CONCEPT PAPER

Childhood lead exposure and adult psychopathology and personality

Provisional Paper Title: Childhood lead exposure and adult psychopathology and personality

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Today's Date: May 11th, 2018

Objective of the study:

Children exposed to lead, a neurotoxin, have been found to suffer from disrupted cognitive and emotional development (Bellinger 2008), with childhood lead exposure linked to lower IQ (Lanphear et al. 2005), poorer academic achievement (Chandramouli et al. 2009), and greater rates of emotion and behavior problems, particularly inattention, hyperactivity, and antisocial behavior (Needleman et al. 1996; Nigg Joel T. et al. 2009; Silva et al. 1988). While follow-up studies in lead-tested child cohorts, including the Dunedin Study, have reported that lead-associated IQ deficits persist into adulthood (Mazumdar et al. 2011; Reuben et al. 2017), the long-term emotional and behavioral consequences of early-life lead exposure remain largely unexamined.

In adults, lead exposure has been linked to a variety of mental health concerns, although there is, in general, a paucity of adult mental health studies in the environmental epidemiology literature. The few examinations of psychiatric outcomes following adult lead exposure have reported: 1) increased odds of major depression and panic disorder among adult respondents to the US-National Health and Nutrition Examination Survey (Bouchard et al. 2009); 2) greater depression and phobic anxiety symptoms among older members of the Nurses' Health Study (Eum et al. 2012); and 3) greater phobic anxiety, somatization, hostility, and global distress among members of the VA-Normative Aging Study (Rajan et al. 2007; Rhodes et al. 2003).

While lead exposure has been linked cross-sectionally to behavioral dysfunction in both children and adults, few studies have undertaken long-term follow-up in lead-exposed children to determine whether early emotion and behavior problems persist or evolve across time. One US case-control study using linked health records and clinical interview to identify cases of psychosis in two lead-tested child cohorts (total N=200) reported a 2-fold increased risk for schizophrenia spectrum disorder in adulthood for children with high blood-lead levels (roughly >15ug/dL; Opler et al. 2008). In the only comprehensive adult psychiatric follow-up yet conducted in a lead-tested child cohort, female members of the Australian Port Pirie Study who had greater childhood blood-lead levels reported greater social phobia, anxiety, and substance abuse problems during clinical interview in adulthood (mean age=26.3), although all lead-symptom associations were significantly attenuated by adjustment for childhood covariates (N=210; McFarlane et al. 2013).

Even fewer studies have examined personality traits in relation to lead exposure, but adults occupationally exposed to lead have reported feeling angrier and more tense, tired, and depressed than their less exposed peers (Baker et al. 1984; Lilis et al. 1977) – emotional symptoms which seem to improve gradually with the abatement of lead

exposure (Baker et al. 1985). In the one cohort of lead-tested children that have received personality testing, young adult members of the Cincinnati Lead Study (age 19 to 24) with greater childhood lead exposures tested higher, on average, than cohort peers on four of the six subscales of the Psychopathic Personality Inventory (Wright et al. 2009). Alterations in emotion regulation and adult personality have consequently been proposed as explanatory mechanisms for the reported link seen between childhood blood-lead levels and adolescent delinquency (Dietrich et al. 2001) and young adult criminal arrests (Wright et al. 2008) in the same cohort.

If childhood lead exposure leads to greater adult psychopathology or altered adult personality, the implications for public health would be significant. Millions of adults living in developed countries were historically exposed to high levels of lead as children, in the years before environmental lead was regulated (Pirkle et al. 1994), and millions of children living in developing countries still face high lead exposures (Roy et al. 2009; World Health Organization, Regional Office for Africa 2015; Yan et al. 2013).

This proposed study would seek to conduct a rigorous test of whether individuals exposed to high levels of lead as children experience greater psychopathology symptoms as adults or tend to develop disadvantageous personality traits, such as those associated with the risk of mental illness (Kotov et al. 2010; Malouff et al. 2005) poor health (Graham et al. 2017; Jokela et al. 2013), or antisocial behavior (Wright et al. 2009). Using Dunedin Study data we will be able to undertake: 1) the longest and largest psychiatric follow-up to date in a lead-tested child cohort; 2) the only follow-up to use repeated clinical interviews to assess psychopathology symptoms across adulthood; 3) the only follow-up to use comprehensive, hierarchical measures of psychopathology capable of fully capturing the potentially broad, nonspecific effects of lead exposure on mental health; and 4) the only follow-up to use repeated broad-spectrum measures of adult personality. Importantly, we will be able to conduct these follow-ups in a sample where the extent of children's exposure to lead was unrelated to their socioeconomic origins, removing a potentially important confound that is present in most studies of children and lead (Wilson and Wilson 2016).

