same baseline and fully adjusted modeling approach specified under Aim 1. Sensitivity tests will determine whether significant longitudinal-LTL-differences are accompanied by declines on other biomarkers indicative of biological (as opposed to chronological) aging (e.g., the methylation Pace of Aging). Given uncertainty about the interpretation of telomere lengthening we will also conduct sensitivity tests excluding Study members whose telomeres lengthened from age 26 to 38 (~13% of the cohort).

Because lead exposure data are not available for all Dunedin Study members, we will also test for selective missingness and control for any possible selectivity in all analyses.

Variables needed at which ages:

Predictor

lead11ug_dl	Blood lead (uncorrected) at age 11

Outcomes

TeloBld26	Telomere length at 26, blood source only
TSratio_26	Telomere length at 26
TeloBld38	Telomere length at 38, blood source only
TSratio_38	Telomere length at 38

Covariates

sex	
SESchildhd	Family SES averaged from birth to age 15,
source_26	Blood or buccal swab at 26
source_32	Blood or buccal swab at 32
source_38	Blood or buccal swab at 38
	Whole white blood cell count at age 26
	Individual counts of the 5 main white blood cells at age 26
	White blood cell count at age 38
	Individual counts of the 5 main white blood cells at age 38

PackYrLifTm26	Lifetime pack years to phase26
PackYrLifTm38	Lifetime pack years to phase38
bmip26	BMI phase 26
bmip38	BMI phase 38

Variables for sensitivity tests

Previously identified lead-related outcomes

infMem45	Informant reported memory difficulties at 45
infAtt45	Informant reported attention difficulties at 45
IQ79std	Full Scale IQ, mean of age 7 and 9, standardized
fsIQ45_STD	Full Scale IQ at 45, standardized
sa_tot	Mean cortical surface area at 45
bihippocampus	Bilateral hippocampal volume at 45
averagefa	Average fractional anisotropy at 45
brainage_centered	Brain age at 45
brainAGE	Brain age gap estimate at 45
P_B	P-factor at 45
P_BF45	P Factor, BF45, June2019
EXT_CF45	Externalizing Factor, CF45, June2019
INT_CF45	Internalizing Factor, CF45, June2019
THD_CF45	Thought Disorder Factor, CF45, June2019
BFagre45	Big five agreeableness @ 45, informants
BFcons45	Big five conscientiousness at 45, informants
BFneur45	Big five neuroticism at 45, informants

Measures of biological aging

PoAm45	Pace of Aging Methyl, p45, 4 May 2020

Significance of the Study (for theory, research methods or clinical practice):

Knowledge about lead-telomere associations could help lower the burden of disease. It will be years before most individuals lead-exposed in childhood are sufficiently aged for age-related disease endpoints to emerge. Shorter telomere length represents an intermediate measure, which has been plausibly linked to risk for dementia,[17] diabetes,[18] cancer,[19] and cardiovascular disease.[20] Identification of telomere erosion in adults lead-exposed as children would raise the possibility that interventions to slow telomere attrition could reduce burden of disease if targeted at this population. Follow-up studies can evaluate differences in telomere length by age 45 and via related measures of DNA methylation-based telomere length estimators.

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