CONCEPT PAPER

Childhood lead exposure and adult cardiovascular disease

Provisional Paper Title: Implications of childhood lead exposure for adult cardiovascular disease.

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Objective of the study:

Chronic lead exposure, even at low levels (<5 ug/dL), is considered to cause hypertension (Vaziri, 2008), and adult occupational and residential exposure to lead has been linked to increased rates of coronary heart disease, peripheral arterial disease, alterations in cardiac rhythm, elevations in blood homocysteine levels, and ischemic heart disease (Navas-Acien, Guallar, Silbergeld, & Rothenberg, 2007). Animal studies suggest that this pathology is induced through oxidative stress (Vaziri & Sica, 2004).

Children are known to suffer hypertensive effects of lead exposure (Gump et al., 2005) but no studies appear to have yet examined adult cardiovascular outcomes in lead-exposed children. Increased cardiovascular disease could arise in adults exposed to lead as children via (1) delayed or "silent" epigenetic dysregulation, which has been seen in other organ systems (e.g., Eid & Zawia, 2016), or via (2) direct toxicity from lead remobilized from bone (Hu, Rabinowitz, & Smith, 1998). A third mechanism is also possible, wherein childhood lead exposure may lead to greater cardiovascular disease indirectly through health risk behaviors arising from compromised brain function. Children exposed to lead leave school earlier and attain lower socioeconomic status occupations in adulthood than less exposed peers, a phenomenon attributed, in part, to impaired self-regulatory and cognitive abilities (Bellinger, 2008; Reuben et al., 2017). Low educational attainment, low cognitive ability, and poor self-control early in life together predict increased risk for cardiovascular disease later on (Israel et al., 2014).

Should children exposed to lead suffer greater rates of hypertension and cardiovascular disease in adulthood, the public health implications would be profound. Millions of adults now entering midlife and older age were exposed to high levels of lead as children (Pirkle et al., 1994).

This proposed study would seek to evaluate whether middle-aged adults exposed to high levels of lead as children suffer from greater rates of cardiovascular disease or poorer cardiovascular health than their peers with lower childhood lead exposures.

Additionally, a number of polymorphisms have been identified that are believed to influence susceptibility to lead, including those that alter lead uptake, retention, and bioavailability (Ding et al., 2016). Evidence of these genes' role in lead toxicodynamics comes from experimental studies using animal and cellular models to test hypotheses about molecular mechanisms (Ding et al., 2016) and, additionally, from large, genome-wide association studies, which have provided confirmation of a significant relationship between many of these genes and blood-lead levels (Ng et al., 2015; Warrington et al., 2015). As a secondary goal, we will evaluate whether genes related to lead toxicodynamics modify any associations found between childhood lead exposure and adult cardiovascular fitness.

Data analysis methods:

We will conduct one primary analysis and one secondary analysis:

Primary: Investigating associations between childhood lead and adult cardiovascular disease.

Through correlations and multivariate regressions we will test the association between early life blood lead levels, measured at age 11, and cardiovascular health measures at age 38. We will include potential confounds known to predict adult cardiovascular health (e.g., BMI and cigarette smoking) as well as factors commonly included as confounds in studies of lead exposure and cardiovascular health, including childhood SES (average 1-15) and educational attainment. In addition, we may also include other substance use covariates.

Because childhood lead exposure may influence adult cardiovascular health indirectly, through increased health risk behaviors, mediated linear regression analysis will also be used to evaluate whether human capital (educational attainment, cognitive ability, and self-control; Israel et al., 2014) and cardiovascular health-risks (BMI, cigarette smoking, diabetes) might be potential mediators of any relationship between childhood lead and adult cardiovascular health.

Secondary: Investigating modification of lead-disease associations by polygenic risk.

We will test two potential gene-environment interactions in the relationship between childhood lead exposure and adult cardiovascular disease.

First we will examine whether individual genotype moderates the effects of childhood lead exposure on mid-life cardiovascular health. We will test interactions between SNPs in lead uptake, retention, and bioavailability genes (those identified by Ding et al. 2016) and adult cardiovascular disease using moderated linear regression analysis.

Second, we will examine whether lead exposure modifies the link between a genetic propensity for cardiovascular disease and actual cardiovascular health at mid-life. We will test interactions between a polygenic risk score for coronary heart disease (Hindy, Wiberg, Almgren, Melander, & Orho-Melander, 2018) and lead exposure using moderated linear regression.

An important caveat is that lead exposure data are not available for all Dunedin Study members, so we will need to test for selective missingness, and to control for any possible selectivity in all analyses.

Variables Needed at Which Ages:

Predictors

Blood lead (corrected and uncorrected) at 11 and 21.

Outcomes

Cardiovascular health at 38:
- CVD_10YrRisk38
- Framingham heart age
- Metabolic markers (index and syndrome)
- Endothelial function
- Blood pressure

InflamationFS38.
Diabetes / prediabetes
suPAR

Covariates / potential mediators
sex
average SES 1-15

RxCardiac38
RxStatn38
RxAntiInfl38
BMI at 38
Fitness38
Age 38 human capital factors (from Israel et al. 2014)
- IQ 38
- Adult self-control
- Educational attainment 38

persistent cannabis use
persistent alcohol abuse
smoking variables

Moderators
(*genetic moderation of the association between lead and CVD)*
- Genes involved in lead uptake, retention, and bioavailability (Ding et al., 2016)

(*lead moderation of the association between polygenic score for heart disease and CVD)*
- Polygenic score for coronary heart disease (Hindy et al., 2018)

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

Millions of adults now entering midlife and older age were exposed to high levels of lead as children (Pirkle et al., 1994). If childhood blood levels are found to predict adult cardiovascular disease it would suggest that millions may be at greater risk of these diseases as they age and, potentially, of premature mortality. Identification of potentially mediating behavioral factors (e.g., educational attainment, cigarette smoking, etc.) and potentially moderating genomic factors would hold important implications for clinical practice and public health, particularly for decisions about whom to target with interventions to improve cardiovascular health, for how long and at what cost. This study would also inform efforts to remove lead from the current environment, in both developed and developing countries.

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Data Security Agreement

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Proposing Author	Aaron Reuben
Today's Date	March 13th, 2018

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement

_ASR I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)

_ASR My project is covered by Duke or Otago IRB OR I have /will obtain IRB approval from my home institution.

_ASR I will treat all data as "restricted" and store in a secure fashion.

_ASR I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

_ASR I will not post data online or submit the data file to a journal for them to post.
Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to Terrie or Avshalom for strategies for dealing with data sharing requests from Journals.

_ASR Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.

_ASR I will submit analysis scripts and new variable documentation to project data manager after manuscript gets accepted for publication.

_ASR I will return all data files to the Data Manager after the project is complete. Collaborators and graduates of DPPP may not take a data file away from the DPPP office. The data remains the property of the Study and cannot be used for further analyses without express, written permission.

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Signature: ...../s/ Aaron Samuel Reuben.....

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