Data analysis methods:

We will conduct two primary analyses and one secondary analysis:

Primary analysis 1: Investigating associations between childhood blood lead and adult psychopathology.

Through correlations and multivariate regressions we will test the association between early life blood-lead levels, measured at age 11, and adult mental health, measured through the p-factor and its constituent psychiatric spectra of Externalizing, Internalizing, and Thought Disorder, calculated as factor scores derived from symptom scales produced at each assessment wave across ages 18 to 38. We will include potential confounds known to predict adult psychopathology (e.g., family history of mental illness, child physical health) as well as factors commonly included as confounds in studies of health effects of lead exposure, including sex, childhood SES (average 1-15), and maternal IQ.

Primary analysis 2: Investigating associations between childhood lead and adult personality.

Through correlations and multivariate regressions we will also test the association

between early life blood-lead levels, measured at age 11, and adult personality measured through informant-reported scores on the Big Five Inventory assessed at ages 26, 32, and 38 years and averaged. For consistency we will include the same covariates utilized for the tests of the adult psychopathology outcomes.

Secondary analysis: Investigating associations between childhood blood-lead levels and child externalizing and internalizing problems.

If significant associations between child blood-lead level and adult psychopathology are identified in the primary analysis, a secondary analysis will ask if similar psychopathology symptoms are detectible in childhood, contemporaneous with blood-lead measurement. We will use measures of childhood externalizing and internalizing problems assessed at age 11 years, using the hyperactivity, antisocial behavior, and internalizing problems subscales produced by the Rutter Child Scales reported on by parents and teachers. We will include the same covariates selected for the primary analyses.

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 (uncorrected) at age 11

Outcomes
Adult Psychopathology

P_B – general psychopathology factor score from the Bi-Factor model
EXT_CF – Externalizing factor score from the Correlated Factors model
INT_CF – Internalizing factor score from the Correlated Factors model
THD_CF– Thought Disorder factor score from the Correlated Factors model

Adult Personality

BF Extroversion – at ages 26, 32, and 38
BF Agreeableness – at ages 26, 32, and 38
BF Conscientiousness – at ages 26, 32, and 38
BF Openness – at ages 26, 32, and 38
BF Neuroticism – at ages 26, 32, and 38

*Child Externalizing and Internalizing Problems (*Rutter Child Behavior Scales):

phyper11, thyper11 – hyperactivity reported by parents & teachers at age 11
pantis11, tantis11 – antisocial behavior reported by parents & teachers at age 11
pneuro11, tneuro11 – internalizing problems reported by parents & teachers, 11

Covariates
sex
sesav115 - average SES 1-15
momiq3 – maternal IQ
prsev – proportion of family members with indicators of disorder severity (family mental health history)

GPIsc – count of perinatal complications
hlthRat311 – child health rating ages 3 to 11

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

Millions of adults living in developed countries were historically exposed to high levels of lead as children, and millions of children living in developing countries still face high lead exposures. If childhood blood lead levels are found to predict adult mental health symptoms and personality traits, it would suggest that persistent environmental toxins may play a greater role in the global prevalence of mental illness and have a greater influence on life trajectories than previously assumed. Regardless of its findings, this study will hold implications for clinical practice and public health, particularly for decisions about the scope and duration of public responses to community lead exposure events. 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	May 11th, 2018

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

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_ASR I will treat all data as "restricted" and store in a secure fashion.
My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.

_ASR I will not "sync" the data to a mobile device.

_ASR In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)

_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 I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

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

CONCEPT PAPER RESPONSE FORM

A.

Provisional Paper Title	Childhood lead exposure and adult psychopathology and personality
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Other Contributors	Jon Schaefer, Terrie Moffitt, Avshalom Caspi, Richie Poulton, Sandhya Ramrakha, HonaLee Harrington, Renate Houts, Jonathan Broadbent
Potential Journals	
Today's Date	May 11th, 2018
Intended Submission Date	Fall 2018

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B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature: