The Early Life Environment and Adult Cognitive and Mental Health

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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Abstract

Many diverse adult diseases, from diabetes to dementia, are increasingly viewed as arising, in part, from early-life environmental influences. The so-called Developmental Origins of Health and Disease (DOHaD) research paradigm offers the potential to improve our understanding of the etiology of many hard-to-treat adult diseases by focusing researcher's attention on the pre and post-natal and early childhood years, where small interventions could pay large dividends later on. Along with great potential, the DOHaD framework offers great challenges, as it is logistically and conceptually difficult to investigate the environmental origins of chronic diseases that may manifest only decades after harmful exposures.

This dissertation presents a series of five original studies that sought to answer open empirical questions about the developmental origins of health and disease focusing on early-life factors that influence the health and aging of the brain. Three increasingly broad "levels" of the early-life environment are considered across three sequential dissertation chapters: (1) the individual micro-physical level, (2) the family level, and (3) the neighborhood level. At each level this dissertation considers at least one exposure that has relevance to researchers and policy makers, either because, like exposure to neighborhood vegetation / greenery, it may offer a good route for intervention (e.g., the exposure is potentially modifiable) or because, like exposure to the

heavy metal lead, it is understood to be more widespread than previously assumed. Studies were conducted using data from two population-representative longitudinal birth cohorts, the New Zealand-based Dunedin Multidisciplinary Health and Development Study (born in 1972-1973) and the United Kingdom-based Environmental Risk Longitudinal Twin Study (born in 1994-1995).

Across the five studies, results supported the DOHaD framework and provided new evidence about the long-term consequences of childhood exposure to lead, adversity (e.g., physical and emotional abuse, household dysfunction, etc.), and neighborhood disadvantage. These negative early-life events / exposures at the micro-physical, family, and neighborhood-levels associated, across multiple decades, with subtle and diverse poor brain-related outcomes later in life, including diminished cognitive capacity, increased symptoms of psychopathology, altered epigenetic controls, disadvantageous personality styles, and worse physical health. Results collectively reinforce the view that the early-life represents a profound window of vulnerability and opportunity, with a lifespan perspective offering great potential for more efficacious public health research, clinical practice, and policy, as the diseases of the adult likely have roots in the life of the child.

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1. Introduction: Why Study the Early Life Environment?

Since David Barker reported, in the mid-1980s, that adults' risk of cardiovascular disease could be predicted by their mothers' nutritional status during pregnancy, many difficult-to-treat "adult" diseases have come to be viewed as arising, in part, from early life environmental influences.[1] Under the so-called Developmental Origins of Health and Disease (DOHaD) framework, adult diseases as diverse as diabetes, hypertension, mental illness, and dementia may all be considered pediatric diseases, "not because they show up in children but because they originate during development."[2(p5)]

The DOHaD framework offers hope that we may someday eradicate a number of chronic diseases that plague society by intervening early to avoid pathology before it begins, much as we eradicate infectious diseases through immunization. The framework arrives with notable research challenges, however, as it is logistically and conceptually difficult to investigate the environmental origins of chronic diseases that may manifest only decades after exposure. Individual differences in susceptibility driven by genetics, personality, and community or culture only complicate the picture. The DOHaD framework provides fertile ground for both research innovation and frustration.

This dissertation will attempt to answer a number of open empirical questions about the role of the early life physical and psychosocial environment in determining risk for disease and impairment in adulthood, focusing on those factors that influence the health and aging of the organ most at-risk in developing children: the brain.[3] While DOHaD has its roots in the study of cardiovascular disease, its implications for brain health have been the most clear, with childhood exposure to poor nutrition, psychosocial adversity, infections, and toxic chemicals all implicated in poor adult cognitive and psychological health.[2] Notably, cognitive ability and psychological health hold an outsized influence over an individual's life trajectory, determining, in part, their

educational attainment, earning potential, social-contacts, health risk behaviors, quality of relationships, and overall job success and socioeconomic status.[4]

This dissertation answers open empirical question by reporting the results of five original research studies that collectively investigate potential early life environmental exposures within three increasingly broad "levels": (1) the individual (micro-physical), (2) the family, and (3) the neighborhood. At each level this dissertation considers at least one exposure that has relevance to researchers and policy makers, either because, like exposure to neighborhood greenery, it may offer a good route for intervention (e.g., the exposure is potentially modifiable) or because, like exposure to lead, it is understood to be more widespread than previously assumed.[5] Empirical questions investigated include:

1. What are the types of early life environmental exposures that uniquely alter adult disease risk?
2. How might they embed themselves biologically?
3. How might they embed themselves psychologically?
4. What role do factors potentially related to exposure, like family social class, play in moderating or confounding associations?
5. What methodological approaches might improve causal inference in domains where experimental studies are impossible or unethical?

2. The Individual (Micro-Physical) Level: Childhood Lead Exposure

What we eat, breathe, and drink early in life influences the course of our development in ways that help determine our health later on.[3] At the level of the individual micro-physical environment, childhood exposures to lead, a neurotoxic heavy metal, represents one of the best described chemical stressors that millions of children still face around the world. While immediate consequences of lead exposure on child cognitive and behavioral development have been well described,[6] the long-term consequences remain poorly characterized. This is an important topic to study now for two reasons. First, recent and on-going community lead-exposure events across the United States have returned the issue to the nation's attention, opening a window for possible policy intervention. [7–10] Second, the generation of individuals with the highest childhood lead exposures (those born in the 1960's, 1970's, and 1980's)[11] are entering the stage of life where age-related and cognitive neurodegenerative disorders emerge.[12] This chapter presents two original studies that investigate the long-term implications of childhood lead exposure on adult cognitive and mental health, among other outcomes.

2.1 Childhood lead exposure is associated with lower cognitive function and socioeconomic status at age 38 years and with cognitive decline and downward social mobility.

The following original research report was published in the Journal of the American Medical Association (JAMA) in 2017, with the title, "Association of childhood blood-lead levels with cognitive function and socioeconomic status at age 38 years and with IQ change and socioeconomic mobility between childhood and adulthood." The authors were as follows: Aaron Reuben, M.E.M., Avshalom Caspi, Ph.D., Daniel W.

Belsky, Ph.D., Jonathan Broadbent, Ph.D., Honalee Harrington, B.A., Karen Sugden, Ph.D.,[1] Renate M. Houts, Ph.D., Sandhya Ramrakha, Ph.D, Richie Poulton, Ph.D., & Terrie E. Moffitt, Ph.D.

2.1.1 Abstract

Importance. Many children in the US and around the world are exposed to lead, a developmental neurotoxin. The long-term cognitive and socioeconomic consequences of lead exposure are uncertain.

Objective. To test the hypothesis that childhood lead exposure is associated with cognitive function and socioeconomic status in adulthood and with changes in IQ and socioeconomic mobility between childhood and midlife.

Design, Setting, and Participants. Prospective cohort study based on a population-representative 1972-73 birth cohort from New Zealand, the Dunedin Multidisciplinary Health and Development Study, followed to age 38 years (December, 2012).

Exposure. Childhood lead exposure ascertained as blood-lead levels measured at 11 years. High blood-lead levels were observed among children from all socioeconomic status levels in this cohort.

Main Outcomes and Measures. The IQ (primary outcome) and indexes of Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed (secondary outcomes) were assessed at 38 years using the Wechsler Adult Intelligence Scale–IV (WAIS-IV; IQ range 40-160). Socioeconomic status (primary outcome) was

assessed at 38 years using the New Zealand Socioeconomic Index-2006, (NZSEI-06; range 10=lowest-90=highest).

Results. Of 1037 original participants, 1007 were alive at 38 years, of whom 565 (56%) had been lead tested at 11 years (54% male; 93% white). Mean blood-lead level at 11 years was 10.99μg/dL (SD=4.63). Among blood-tested participants included at 38 years, mean WAIS-IV score was 101.16 (SD=14.82) and mean NZSEI-06 score was 49.75 (SD=17.12). After adjusting for maternal IQ, childhood IQ, and childhood socioeconomic status, each 5μg/dL higher level of blood-lead in childhood was associated with a 1.61-point lower score (95%CI:-2.48,-0.74) in adult IQ, a 2.07-point lower score (95%CI:-3.14,-1.01) in Perceptual Reasoning, and a 1.26-point lower score (95%CI:-2.38,-0.14) in Working Memory. Lead-associated deficits in Verbal Comprehension and Processing Speed were not statistically significant. After adjusting for confounders, each 5μg/dL higher level of blood-lead in childhood was associated with a 1.79-unit lower score (95%CI:-3.17,-0.40) in socioeconomic status. An association between greater blood-lead levels and a decline in IQ and socioeconomic status from childhood to adulthood was observed, with 40% of the association with downward mobility mediated by cognitive decline from childhood.

Conclusion and Relevance. In this cohort born in New Zealand in 1972-1973, childhood lead exposure was associated with lower cognitive function and socioeconomic status at age 38 years and with declines in IQ and downward social mobility. Childhood lead exposure may have long-term ramifications.

2.1.2 Introduction

Lead is a ubiquitous pollutant. Policies that eliminated lead from paint and gasoline were thought to have eliminated lead from most communities in the developed world. But the water crisis in Flint, Michigan has triggered renewed concern about lead poisoning.[5] Inhabitants of many U.S. cities are still exposed to high lead levels.[13]

Exposure to lead in childhood may adversely affect brain health and disrupt cognitive development.[6] It is unknown if this disruption results in cognitive decline and altered socioeconomic trajectories by midlife, yet young adults with histories of childhood lead exposure have been reported to have lowered intellectual function[14,15] and altered brain structure,[16,17] suggesting that cognitive impairment persists at least to young adulthood. Few studies have yet documented longer-term cognitive consequences of childhood lead exposure, however, and none appear to have evaluated socioeconomic repercussions, apart from one study of highly-exposed, lead-poisoned children.[18] To our knowledge, the longest-term cognitive follow-ups have been to age 30 years, in a cohort too small (N=43) to adequately detect associations after adjusting for potential confounds.[19]

The Dunedin Multidisciplinary Health and Development Study follows a population-representative cohort of children born in New Zealand in 1972-1973. The most recent assessment included cognitive and socioeconomic evaluations and was completed when participants were 38 years old. In the 1970s and 1980s, lead exposures in New Zealand cities were consistently higher than international standards, largely due to poor air quality related to motor-vehicle emissions.[20] Consequently, childhood blood-

lead levels in the Dunedin cohort were similar to those of other cohorts tested in the early 1980s from larger developed cities.[21] However, unlike with other cohorts,[22,23] a social gradient in lead exposure was not observed. This provided an opportunity to test the hypothesis that childhood lead exposure is associated with cognitive impairment and downward socioeconomic mobility by midlife without having to disentangle such exposure from correlated socioeconomic disadvantages. Analyses also tested if the association between blood-lead levels and downward social mobility was mediated by cognitive decline.

2.1.3 Methods

2.1.3.1 Study Design and Population

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a birth cohort. The full cohort were all of the 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. The cohort represented the full range of socioeconomic status in the general population of New Zealand's South Island.[24] On adult health, the cohort matches the New Zealand National Health and Nutrition Survey on key health indicators (e.g. body mass index, smoking, visits to a physician).[24] The cohort is primarily white; fewer than 7% self-identify as having non-Caucasian ancestry, matching the demographics of the South Island.[24] Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and the most recent data

collection was completed in December 2012, at age 38 years. Written informed consent was obtained from cohort participants and study protocols were approved by the institutional ethical review boards of the participating universities.

2.1.3.2 Measurement of childhood blood-lead levels

Approximately 30 ml of venous blood was collected from each 11-year-old who participated in the assessment carried out at the Research Unit and who freely agreed to give blood; 579 of the 803 children (72%) who attended the Unit agreed to give blood. A further 122 children were assessed at age 11 years in their schools, where blood could not be drawn; these children tended to live outside city limits. Whole blood samples were analyzed through graphite fumance atomic absorption spectrophotometry. Blood-lead is reported in micrograms per deciliter (1μg/dL=0.0483μmol/l). Details on the method of blood collection, division, storage, quality assurance and analysis procedures have been described previously.[21]

2.1.3.3 Measurement of cognitive functioning

Cognitive performance in adulthood was a primary outcome. It was assessed using the Wechsler Adult Intelligence Scale –IV (WAIS-IV; score range 40-160) at age 38 years.[25] The WAIS-IV generates the overall full-scale IQ, and in addition four WAIS-IV index scores assess abilities that make up the IQ: secondary outcomes Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. Cognitive performance in childhood was assessed using the Wechsler Intelligence Scale

for Children-Revised (WISC-R; score range 40-160)[26,27] at ages 7 and 9 years (measured prior to blood-lead evaluation at age 11 years) and averaged.

2.1.3.4 Measurement of socioeconomic status

Socioeconomic status in adulthood was a primary outcome. Socioeconomic status was assigned based on each participant's current occupation at age 38 years. The New Zealand Socioeconomic Index (NZSEI-06) codes each occupation based on its associated education-level and income in the NZ Census.[28] (19 unemployed participants' socioeconomic status was assigned based on their most recent occupation in their thirties; 14 homemakers' socioeconomic status was imputed from their education, following the NZSEI-06 algorithm.) Scores range from 10 (low status) to 90 (high status). The NZSEI-06 scores are further grouped into six socioeconomic status groups.[28] Examples of occupations in the six groups include medical practitioner (NZSEI code = 90; group 6); engineering professional (66; group 5); database administrator (59; group 4); personal assistant (44; group 3); office cashier (28; group 2); fish filleter (23; group 1). Childhood socioeconomic status was defined as the mean of the highest occupational status level of either parent across Study assessments from the participants' birth through age 15 years, measured using the Elley-Irving scale,[29] the forerunner of NZSEI, which also assigned occupations into one of six socioeconomic status groups (6 = professional; 1 = unskilled laborer).

2.1.3.5 Statistical analysis

First, sample descriptive statistics were generated for the sample as a whole and separately for study members with and without blood-lead data. Differences between those with and without blood-lead data were examined using t-tests or chi-square tests as appropriate. Pearson correlations between all study variables were calculated using standard procedures (i.e., PROC CORR) in SAS v 9.3.

Second, the association between childhood blood-lead levels and adult outcomes was tested using Ordinary Least Squares multiple regression. The two pre-specified primary outcome variables were adult IQ (measured with the WAIS-IV) and adult socioeconomic status (measured with the NZSEI-06 score), respectively. Each outcome was examined using two models: (1) a "sex adjusted" model in which the outcome was regressed on childhood blood-lead levels and sex, and (2) a "fully adjusted" model in which the outcome was regressed on childhood blood-lead levels and the following covariates: sex, childhood IQ, maternal IQ (assessed via the Science Research Associates verbal test[30] administered to the Study mothers when the participants were 3 years old) and childhood socioeconomic status. The goal of the fully adjusted model was to evaluate the association between childhood blood-lead levels and adult IQ and socioeconomic status using an analysis of covariance model of IQ and socioeconomic status change. Lead level was analyzed as a continuous measure. However, it is presented in terms of 5μg/dL units because the historic "level of concern" during the participants' childhood was 10μg/dL and today it is 5μg/dl, making this unit meaningful to clinicians and policymakers. Moreover, 5μg/dL represents approximately 1 SD of

blood-lead level in the cohort. We also compared mean primary outcomes for participants with versus without childhood blood-lead levels above the historic international "level of concern" during their childhood (>10μg/dL).

Prespecified exploratory analyses tested associations between childhood blood-lead level and the four constituent abilities making up the IQ. No adjustments were made for the four multiple comparisons of secondary outcomes, so these should be interpreted as exploratory.

Only participants who had complete data on all covariates for each outcome were included in each model; no data were imputed. For adult IQ, 533 (94%) participants were analyzed; for adult socioeconomic status, 541 (96%) of participants were analyzed.

Third, in addition to the analysis of covariance, for illustrative purposes, change in IQ from childhood to adulthood as well as socioeconomic mobility were evaluated using change scores. Childhood IQ was subtracted from adulthood IQ where both IQs were measured on matched scales. IQ decline relative to cohort norms was signified by negative scores. Childhood (i.e., parental) socioeconomic status was subtracted from adult socioeconomic status, where both variables were measured on matched 6-category scales.[19,20] Downward mobility was signified by negative scores.

Fourth, whether cognitive decline from childhood to adulthood mediated the association between childhood blood-lead levels and downward change in socioeconomic status was tested. Ordinary Least Squares regression was used to

estimate a single-mediator model, using the Sobel test[22] to estimate the significance of the mediation effect (see Supplementary Materials**)**.

Analyses were conducted using SAS v9.3. Regression coefficients refer to dose increments of 5μg/dL in childhood blood-level. The threshold for statistical significance was $P<.05$, two-tailed. For sensitivity analyses all statistical analyses were repeated after subjecting the lead measure to a logarithmic transformation and a correction for hematocrit levels, and after incorporating two additional covariates into the fully-adjusted analysis of covariance: maternal smoking during pregnancy (assessed via maternal interview) and child birth weight (from hospital records).

2.1.4. Results

Of 1037 original cohort participants, 1007 were still alive at age 38 years, 565 (56%) of whom had been lead-tested at age 11 years (303[54%] male; 525[93%] white). Participants alive at age 38 years with childhood blood-lead data (N=565) and without childhood blood-lead data (N=442) did not differ to a statistically significant extent from each other in terms of their mothers' IQs, or their social class origins, but those without blood-lead data did have lower mean childhood IQs as a group (children not tested at the Unit tended to live outside city limits and such non-urban residents tended to have marginally lower IQs, 98.91 vs 101.01),[31] $\text{Difference}_{\text{No Lead – Lead}}$=-2.10, 95%CI (-3.99, -0.19), P=0.03 (Table 1). Correlations among primary study variables are shown in Table 2.

Table 1. Comparison of participants with and without lead data at age 11 years on primary study variables.

	Alive at age 38 years									
	Full Sample (N = 1037)			Lead Data at age 11 (N = 565)			No Lead Data at age 11 (N = 442)			Lead vs No Lead
	N	Mean	% or SD	N	Mean	% or SD	N	Mean	% or SD	*P* Value
Male	535		(51.7%)	303		(53.6%)	214		(44.8%)	0.10
Childhood Blood-Lead Level				565	10.99	(4.63)		--	--	
Maternal Verbal IQ	1011	39.75	(14.77)	557	40.41	(14.22)	425	39.19	(15.42)	0.20
WISC-R Childhood Full-Scale IQ	986	100.00	(15.00)	563	101.01	(14.22)	398	98.91	(15.53)	0.03
Childhood Socioeconomic Status	1031	3.75	(1.14)	563	3.80	(1.12)	438	3.69	(1.17)	0.13
WAIS-IV Age-38 Full-Scale IQ	942	100.00	(15.00)	542	101.16	(14.82)	400	98.43	(15.11)	0.006
Age-38 Socioeconomic Status	953	48.83	(17.11)	550	49.75	(17.12)	403	47.58	(17.03)	0.05

Note. Maternal verbal IQ was assessed with the Thurstone scale, which is not scaled to a mean of 100. Socioeconomic status was assessed in childhood using the Elley-Irving scale (range 1 lowest – 6 highest) and at age 38 years using the New Zealand Socioeconomic Index-2006, (NZSEI-06; range 10 lowest - 90 highest). SD = standard deviation

Table 2: Pearson correlations among primary study variables.

	Variable	1	2	3	4	5	6
1	Childhood Blood-Lead Level	--					
2	Maternal Verbal IQ	-0.06	--				
3	WISC-R Childhood IQ	-0.03	0.38***	--			
4	Childhood Socioeconomic Status	0.03	0.36***	0.41***	--		
5	WAIS-IV Age-38 Full-Scale IQ	-0.11*	0.44***	0.76***	0.38***	--	
6	Age-38 Socioeconomic Status	-0.11**	0.24***	0.43***	0.35***	0.49***	--

Note. Socioeconomic status was assessed in childhood using the Elley-Irving scale (range 1 lowest – 6 highest) and at age 38 years using the New Zealand Socioeconomic Index-2006, (NZSEI-06; range 10 lowest - 90 highest). *$P < .05$, **$P < .01$, ***$P < .001$.

Childhood blood-lead levels ranged from 4 to 31 μg/dL (mean=10.99, SD=4.63). 259 participants (46%; 157[61%] male) had blood-lead levels above the historic international "level of concern" (10μg/dL) and 531 (94%; 288[54%] male) had levels above the current normal reference value (5μg/dL).[25] Females had lower lead levels than males (Female N=262, mean=10.42; Male N=303, mean=11.49, $\text{Difference}_{\text{Female – Male}}$=-1.07; 95%CI (-1.82, -0.30); *P*=.007). There was no significant socioeconomic gradient in lead exposure in the Dunedin cohort children. High blood-lead levels were observed among children from all socioeconomic status groups (Figure 1).

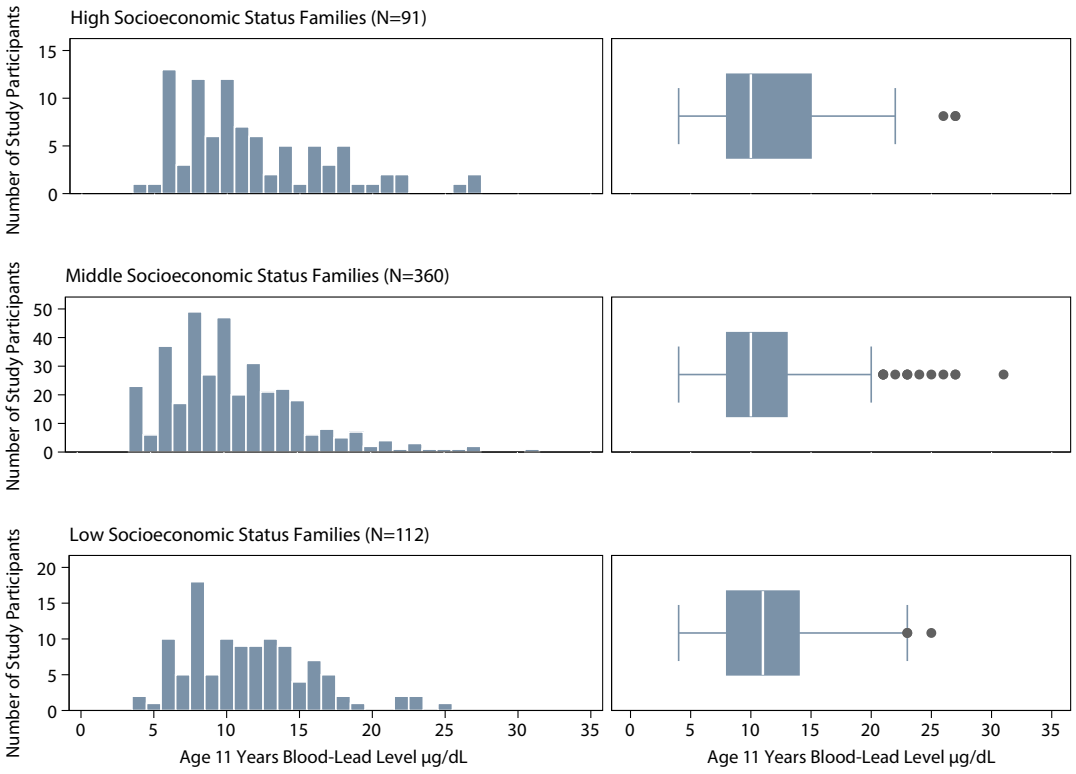

Figure 1: Distribution of blood-lead levels at age 11 years in Dunedin cohort children grouped by socioeconomic status.

Note. Histograms and box plots depicting the distribution of childhood blood-lead levels for participants from low, middle, and high socioeconomic status families based on the 6-point Elley-Irving scale coding participants' parents' occupations and their associated income and education levels. Low childhood family socioeconomic status includes categories 1 and 2 on the 6-point scale; middle status includes categories 3 and 4; high status includes categories 5 and 6. Histogram interval bins represent whole integers of blood-lead level. Shown in each box plot are the median value (white line), the 25th and 75th percentiles (box outer borders), and a lower-bound value equal to the 25th percentile minus 150% of the interquartile range and an upper-bound value equal to the 75th percentile plus 150% of the interquartile range (whiskers). High blood-lead levels were observed in all status groups. N=563 (two participants were not assigned a childhood socioeconomic status score).

Higher childhood blood-lead level was associated with poorer adult cognitive performance. Children with higher blood-lead levels at age 11 years scored lower than cohort peers on mean IQ tested at age 38 years (Table 3, Panel A). After controlling for participants' own childhood IQ score, their mothers' IQ score, and their socioeconomic background, each 5μg/dL higher level of blood-lead in childhood was associated with an additional 1.61-point lower score (95%CI: -2.48, -0.74, *P*<.001) in full-scale IQ. Pre-specified exploratory analyses of the four constituent abilities making up the IQ showed children with higher levels of blood-lead at age 11 years scored lowest on indexes tapping perceptual reasoning and working memory (Table 3, Panel A). Figure 2 Panel **A** depicts the mean IQs at age 38 years of participants at each childhood blood-lead level. Participants with childhood blood-lead levels above the historic international "level of concern" (>10μg/dL) tested 4.25 mean IQ points lower in adulthood (95%CI: -6.75, -1.75, *P*<.001) than their peers with lower blood-lead levels (after adjusting for childhood IQ

and the other covariates, 2.73 IQ points lower, (95%CI: -4.34, -1.12, *P*<.001). To evaluate IQ decline from childhood to adulthood, participants' adult IQ scores were compared to their childhood IQ scores (Figure 3A). Participants above the "level of concern" exhibited a mean decline of 1.68 IQ points from childhood to adulthood. In contrast, those at or below the "level of concern" exhibited a mean increase of 1.22 IQ points from childhood to adulthood, a significant difference of 2.90 IQ points (95%CI: 1.20, 4.61, *P*<.001).

Higher childhood blood-lead level was also associated with lower adult socioeconomic status. Children with higher blood-lead levels at age 11 years attained lower levels of socioeconomic status as adults than cohort peers (Table 3, Panel B). After controlling for participants' own childhood IQ score, their mothers' IQ score, and their socioeconomic background, each 5μg/dL higher level of blood-lead in childhood was associated with an additional 1.79-unit lower score (95%CI: -3.17, -0.40, *P*=.01) in socioeconomic status. Figure 2 Panel B depicts the mean socioeconomic status at age 38 years of participants at each childhood blood-lead level. Participants with childhood blood-lead levels above the historic international "level of concern" (>10μg/dL) attained a mean socioeconomic level 4.51 points lower in adulthood (95%CI: -7.38,-1.64, *P*=.002) than their peers with lower blood-lead levels (after adjusting for childhood socioeconomic status and the other covariates, 3.42 units lower, 95%CI: -5.98,-0.85, *P*=.009). To evaluate socioeconomic mobility directly, participants' adult socioeconomic

status was compared to that of their parents' on the same 6-point social class scale (Figure 3B). Participants above the "level of concern" exhibited an absolute mean decline of 0.18 social class scale points on the 6-point scale. In contrast, those at or below the "level of concern" exhibited a mean increase of 0.12 social class scale points from childhood to adulthood, a significant difference of 0.30 scale points (95%CI: 0.04, 0.55, *P*=.02).

Table 3: Association between childhood blood-lead levels and two primary outcomes at age 38 years: adult IQ (Panel A) and adult socioeconomic status (Panel B). Secondary outcomes were Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed.

(A)

	Sex adjusted			Fully adjusted		
	b	**95% CI**	***P***	**b**	**95% CI**	***P***
WAIS-IV Full-Scale IQ	-1.97	(-3.34, -0.59)	0.005	-1.61	(-2.48, -0.74)	<0.001
WAIS-IV Verbal Comprehension IQ	-1.39	(-3.01, 0.23)	0.09	-1.01	(-2.18, 0.16)	0.09
WAIS-IV Perceptual Reasoning IQ	-2.36	(-3.69, -1.03)	<0.001	-2.07	(-3.14, -1.01)	<0.001
WAIS-IV Working Memory IQ	-1.52	(-2.95, -0.08)	0.04	-1.26	(-2.38, -0.14)	0.03
WAIS-IV Processing Speed IQ	-0.91	(-2.19, 0.37)	0.16	-0.70	(-1.85, 0.45)	0.23

(B)

	Sex adjusted			Fully adjusted		
	b	**95% CI**	***P***	**b**	**95% CI**	***P***
Socioeconomic status	-1.94	(-3.50, -0.37)	0.02	-1.79	(-3.17, -0.40)	0.01

Note. CI = Confidence Interval. Covariates in the fully adjusted model were sex, maternal IQ, participants' childhood IQ and childhood socioeconomic status. N= 533-541. Of the Study participants alive at age 38 years with childhood blood-lead measured, 533 (94%) also had present data on all the covariates and the IQ outcome measures. Of those alive at age 38 years with childhood blood-lead measured, 541

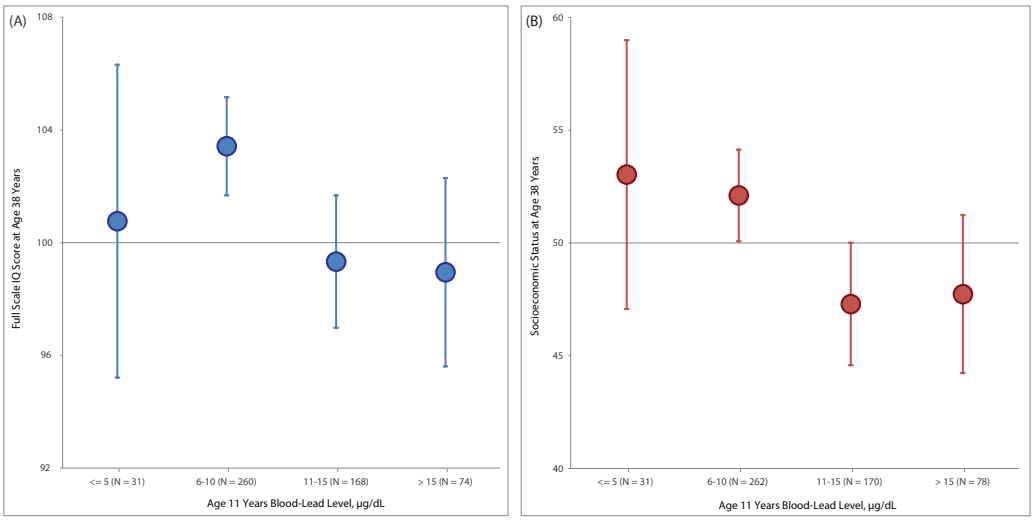

Figure 2: Association of childhood blood-lead level with WAIS-IV IQ (Panel A) and socioeconomic status (Panel B) in adulthood (unadjusted for covariates).

Note. Mean outcomes in adulthood with 95% confidence intervals (error bars) for each 5µg/dL higher level of blood-lead in childhood. Each 5µg/dL higher level of blood-lead in childhood was associated with an additional 1.97-point lower score (95%CI: -3.34, -0.59, *P*=.005) in adult WAIS-IV full-scale IQ and an additional 1.94-unit lower score (95%CI: -3.50, -0.37, *P*=.02) in adult socioeconomic status (see Table 3). Socioeconomic status was assessed at age 38 years using the New Zealand Socioeconomic Index-2006 (NZSEI-06; range 10 = lowest - 90 = highest).

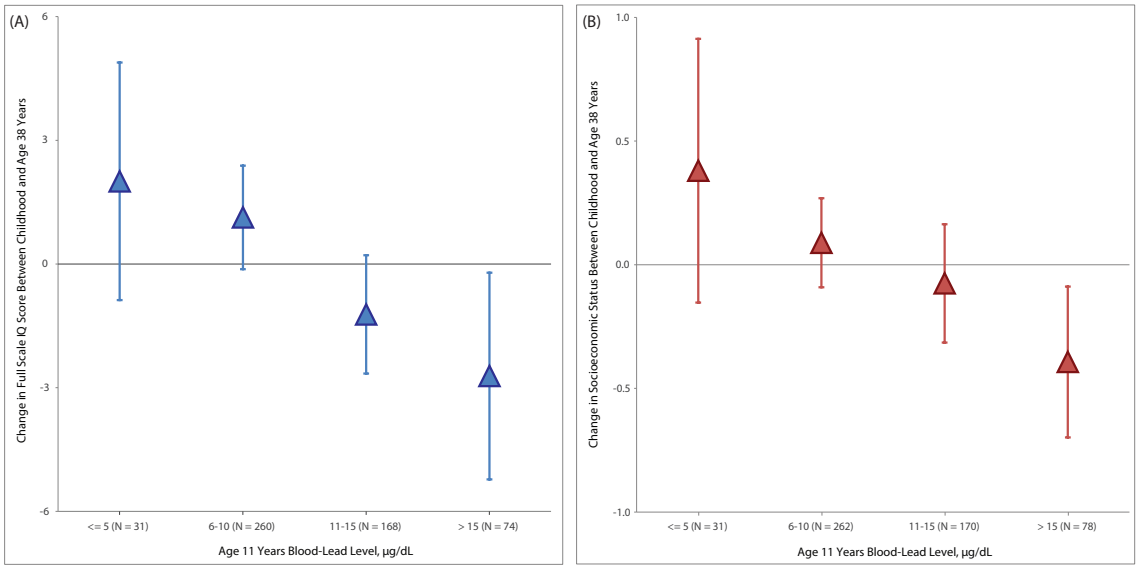

Figure 3: Association of childhood blood-lead level with cognitive decline (Panel A) and downward socioeconomic mobility (Panel B) into adulthood (unadjusted for covariates).

Note. Mean change in outcome from childhood to adulthood with 95% confidence intervals (error bars) for each 5μg/dL higher level of blood-lead in childhood. To create IQ change scores, childhood IQ was subtracted from adulthood IQ where both IQs were measured on matched scales (WISC-R for child IQ and WAIS-IV for adult IQ). To create socioeconomic status change scores, childhood (i.e., parental) socioeconomic status was subtracted from adult socioeconomic status where both status variables were measured on comparable 6-category scales (the Elley-Irving scale for childhood and the New Zealand Socioeconomic Index for adulthood) assessing socioeconomic status in New Zealand by assigning occupations into one of six socioeconomic status groups (6 = professional; 1 = unskilled laborer). Each 5μg/dL higher level of blood-lead in childhood was associated with a 1.61-point decline (95%CI: -2.48,-0.74, P<.001) in full-scale IQ and with a 1.79-unit decline (95%CI: -3.17, -0.40, P=.01) in socioeconomic status (see Table 3).

The association between childhood blood-lead levels and socioeconomic status decline from childhood to adulthood was partially but significantly mediated by decline in IQ from childhood to adulthood, after adjusting for covariates. IQ decline accounted for 40% of the association between childhood blood-lead levels and downward socioeconomic mobility, significantly reducing the association between childhood blood-lead levels and socioeconomic status change, Sobel test of mediation P=.002.

2.1.5 Discussion

This longitudinal analysis of the association between childhood blood-lead levels and adult cognitive function and socioeconomic status revealed three findings. First, childhood blood-lead level was associated with lower adult cognitive performance nearly three decades later, particularly on tests assessing perceptual reasoning and working memory ability, reflecting cognitive decline following childhood lead exposure. These associations were significant after adjusting for the participant's own childhood IQ, their mother's IQ, and their social class background. Second, childhood blood-lead level was associated with lower adult socioeconomic status, reflecting downward social mobility following childhood lead exposure. These associations too were significant after adjusting for the participant's own childhood IQ, their mother's IQ, and their social class background. Third, the relationship between childhood lead exposure and

downward social mobility by midlife was partially, but significantly, mediated by cognitive decline following childhood lead exposure.

These results suggest that cognitive impairment associated with childhood lead exposure can persist and may worsen somewhat across decades (27 years in this study) to age 38 years. Each 5μg/dL higher blood-lead level in childhood was associated with an additional 1.61-point lower score in adult IQ after adjusting for covariates. The effect sizes for adult cognitive impairment that were detected are small and do not constitute the extent of impairment that would attract clinical treatment. They are, however, similar to IQ deficits associated with other notable childhood risk factors, such as very low birth weight.[32] Despite being mild, the cognitive decline evident among lead-exposed children was accompanied by altered socioeconomic life trajectories, measurable as small but detectable downward social mobility by midlife for the most-exposed children regardless of their origins.

This study had the advantage of being able to use lead assays archived three decades ago, in a representative sample of children that is relatively large by the standards of research studies on lead exposure, and which has been followed to midlife. A strength of this study was the lack of social gradient in lead exposure observed in the Dunedin cohort. This afforded the opportunity to examine the long-term association between childhood lead exposure and adult outcomes without having to first disentangle exposure to lead from exposure to other harmful and often intertwined

adversities, particularly poverty. The study's findings are thus consistent with, but cannot prove, the hypothesis that lead exerts a degradative effect on cognitive ability and a downward pull on socioeconomic status over time regardless of where children start off in life. That said, these findings may not generalize to those settings where, as in the U.S., lead exposure is concentrated among the poor in larger cities and near former lead-emitting industries.[33] As this study's sample was primarily Caucasian, the findings also require replication in more ethnically-diverse samples.

There are limitations to this study. 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 level gradient observed in the Dunedin cohort was nearly entirely (94% of participants) above the current blood-lead reference value for clinical attention (5μg/dL). This study's results may not, therefore, be informative about the long-term consequences of very low lead exposures (<7.5μg/dL). Because the only measure of childhood lead exposure was taken at age 11 years this study could not evaluate sensitive periods of vulnerability to lead or evaluate cumulative exposure across childhood, although blood-lead level measured at school-age may be "a reasonable proxy for lifetime exposure" up to that point.[6(p174)] There were also no measures of cumulative lead exposure to midlife, such as cortical bone-lead level. This study could not, therefore, evaluate the differential influences of early-life versus later-life lead exposure. Recent studies of older adults suggest that lead exposure in adulthood

associates with impaired cognitive function and accelerated cognitive decline in late life.[34] While cumulative lead exposure in adulthood is an important metric for understanding the potential harms of lead absorbed across the lifespan, this study was focused on understanding the long-term consequences of early-life lead exposure. During the lifetime of the Dunedin cohort participants, lead exposure was reduced after childhood, as New Zealand began to phase lead out of its gasoline in the late 1980's and removed it entirely in 1996.[20] In many similar developed-country cities, adults now in their middle age will have also experienced their greatest lead exposures during childhood.[35] In addition, this study was observational and correlational, and therefore does not establish a causal relation between lead exposure and outcomes, such as would be the case in a hypothetical experiment with children randomly assigned to lead exposure.

Notwithstanding its limitations, this study may hold implications for clinical practice and public policy. The results indicate that childhood exposures to lead can be linked with cognitive and socioeconomic outcomes detectable more than three decades later. For the clinician, evidence of cognitive decline from childhood to adulthood may argue for increased attention to possible early intervention with lead-exposed children. For communities that have experienced collective lead exposure events, and for countries where lead exposures are still routinely above health standards, the findings raise questions about the reasonable duration and magnitude of public responses. Just as

the problem of toxic lead exposure in homes appears to persist, so too do the poor outcomes associated with such exposure. Short-lived public responses to community lead exposure may not be enough.

2.1.5.1 Conclusion

In this cohort born in New Zealand in 1972-1973, childhood lead exposure was associated with lower cognitive function and socioeconomic status at age 38 years and with declines in IQ and downward social mobility. Childhood lead exposure may have long-term ramifications.

2.2 Childhood lead exposure is associated with adult personality difficulties and lifelong poor mental health

The following original research report was published in JAMA-Psychiatry in 2019 with the title, "Association of Childhood Lead Exposure With Adult Personality Traits and Lifelong Mental Health." The authors were as follows: Aaron Reuben, M.E.M., Jonathan D. Schaefer, M.A., Terrie E. Moffitt, Ph.D., Jonathan Broadbent, Ph.D., Honalee Harrington, B.A., Renate M. Houts, Ph.D., Sandhya Ramrakha, Ph.D, Richie Poulton, Ph.D., &. Avshalom Caspi, Ph.D.

2.2.1. Abstract

Importance. Millions of adults now entering middle-age were exposed to high levels of lead, a developmental neurotoxin, as children. While childhood lead exposure has been linked to disrupted behavioral development, the long-term consequences for adult mental and behavioral health have not been fully characterized.

Objective. To test the hypothesis that childhood lead exposure is associated with greater psychopathology across the life-course and with differences in adult personality.

Design, Setting, and Participants. Prospective cohort study based on a population-representative 1972-73 birth cohort from New Zealand, the Dunedin Multidisciplinary Health and Development Study, followed to age 38 years.

Exposure. Childhood lead exposure ascertained as blood-lead levels measured at age 11 years. Blood-lead levels were unrelated to family socioeconomic status.

Main Outcomes and Measures. Primary outcomes were: adult mental disorder symptoms, assessed via clinical interview at ages 18, 21, 26, 32, and 38, and transformed through confirmatory factor analysis into continuous measures of General Psychopathology (the "p-factor") and Internalizing, Externalizing, and Thought Disorder symptoms (all standardized to M=100, SD=15); and adult personality, assessed via informant-report using the Big Five Personality Inventory (assessing Neuroticism, Extraversion, Openness-to-Experience, Agreeableness, and Conscientiousness) at ages 26, 32, and 38 (all scores standardized to M=0, SD=1). Hypotheses were formulated after data-collection; an analysis plan was posted in advance.

Results. Of 1037 original participants, 579 (56%) were lead-tested at age 11 years (54% male). Mean blood-lead level was 11.08μg/dL (SD=4.96). After adjusting for study covariates, each 5μg/dL increase in childhood blood lead-level was associated with a 1.34-point increase in General Psychopathology (95%CI: 0.11, 2.57, *P*=.033), driven by Internalizing (b=1.41, 95%CI: 0.19, 2.62, *P*=.024) and Thought Disorder (b=1.30, 95%CI: 0.06, 2.54, *P*=.040) symptoms. Each 5μg/dL increase in childhood blood lead-level was also associated with a .10-SD increase in Neuroticism (95%CI:.02, .18, *P*=.016), a .09-SD decrease in Agreeableness (95%CI:.-.18, -.01, *P*=.033), and a .14-SD decrease in Conscientiousness (95%CI:.-.25, -.03, *P*=.010). Associations with informant-rated Extraversion and Openness-to-Experience were non-significant.

Conclusion and Relevance. In this multi-decade, longitudinal study of lead-exposed children, higher childhood blood-lead level predicted greater psychopathology across the life-course and more problematic adult personality styles. Childhood lead exposure may have long-term consequences for adult mental health and personality

2.2.2. Introduction

Millions of adults now entering middle-age were exposed to high levels of lead as children,[22] a phenomenon that accompanied the peak use of lead in gasoline, around the world, from the 1940s through the early 1990s.[36] From 1976 to 1980, the average child living in the United States (US) had blood-lead levels (BLLs) three-times higher (>15ug/dL)[22] than the current reference value for clinical attention, 5ug/dL.[37] Lead-exposed children have been found to suffer from disrupted cognitive and behavioral development,[6] with childhood lead exposure linked to lower child IQ,[38] poorer academic achievement,[39] and greater rates of child behavior problems, particularly inattention, hyperactivity, and antisocial behavior.[21,40,41] Adults exposed to lead have, meanwhile, been found to be at increased risk of developing some psychiatric conditions.[42–45] While follow-up studies of lead-tested children have reported the persistence of lead-related cognitive deficits well into adulthood,[19,46] apart from antisocial outcomes, the long-term mental and behavioral health consequences of early-life lead exposure have not been fully characterized.

To date, to our knowledge, two studies have undertaken long-term follow-up in lead-exposed children to determine whether early behavior problems persist or evolve into adult mental health concerns. (A larger number of studies have examined whether adolescents and young adults exposed to lead as children display more antisocial and criminal behaviors, with most studies, though not all, suggesting that they do).[47–51] One, a US study using linked health records and clinical interviews to identify cases of psychosis in two lead-tested child cohorts born in the late 1960s (total N=200, age range 30-35 years at follow-up), reported a 2-fold increased risk of schizophrenia spectrum disorder in adulthood for individuals with high BLLs as children (roughly >15ug/dL).[52] The other, the only comprehensive adult psychiatric follow-up yet conducted in a lead-tested child cohort (N=210; cohort born in the early 1980s), reported greater social phobia, anxiety, and substance abuse problems in adulthood (mean age at follow-up=26.3) for Australian women who had greater BLLs as children, although all associations were attenuated to non-significance by statistical adjustment for study covariates, including parental educational/occupational attainment.[53]

This existing evidence base has limitations. First, because of small sample sizes, these studies had limited power to detect effects. Second, because they considered only specific disorders (e.g., schizophrenia) or else relied upon right-hand censored, single-time-point clinical interviews to assess psychiatric problems, these studies likely under-detected episodes of illness and over-looked disorders that have a pattern of re-

occurrence.[54] Third, it is now appreciated that most psychiatric disorders are dimensional constructs, not discrete categorical entities.[55] Individuals who meet criteria for one disorder typically also meet criteria for others, both cross-sectionally and across the life-course.[56–58] Empirical evidence suggests that psychiatric illnesses can be represented by three higher-order dimensions –Internalizing, Externalizing, and Thought Disorders (e.g., psychotic experiences)[59]— which are intercorrelated and may reflect a common liability towards psychopathology in general, labeled the "p-factor."[60–62] The p-factor may be a particularly appropriate outcome for studies linking environmental toxins to mental disorder because 1) the few previous studies of lead and psychopathology suggest that lead exposure may increase the risk of internalizing, externalizing, *and* thought disorders, without particular specificity, and 2) the continuous and omnibus nature of "p" allows investigators to easily test for dose-effect relationships.

While epidemiologists have hypothesized a relationship between child lead exposure and adult psychopathology, another way of considering the link between lead and behavioral dysfunction focuses on personality features that may impair an individual's capacity to lead a happy, successful life. Decades of research using the Big-Five framework to represent the five broadest factors of personality[63] have identified a blend of poor impulse control, high antagonism, and a tendency towards negative emotionality that has a detrimental effect on love, work, and health, and which appears

to predispose individuals to psychiatric illness.[64–66] Few studies have examined personality traits in relation to lead exposure, but adults occupationally exposed to lead have reported feeling angrier and more tired, tense, and depressed than their less-exposed peers[67,68] –emotional symptoms which seem to improve with the abatement of lead exposure.[69] In the one cohort of lead-tested children that received personality testing (born in Cincinnati in the early 1980s, aged 19-24 at follow-up), young adults with greater childhood lead exposure tested higher, on average, than cohort peers on a self-report inventory of psychopathic traits such as impulsivity and egocentricity.[70] Alterations in emotion regulation and adult personality have consequently been proposed as explanatory mechanisms for the reported link between childhood BLLs and adolescent delinquency[71] and young adult criminal arrests[72] also observed in this Cincinnati-cohort.

Here we undertake the longest and largest psychiatric follow-up to date in a cohort of adults who were lead-exposed and lead-tested as children, as well as the only follow-up to use: 1) repeated clinical interviews assessing psychopathology symptoms across adulthood, up to age 38, 2) comprehensive, dimensional measures of psychopathology that account for severity, co-morbidity, and re-occurrence, and 3) a broad measure of adult personality (the Big Five)[63] that did not rely on self-report. Critically, we conduct these follow-ups in a sample where the extent of children's

exposure to lead was unrelated to their socioeconomic origins[46] (Figure 1), removing a potentially important confound that is present in most studies of children and lead.[73]

2.2.3 Methods

2.2.3.1 Study Design and Population

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a birth cohort. 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. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island.[24] On adult health, the cohort matches the New Zealand National Health and Nutrition Survey on key indicators (e.g. body mass index, smoking, visits to a physician).[24] The cohort is primarily white; fewer than 7% self-identify as having non-Caucasian ancestry, matching the demographics of the South Island.[24] Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and the most recent data collection was completed in December 2012, at age 38 years. Written informed consent was obtained from parents and cohort participants, and Study protocols were approved by the institutional ethical review boards of the participating universities.

2.2.3.2 Measures

Childhood blood-lead levels.

Approximately 30ml of venous blood was collected at age 11 from 579 of the 803 children (72.1%) who participated in the assessment carried out at the Research Unit and who freely agreed to give blood. A further 122 children were assessed in their schools, where blood could not be drawn. Whole blood samples were analyzed through graphite fumance atomic absorption spectrophotometry. Blood-lead is reported in micrograms per deciliter (1μg/dL=0.0483μmol/l). Details on the method of blood collection, storage, and analysis have been described previously.[21] Child BLLs ranged from 4 to 50ug/dL (M=11.08, SD=4.96). The majority (94.0%) of Study members had BLLs above the current reference value for clinical attention (5μg/dL).[37]

Psychopathology across the life course.

Assessment of symptoms of mental disorder. The Dunedin Study longitudinally ascertains mental disorders every two to six years, interviewing participants about past-year symptoms. We also used life-history calendar interviews to ascertain indicators of mental disorder occurring in the gaps between assessments, including inpatient treatment, outpatient treatment, or spells taking prescribed psychiatric medication (indicators that are salient and recalled more reliably than individual symptoms). Life-history calendar data indicate that virtually all participants having a disorder

consequential enough to be associated with treatment have been detected in our net of past-year diagnoses made at ages 18, 21, 26, 32 and 38. Specifically, we identified only 11 people who reported treatment but had not been captured in our net of diagnoses from ages 18-38 (most of whom had a brief postnatal depression).

Psychopathology symptoms were assessed via private structured interviews using the Diagnostic Interview Schedule (DIS)[74] at ages 18, 21, 26, 32 and 38. Interviewers were health professionals, had completed a two-week training course to criterion, and were re-trained periodically as needed throughout data-collection. We studied DSM-defined symptoms of the following disorders that were repeatedly assessed in our longitudinal study: alcohol dependence, cannabis dependence, dependence on hard drugs, tobacco dependence (assessed with the Fagerstrom Test for Nicotine Dependence),[75] conduct disorder, major depression, generalized anxiety disorder, fears/phobias, obsessive compulsive disorder, mania, and positive and negative schizophrenia symptoms. Ordinal measures represented the number of the seven (e.g., mania, generalized anxiety disorder) to ten (e.g., alcohol dependence, cannabis dependence) possible DSM-defined symptoms associated with each disorder. Fears/phobias were assessed as the count of diagnoses for simple phobia, social phobia, agoraphobia and panic disorder that a Study member reported at each assessment. Symptoms were assessed without regard for hierarchical exclusionary rules, to facilitate the examination of co-morbidity. Each of the 11 disorders were assessed at least three

times. Elsewhere we have shown that the past-year prevalence rates of psychiatric disorders in the Dunedin cohort are similar to prevalence rates in nation-wide surveys of the US and New Zealand.[54,76]

The structure of psychopathology from ages 18 to 38. The methods used to compute our hierarchical measures of psychopathology in the Dunedin cohort have been described previously.[60] Briefly, we used confirmatory factor analysis to calculate factor scores representing Internalizing (with loadings from depression, anxiety, and fear/phobia symptoms), Externalizing (with loadings from substance dependence and conduct disorder symptoms), and Thought Disorders (with loading from obsessive-compulsive, manic, and psychotic symptoms), as well as General Psychopathology, the "p-factor" (with loadings from all 11 assessed disorders). Fit indices met criteria for good model fit. For expository purposes, we scaled Study members' scores on all factors to M=100, SD=15.

Adult personality.

At ages 26, 32, and 38 years, Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to describe each Study member using a 25-item version of the Big Five Inventory measuring the personality traits of Neuroticism, Extraversion, Openness-to-Experience, Agreeableness, and Conscientiousness.[77] We created cross-age composites for each of the traits. In the

analysis sample, these measures correlated with Study members' scores on General Psychopathology at r=.42, *P*<.001 (Neuroticism); r=.00, *P*=.991 (Extraversion); r=.03, *P*=.381 (Openness to Experience); r=-.30, *P*<.001 (Agreeableness); and r=-.30, *P*<.001 (Conscientiousness).

Child externalizing and internalizing problems.

At age 11, parents and teachers completed the Rutter Child Scale (RCS),[78] a questionnaire that inquires about the major areas of behavioral and emotional functioning during the past year. Parents and teachers rated each behavior on the RCS as "does not apply"(0), "applies somewhat"(1), or "certainly applies"(2). Child externalizing problems were assessed using scores for the 8-item "antisocial" scale and scores for four items that address hyperactivity. Items on the antisocial-scale describe children who frequently fight, bully other children, lie, disobey, steal, destroy belongings, and have irritable tempers. Items contributing to the measurement of hyperactivity describe children who are "very restless," "hardly ever still," "squirmy," "fidgety," and unable to "settle into anything." Child internalizing problems were assessed using scores on six items that describe children who "worry about many things" and "often appear miserable," "unhappy," and "tearful." Details about the reliability and validity of the parent and teacher versions of the scale have been described previously.[79,80] Parent and teacher scores were averaged.

Covariates.

Study covariates included family-level risk factors known to relate to childhood lead exposure or adult psychopathology and personality, including family socioeconomic status, maternal IQ, and family history of mental illness.

Childhood family socioeconomic status was defined as the mean of the highest occupational status level of either parent across Study assessments from the participants' birth through age 15 years, measured using the Elley-Irving scale, which assigned occupations into one of six socioeconomic status groups (6=professional; 1=unskilled laborer; M=3.75, SD=1.14).[29]

Maternal IQ was assessed via the SRA verbal test (which is not scaled to a mean of 100) administered to the Study mothers when the Study members were 3 years old (M=39.75, SD=14.77).[30]

Family histories of mental illness were collected in 2003-2005, when the Study members were 30-33 years of age, by interviewing the Study members as well as both of their parents. As described previously,[81] family psychiatric history data were collected about each participant`s biological parents, grandparents, and siblings. Data on 7,856 family members of the Study members were used (average of 8 family members; range 3-16) to construct family histories, assessed by means of the Family History Screen (FHS)[82] and supplemented with items to broaden coverage of substance-use disorders and psychosis. A family member was considered to have a positive history of disorder if

the majority of informants reported that the family member displayed at least one indicator of mental illness. Indicators included: 1) suffering from a "serious mental illness, emotional problem, or nervous breakdown," 2) ever receiving medical or psychological treatment for a mental health issue, or 3) suffering from marked functional impairment due to a mental health issue. The family history of mental illness for each Study member was calculated as the proportion of members in the family with a positive history of disorder, taking into account genetic relatedness (M=0.25, SD=0.21).

2.2.3.3 Statistical analysis

First, we tested the association between childhood BLLs and adult General Psychopathology using Ordinary Least Squares multiple linear regression. We also tested for specificity in the relationship between childhood lead exposure and adult psychopathology by examining whether BLLs predicted scores on the Internalizing, Externalizing, and Thought Disorder factors. Each outcome was examined using two models: 1) a "sex-adjusted" model in which the outcome was regressed on childhood BLL and sex, and 2) a "fully-adjusted" model that included all covariates. We used these same models to test associations between childhood BLLs and scores on informant-report measures of adult personality. Post-hoc sensitivity tests were also conducted to examine possible sex differences in the association between childhood BLLs and the adult outcome measures.[83] The models specified above were re-run with a sex-by-lead

interaction term included; these terms were non-significant in all models (p-values ranged from .133 to .656).

Second, we repeated these analyses using measures of childhood externalizing and internalizing problems (i.e., antisocial behavior, hyperactivity, and internalizing problems) in place of adult outcomes. These models allowed us to test whether the impact of lead on psychopathology could be seen as early as age 11.

Only participants who had complete data on all covariates for each outcome were included in each model; no data were imputed. For adult psychopathology, 551 (95.2%) participants were analyzed; for adult personality, 539 (93.1%) participants were analyzed; for childhood externalizing and internalizing problems, 552 (96.3%) participants were analyzed. Lead level was analyzed as a continuous measure and is presented here in 5μg/dL units, which correspond to approximately 1-standard deviation of BLL in the cohort.

Comparing cases who were lead-tested at age 11 versus cases not tested.

579 Study members had been lead tested in childhood (55.8% of the full cohort). Study members with and without (n=458, 44.2%) blood-lead data were similar on all study covariates, including their social class origins, their mother's IQ scores, and their family history of mental illness. As a group, those without blood-lead data did, however, display greater internalizing problems at age 11 years (M=-.06 z-scored units

for children with blood-lead data, M=.10 z-scored units for children without; difference of .16, P=.016).

2.2.4 Results

2.2.4.1 Do children with greater exposure to lead in childhood score higher on measures of psychopathology in adulthood?

Figure 4 depicts the mean adult General Psychopathology scores of participants at each childhood BLL. Participants with childhood BLLs above the historic international "level of concern" for clinical attention (>10μg/dL)[37] tested an average of 2.52 points higher (95%CI: .14, 4.90; *P*=.038) in General Psychopathology than their peers with lower BLLs (after adjusting for covariates, 2.30 points higher; 95%CI: -0.02, 4.62 *P*=.052).

Results from the multiple linear regressions testing associations between blood-lead at age 11 and psychopathology from ages 18-38 can be seen in Table 4. After adjusting for covariates, each 5μg/dL increase in childhood BLL was associated with a 1.34-point increase (95%CI: 0.11, 2.57, *P*=.033) in General Psychopathology. Examination of models testing associations between BLLs and factor scores for Internalizing, Externalizing, and Thought Disorder symptoms indicated that the association between BLLs and General Psychopathology was driven primarily by associations between childhood BLL and Internalizing and Thought Disorder symptoms. After adjusting for covariates, each 5μg/dL increase in childhood BLL was associated with a 1.41-point

increase (95%CI: 0.19, 2.62, *P*=.024) in Internalizing and a 1.30-point increase (95%CI: 0.06, 2.54, *P*=.040) in Thought Disorder symptoms.

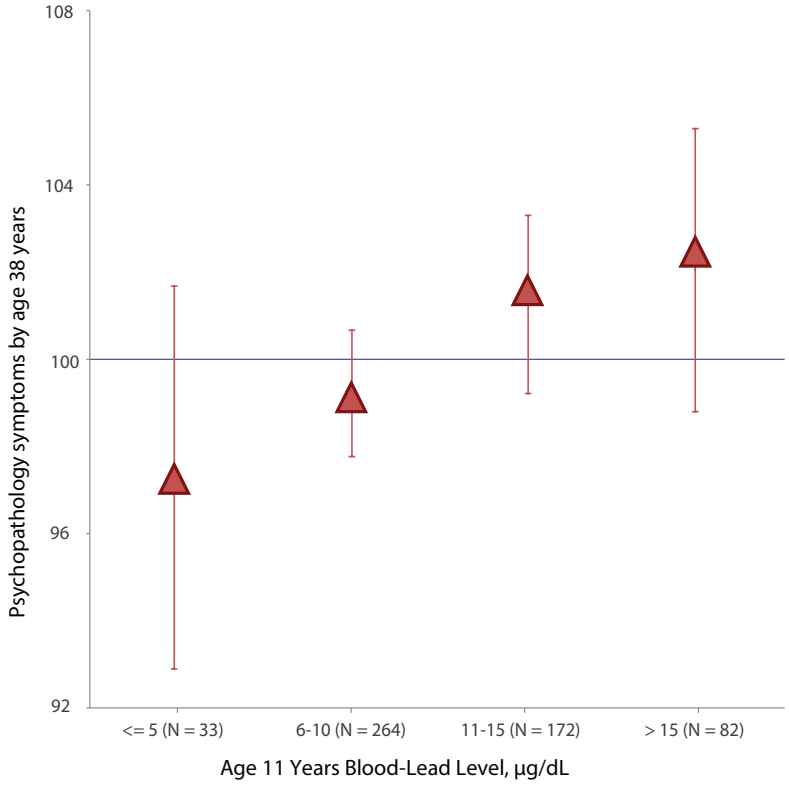

Figure 4: Association of childhood blood-lead level with adult General Psychopathology (unadjusted for covariates).

Note. Figure presents mean General Psychopathology scores in adulthood with 95% confidence intervals (error bars) for each 5μg/dL higher level of blood-lead in childhood. Each 5μg/dL higher level of blood-lead in childhood was associated with an additional 1.49-point higher score (95%CI: 0.21, 2.77, *P*=.022) in adult General Psychopathology on a scale standardized to M=100 (blue horizontal line), SD=15. Of the 579 Study participants with childhood blood-lead measured, 551 (95.2%) also had present data on all the covariates and the psychopathology outcome measures.

Table 4: Association between childhood blood-lead level and adult psychopathology symptoms assessed across ages 18 to 38 years.

	Sex adjusted			Fully adjusted		
	b	**95% CI**	***P***	**b**	**95% CI**	***P***
General psychopathology	1.49	(0.22, 2.77)	.024	.34	(0.11, 2.57)	.033
Externalizing symptoms	0.80	(-0.47, 2.06)	.211	.73	(-0.52, 1.97)	.252
Internalizing symptoms	1.57	(0.30, 2.83)	.016	.41	(0.19, 2.62)	.024
Thought disorder symptoms	1.44	(0.16, 2.72)	.030	.30	(0.06, 2.54)	.040

Note. CI = Confidence Interval. Covariates in the fully adjusted model were sex, childhood socioeconomic status, maternal IQ, and family history of mental illness. Of the 579 Study participants with childhood blood-lead measured, 551 (95.2%) also had present data on all the covariates and the psychopathology outcome measures. Regression coefficients indicate change in outcome per 5μg/dL increase in childhood blood-lead level. General Psychopathology and its constituent psychiatric spectra are standardized to M=100, SD=15.

2.2.4.2 Is lead exposure in childhood associated with adult personality differences?

Results from the multiple linear regressions testing associations between childhood BLL and our informant-reported measures of adult personality can be seen in Table 5. Consistent with our adult psychopathology results, we found that after adjustment for covariates, Study members with higher BLLs at age 11 were viewed in adulthood by their informants as more Neurotic (b=.10, 95%CI:.02, .18, *P*=.016), less

Agreeable (b=-.09, 95%CI:.-.18, -.01, *P*=.033), and less Conscientious (b=.-14, 95%CI:.-.25, -.03, *P*=.010). Associations with informant-rated Extraversion and Openness-to-Experience were non-significant.

Table 5. Association between childhood blood-lead level and adult personality traits (the Big Five) assessed by informant report across ages 26 to 38 years.

	Sex adjusted			Fully adjusted		
	b	**95% CI**	***P***	**b**	**95% CI**	***P***
Neuroticism	.10	(.02, .19)	.014	.10	(.02, .18)	.016
Extraversion	-.08	(-.17, .01)	.089	-.08	(-.17, .01)	.061
Openness to Experience	-.07	(-.16, -.003)	.166	-.07	(-.16, -.003)	.152
Agreeableness	-.09	(-.25, -.03)	.042	-.09	(-.25, -.03)	.033
Conscientiousness	-.14	(-.25, -.03)	010	-.14	(-.25, -.03)	.010

Note. CI = Confidence Interval. Covariates in the fully adjusted model were sex, childhood socioeconomic status, maternal IQ, and family history of mental illness. Of the 579 Study participants with childhood blood-lead measured, 539 (93.1%) also had present data on all the covariates and the personality outcome measures. Regression coefficients indicate change in outcome in standard deviation units per 5μg/dL increase in childhood blood-lead level. The Big Five personality traits scores are standardized to M=0, SD=1.

2.2.4.3 How early can lead-related psychiatric differences be detected?

Following the detection of significant associations between child BLLs and both a) adult psychopathology symptoms and b) adult personality difficulties, we tested whether psychiatric problems related to lead exposure could be detected as early as age 11, when BLLs were assessed. The Dunedin Study reported in 1988 that children with higher age-11 BLLs tended to score higher on concurrent, parent-report measures of hyperactivity and inattention symptoms.[21] We tested whether Study members with higher age-11 BLLs also scored higher on age-11 measures assessing a broader suite of early-life externalizing and internalizing problems, including parent and teacher-report measures of antisocial behavior, hyperactivity, and internalizing problems. We found that they did (Table 6), suggesting that that the association between lead exposure and psychopathology may begin to manifest broadly well before adulthood.

Table 6. Association between childhood blood-lead levels and concurrent child externalizing and internalizing problems assessed by parent and teacher report at age 11 years.

	Sex adjusted			Fully adjusted		
	b	**95% CI**	***P***	**b**	**95% CI**	***P***
Antisocial behavior	.11	(.03, .19)	.010	.11	(.03, .19)	.010
Hyperactivity	.17	(.08, .26)	<.001	.17	(.08, .26)	<.001
Internalizing problems	.12	(.03, .20)	.007	.12	(.03, .20)	.007

2.2.5 Discussion

This multi-decade, longitudinal analysis of the association between childhood BLLs and adult mental health and personality generated three findings. First, across nearly three decades of follow-up, childhood BLLs were associated with higher levels of General Psychopathology, driven primarily by greater rates of internalizing and thought disorder symptoms. Second, childhood BLLs were associated with higher Neuroticism, lower Agreeableness, and lower Conscientiousness. Third, childhood BLLs were associated with greater externalizing and internalizing symptoms assessed contemporaneously with blood-lead measurement, at age 11 years. Each of these findings remained significant after adjusting for participants' social class backgrounds, their mothers' IQs, and their family histories of mental illness.

These results suggest that early-life lead exposure in the era of leaded-gasoline, experienced by individuals who are today adults, may have lead to subtle, life-long differences in emotion and behavior, which are detectible at least up to age 38 years. Are these differences clinically or practically meaningful? On the one hand, the effect sizes reflecting the associations between childhood lead exposure and adult psychopathology and personality are small (around r=.08). This is about one third the size of the association seen, in the Dunedin Study, between psychopathology and other modifiable (e.g., childhood maltreatment, r=.21) and non-modifiable (e.g., family history of mental illness, r=.23) risk factors.[60] Childhood lead exposure may not be a *major* etiological factor in adult psychiatric disease today. On the other hand, compared to other findings from this sample, the associations reported here are similar to those reported for lead and IQ,[46] and are stronger than those reported for lead and criminal offending.[49] On a population basis, even modest alterations in risk can lead to significant shifts in the overall burden of disease.

The finding that associations between childhood BLLs and psychopathology symptoms were observable as early as the age of blood-lead testing suggests that lead-related alterations in emotion and behavior, however modest, likely emerge early and persist across the life-course. Notably, in childhood these psychopathology symptoms tended to involve more externalizing symptoms, particularly hyperactivity, while in adulthood they tended to involve more internalizing symptoms. This suggests that lead-

related alterations in emotion and behavior may demonstrate "heterotypic continuity" in their psychiatric presentation,[84] with either one class of psychiatric disorders creating conditions that lead to another class (e.g., when hyperactivity elicits harsh parenting it may lead to anxiety and depression), or else the same underlying condition (e.g., a general liability to psychopathology) presenting differently across different developmental windows.[60,85]

The association between childhood lead exposure and adult personality traits also suggests that lead-related differences in adult emotion and behavior can be detected not only by asking individuals to self-report on their mental health symptoms but also by simply asking informants who know them well to describe their behavior. Childhood lead exposure may alter how people behave towards or are perceived by others across their lives. The blend of adult personality traits seen in lead-exposed children has been predictive, in other studies, of a number of poor life outcomes, including greater psychopathology, worse physical health, less job satisfaction, and troubled interpersonal relationships.[64,66,86,87]

This study has limitations. First, it used a single, predominantly white cohort born in the 1970s; therefore, its results will require replication in other samples from other countries. Second, although child BLLs in this New Zealand cohort are similar to those recorded in other developed countries at the time of testing,[11,88] the high historic levels of lead-exposure experienced by Dunedin Study members may not generalize to

the relatively lower levels of exposure that are more common for children in developed countries today. Nevertheless, children in many developed and developing countries still experience high lead exposure – from contaminated water, soil, paints, and pipes.[89,90] Third, there was only one time-point of lead testing, which precluded evaluation of sensitive periods for lead effects on behavior or of the effects of cumulative lead dose by adulthood. Finally, this study is observational and does not establish a causal relationship between lead and the tested outcomes.

Despite these limitations, the present study has implications for future research, public policy, and clinical practice. For researchers, these findings add further evidence to the suggestion that environmental toxins may affect important life outcomes through subtle changes in the way individuals feel and behave. Future toxicological studies should consider assessing these subjective outcomes alongside more objective ones like physical health. For policy makers and clinicians, the findings suggest that the generation of adult patients with a history of childhood lead exposure may benefit from increased screening and access to mental-health services.[91] As the generation of lead-exposed individuals age, it is also possible that bone loss during menopause and osteoporosis may result in childhood-lead stored in bone being recirculated throughout the body, suggesting the testable hypothesis that the long-term consequences of childhood lead exposure may evolve or expand over time.[92] It is possible that

yesteryear's pediatric challenges may represent emerging concerns for geriatric psychiatry.

2.2.5.1 Conclusions

In this multi-decade, longitudinal study of lead-exposed children, higher childhood blood-lead level predicted greater psychopathology across the life-course and difficult adult personality styles. Childhood lead exposure may have long-term psychiatric and behavioral consequences.

3. The Family Level: Adverse Childhood Experiences

Above the micro-physical level, a child's larger family environment contributes uniquely to their cognitive and psychological development.[93,94] Emerging evidence suggests that childhood exposure to adversity at the family level – so-called Adverse Childhood Experiences – may contribute to poor cognitive and mental health later in life.[95–97] While a number of observational studies have linked childhood exposure to adversity with poor adult outcomes, most studies have been limited by the use of adult self-report about childhood adversity, a data source that requires individuals to have access to, and voluntarily disclose, information about family-level events from decades in the past. This chapter presents an original investigation into methodological considerations in the examination of the long-term consequences of adverse childhood experiences. Specifically, the following is an original empirical contribution that compares the differential prediction of poor mental and cognitive health, among other outcomes, using prospectively recorded as opposed to retrospectively recalled information about childhood adversity.

3.1 Comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health

The following original research report was published in the Journal of Child Psychology & Psychiatry in 2016, with the title, "Lest we forget: Comparing retrospective and prospective assessments of adverse childhood experiences in the

prediction of adult health." The authors were as follows: Aaron Reuben, M.E.M., Terrie E. Moffitt, Ph.D., Avshalom Caspi, Ph.D., Daniel W. Belsky, Ph.D., Honalee Harrington, B.A., Felix Schroeder, B.A., Sean Hogan, M.S.W., Sandhya Ramrakha, Ph.D, Richie Poulton, Ph.D., &. Andrea Danese, MD Ph.D.

3.1.1 Abstract

Background. Adverse childhood experiences (ACEs; e.g., abuse, neglect, parental loss, etc.) have been associated with increased risk for later-life disease and dysfunction using adults' retrospective self-reports of ACEs. Research should test whether associations between ACEs and health outcomes are the same for prospective and retrospective ACE measures.

Methods. We estimated agreement between ACEs prospectively-recorded throughout childhood (by Study staff at Study member ages 3, 5, 7, 9, 11, 13, and 15) and retrospectively-recalled in adulthood (by Study members when they reached age 38), in the population-representative Dunedin cohort (N=1,037). We related both retrospective and prospective ACE measures to physical, mental, cognitive, and social health at midlife measured through both objective (e.g., biomarkers and neuropsychological tests) and subjective (e.g., self-reported) means.

Results. Dunedin and CDC ACE distributions were similar. Retrospective and prospective measures of adversity showed moderate agreement (r=.47, p<.001; weighted Kappa = .31, 95% CI: .27-.35). Both associated with all midlife outcomes. As compared to

prospective ACEs, retrospective ACEs showed stronger associations with life outcomes that were subjectively assessed, and weaker associations with life outcomes that were objectively assessed. Recalled ACEs and poor subjective outcomes were correlated regardless of whether prospectively recorded ACEs were evident. Individuals who recalled more ACEs than had been prospectively recorded were more neurotic than average, and individuals who recalled fewer ACEs than recorded were more agreeable.

Conclusions. Prospective ACE records confirm associations between childhood adversity and negative life outcomes found previously using retrospective ACE reports. However, more agreeable and neurotic dispositions may respectively bias retrospective ACE measures toward underestimating the impact of adversity on objectively measured life outcomes and overestimating the impact of adversity on self-reported outcomes. Risk predictions based on retrospective ACE reports should utilize objective outcome measures. Where objective outcome measurements are difficult to obtain, correction factors may be warranted.

3.1.2 Introduction

In the quest to predict and prevent the development of hard-to-treat and costly later-life diseases, childhood has emerged as a key window of risk determination.[98] In particular, childhood exposures to adverse conditions, including abuse, neglect, and family dysfunction, have been linked to numerous physical diseases and psychological

problems.[97,99–103] These associations are hypothesized to result from alterations in health-risk behaviors (e.g., increased drug use to cope with distress) and/or physiological reactions to chronic stress.[104] They follow a dose-response relationship; exposure to more adversities forecasts poorer health.[96] Such is the concern over the consequences of childhood adversity that many states in the U.S. now monitor for childhood adversity among adults through an Adverse Childhood Experience (ACE) module, provided by the U.S. Center for Disease Control (CDC) in Behavioral Risk Factor Surveillance System surveys.[105]

To date, evidence linking ACEs with adult health comes primarily from studies that measure adults' recollections of childhood adversity. The validity of such retrospective reports has been questioned because of possible misclassification and bias. On the one hand, adult participants may not be able to retrieve episodic memory from their early years (so called infantile amnesia)[106] and may fail to correctly retrieve episodic memory from their distant past, particularly at older ages.[107] On the other hand, adult participants may be more or less likely to report childhood adversity based on individual features. For example, they may choose not to divulge intimate information to avoid distress or embarrassment.[108] Alternatively, the presence of disease, psychopathology or certain personality styles may unconsciously increase an individual's propensity to recall childhood adversity –artificially linking childhood experience and adult disease outcomes.[109–111] Although prospective measures of

childhood adversity are less sensitive to bias linked to individual features, their validity may nevertheless be limited because of other sources of misclassification including under-reporting by caregivers or under-detection by agencies.[108]

The goal of our study was to compare retrospective and prospective measures of ACEs in the prediction of later-life disease and dysfunction. Poor adult health and social outcomes have been associated with prospectively measured ACEs.[97] However, to our knowledge only one previous comparison of outcome predictions from retrospective and prospective measures of ACEs in the same sample has been undertaken.[112] Past comparisons of retrospective and prospective reports of child maltreatment raised concern that these two forms of measurement do not match and, further, do not predict outcomes equally,[113,114] although at least one study has reported low agreement between measures but similar prediction of mental-health outcomes.[115] Furthermore, evidence suggests that retrospective reports of ACEs are inconsistent over time, depending on psychological distress at the time of recall.[109] Here we compare the associations among retrospective and prospective measures of ACEs and physical, cognitive, mental and social health outcomes. Based on previous literature,[108] predicted that our prospective and retrospective ACE measures would show moderate agreement and that both would associate with later-life outcomes. We conducted our comparison in the Dunedin Study, a population-representative longitudinal birth-cohort born in the early 1970s and followed to early midlife. Prospective ACE counts were generated from dossiers that we

compiled for each Study member, which contained information drawn from Study staff assessments and observations, parent and teacher reports, and evidence of social service contacts collected at Study member ages 3, 5, 7, 9, 11, 13, and 15). Retrospective ACE counts were generated from Study member recollections of childhood adversity reported in adulthood.

In addition to potential discrepancies between retrospectively recalled and prospectively recorded ACEs, we anticipated differences in associations of ACE measures with outcomes that are objectively measured as compared to those that are measured subjectively (i.e., through self-report). Health-psychology research has documented that self-reports tend to be suffused with biases stemming from reporters' personality styles, like neuroticism, while objective measures are not.[116] We therefore tested both objective and subjective outcomes measurements.

Finally, because personality styles may also influence recall of ACEs, we tested if reporters' personality styles were associated with discrepant retrospectively recalled and prospectively recorded ACE exposures.

3.1.3 Methods

3.1.3.1 Sample

Participants are members of the Dunedin Study, a longitudinal investigation of health and behavior in a representative birth cohort. Study members (N=1,037; 91% of

eligible births; 52% male) were all of the individuals born between April 1972 and March 1973 in Dunedin, New Zealand (NZ), who were eligible based on residence in the province and who participated in the first assessment at age 3. The cohort represented the full range of socioeconomic status (SES) in the general population of New Zealand's South Island. On adult health, the cohort matches the New Zealand National Health and Nutrition Survey on key health indicators (e.g. body mass index, smoking, visits to the doctor.[24] The cohort is primarily white; fewer than 7% self-identify as having non-Caucasian ancestry, matching the demographics of the South Island.[24] Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 study members still alive took part. In the interest of reproducibility, the analysis plan for this paper was posted in advance. Study member informed consent was obtained, with study protocol approval by the institutional ethical review boards of the participating universities.

3.1.3.2 Measures

Adverse childhood experiences (ACEs).

The U.S. Centers for Disease Control & Prevention (CDC) have articulated a leading approach to conceptualizing ACEs (Felitti et al., 1998). Our measure of ACEs corresponds to the 10 categories of childhood adversity introduced by the CDC Adverse Childhood Experiences Study

(http://www.cdc.gov/violenceprevention/acestudy/prevalence.html): Five types of child harm (physical abuse, emotional abuse, physical neglect, emotional neglect and sexual abuse) and five types of household dysfunction (incarceration of a family member, household substance abuse, household mental illness, loss of a parent, and household partner violence). Because the Dunedin Study began in the early-1970s and the awareness of ACEs in the health sciences dates to the mid-1990s, Dunedin Study operational definitions of retrospective and prospective ACEs were necessarily somewhat different.

Retrospective ACE counts. The ACE Study collects retrospectively recalled ACEs via a self-report questionnaire (**http://www.cdc.gov/violenceprevention/acestudy/prevalence.html**). Our retrospective ACEs measure draws on structured interviews conducted when Dunedin Study participants were adults. Like the CDC ACE Study, we administered the Childhood Trauma Questionnaire (CTQ), which ascertains physical, sexual and emotional abuse, physical neglect, and emotional neglect; the CTQ was administered at age 38. Following the CTQ manual a specific category of harm was present if the Study member had a moderate to severe score. Study members were also interviewed about memories of exposure to family substance abuse, mental illness, and incarceration during childhood via the Family History Screen.[28] Exposure to partner violence was assessed by asking Study participants, "Did you ever see or hear about your mother/father being hit or hurt

by your father/mother/stepfather/stepmother?" We also interviewed participants about parental loss (due to separation, divorce, death, or removal from home).

Prospective ACE counts. Prospective ACE counts were generated from archival Dunedin Study records gathered during 7 biennial assessments carried out from ages 3 to 15 years. The records include: social service contacts; structured notes from assessment staff who interviewed Study children and their parents; structured notes from pediatricians and psychometricians who observed mother-child interactions at the research unit; structured notes from nurses who recorded conditions witnessed at home visits; and notes of concern from teachers who were surveyed about the Study children's behavior and performance. Separately, parental criminality was surveyed via postal questionnaire to the parents. Attrition analysis found no significant difference in exposure to ACEs between those individuals who completed the Study assessment at age 38 and those who did not (X^2 (4, N = 1034) = 7.36, p =.12). Prospective ACEs data were missing for only 3 of the 1037 cohort members.

Archival Study data were reviewed in 2015 by four independent raters who were trained on the CDC definitions of ACEs. Individual ACEs were agreed upon by at least three of the four raters 80% of time. The sole exception was emotional neglect where half the cases were identified by only two raters. Agreement across the full ACE count between the four raters ranged from kappa = .76 to .82, with an average inter-rater agreement kappa of .79.

between the four raters ranged from kappa = .76 to .82, with an average inter-rater agreement kappa of .79.

The completeness of archival Dunedin Study records of adversity varied by the type of ACE considered. Some ACEs (notably childhood sexual abuse) will have been under-detected to the extent that these experiences were not actively queried, reflecting assumptions in the 1970's that sexual abuse was exceedingly rare.[117] To ensure that potential under-detection in any ACE category did not bias the results of our analyses, we repeated the full suite of tests used in this study with each type of ACE iteratively removed from the total ACE count. As presented in the Results section, these "leave-one-out" analyses produced no significant changes to the results.

Prevalence of retrospective and prospective ACEs in the Dunedin cohort. Each ACE type was coded as present (=1) or not, with a theoretical maximum of 10 ACEs. (Following the CDC ACE Study, scores were coded 0, 1, 2, 3, or 4+ for all analyses.) Figure 5, Panel A shows a similar, zero-inflated, distribution of ACEs in the Dunedin study whether ACEs were gathered retrospectively or prospectively. The Figure also documents that the Dunedin ACE distribution resembled that of the CDC ACE Study. According to retrospective reports our cohort experienced more ACEs than they did according to our prospective records. Figure 5, Panel B shows that prospective rates were lower than retrospective rates on many, though not all, types of adversity.

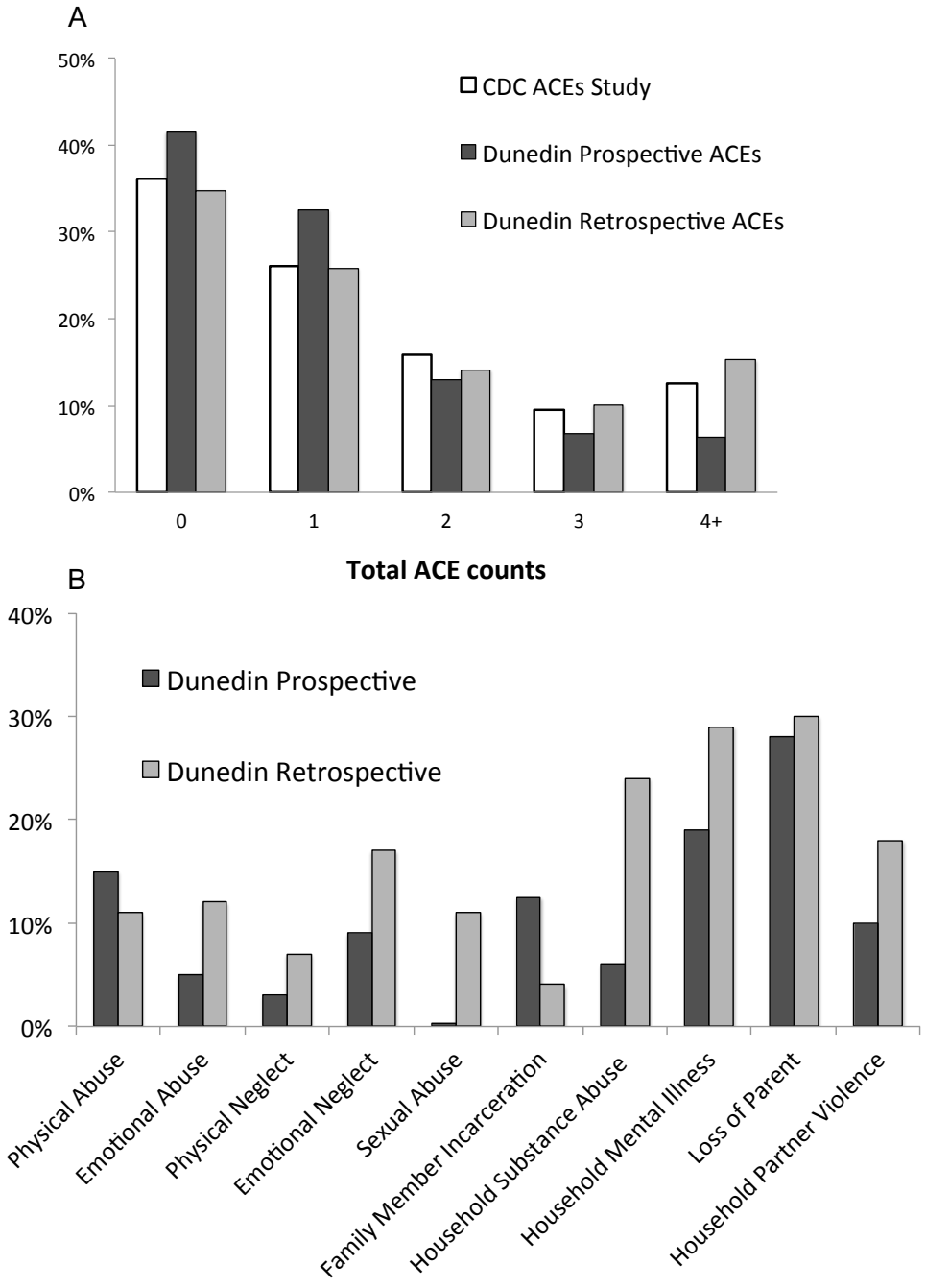

Figure 5: Distribution of ACEs in the Dunedin cohort, recorded prospectively and retrospectively, with comparison of total ACE count distributions reported in the CDC ACEs Study (Panel A) and by individual ACEs (Panel B).

We assessed four outcome domains: physical, cognitive, mental, and social health. In every domain, where possible, each outcome was measured both objectively and subjectively. Table 7 describes the outcome measures, which have been previously published in the Dunedin study.

Table 7: Health and social outcomes.

	Subjective	**Objective**
Domains		
Physical health	*Self-rated poor health*	*Biomarker-indexed poor health*
	Self-rated poor health was measured at age 38 by a 5-point scale in response to the question: "In general, would you say your health is?" Response options were "poor," "fair," "good," "very good" or "excellent".[118]	Biomarker-indexed poor health is an objective measure of physical health taken by summing nine indicators of physical health measured at age 38 including metabolic abnormalities (waist circumference, high-density lipoprotein level, triglyceride level, blood pressure, and glycated hemoglobin), cardiorespiratory fitness, pulmonary function, periodontal disease, and systemic inflammation. Details are provided in Israel et al.[119]
Cognitive health	*Complaints of cognitive impairment*	*Working memory performance on the WAIS-IV*
	Study members reported at age 38 how often in the past year (never, sometimes, or often) they experienced problems with, e.g., keeping track of appointments, remembering why they went to a store, repeating the same story to someone, multi-tasking, thinking when the TV or radio is on, word-finding difficulty, among other items based on symptom criteria for DSM-IV Mild Neurocognitive Disorder. Scores on the 19 questions were summed (score range = 0 to 31; mean (SD) = 9.1(5.3); internal consistency reliability = 0.83). The complaints score was converted to a Z-score, mean = 0, SD = 1.[120]	Working memory performance was assessed at age 38 through the Working Memory Index of the Wechsler Adult Intelligence Scale –IV (WAIS-IV) (Wechsler, 2008).[25]

Mental health	*p-factor of General Psychopathology*	
	Our measure of poor mental health is a general factor of psychopathology, the p-factor, derived from confirmatory factor analysis of symptom-level psychopathology data collected in the Study population between ages 18 and 38. Every 2 to 6 years, Study members were interviewed about past-year symptoms of DSM-defined disorders by trained non-lay interviewers. Details on the p-factor are provided in Caspi et al.[60]	Our study includes no objective measures of mental health as there are no lab tests for mental disorders.
Social health	*Poor Partner Relationship Quality*	
	Poor partner relationship quality was assessed at age 38 through a 28-item survey about shared activities and interests, balance of power, respect and fairness, emotional intimacy and trust, and open communication (α = .93).[121]	Our study includes no objective measure of partner relationship quality as this is generally measured only through self or partner/informant reports. Given the late onset of marriage and high rates of de-facto relationships, divorce is not a useful objective indicator of poor relationship.

Potentially biasing Big Five personality factors.

The Big Five were assessed at age 38 via informants. Study members nominated someone who knew them well; most were best friends, partners, or other family members, with a 97% response rate. These "informants" were mailed questionnaires asking them to describe the Study member using a brief version of the Big Five Inventory,[77] which assesses individual differences in: Extraversion (α = 0.79), Agreeableness (α = 0.75), Neuroticism (α = 0.83), Conscientiousness (α = 0.81), and Openness to Experience (α = 0.85).

3.1.4 Results

3.1.4.1 Do retrospective and prospective ACE measures agree?

Table 8 presents the correlation and agreement (Cohen's Kappa) coefficients between ACE scores measured retrospectively and prospectively. At the item level, agreement between retrospectively recalled and prospectively recorded adversities ranged from excellent (loss of parent) to poor (emotional abuse). At the scale level of total ACE count, the correlation between retrospective and prospective ACE scores was r=.47, p<.001, a moderate effect size. Precise agreement between the number of adverse experiences retrospectively recalled and prospectively recorded was fair (weighted Kappa = .31, 95% CI: .27 - .35).

Table 8: Correlation and agreement among prospective and retrospective ACE measures (N=950).

ACE	Correlation	Agreement
	Pearson's r	*Weighted Kappa*
Child Harm		
Physical abuse	.07*	.07
Emotional abuse	.03	.02
Physical neglect	.14***	.13
Emotional neglect	.07*	.07
Sexual abuse	.10**	.03
Household Dysfunction		
Family member incarceration	.16***	.14
Household substance abuse	.22***	.16
Household mental illness	.16***	.15
Loss of parent	.83***	.83
Household partner violence	.11**	.10
Total ACE count	.47***	.31

Note. *p < .05, **p < .01, ***p < .001.

3.1.4.2 Do retrospective and prospective ACE measures predict later-life health and social outcomes?

Despite only moderate agreement between retrospective and prospective ACE measures, both were associated with later-life outcomes (Table 9). Effect-sizes for associations between prospective ACEs and adult outcomes were small and relatively uniform (from *r*=.11 to *r*=.23, Table 9 Column One). In contrast, effect sizes for associations between retrospective ACEs and outcomes were more variable (Table 9 Column Three). Retrospective ACE associations with objectively measured outcomes had smaller effect-sizes as compared to associations with subjectively measured outcomes (e.g., *r*=.07 for biomarker-indexed poor physical health versus *r*=.18 for self-reported poor physical health). The largest effect-sizes were for associations between retrospective ACEs and outcomes of a more psychological nature (mental and social health; e.g., *r*=.40 for psychopathology).

Table 9: Associations of prospectively recorded and retrospectively reported counts of adverse childhood experiences (ACEs) with physical, cognitive, mental, and social health outcomes by age 38.

		Prospective ACE counts		Retrospective ACE counts	
		Unadjusted	Adjusted for Retrospective ACE Counts	Unadjusted	Adjusted for Prospective ACE Counts
	N	*Effect size (Pearson's r)*		*Effect size (Pearson's r)*	
Self-reported Outcomes					
Physical Health					
Self-reported Poor Health	950	.13*** (.07, .20)	.05 (-.02, .12)	.18*** (.12, .24)	.16*** (.09, .23)
Cognitive Health					
Self-reported Poor Memory	946	.11** (.05, .17)	.06 (-.01, .13)	.13*** (.06, .19)	.10** (.03, .17)
Mental Health					
Self-reported Psychopathology (clinical interview)	950	.23*** (.16, .28)	.05 (-.02, .12)	.40*** (.34, .46)	.38*** (.31, .44)
Social Health					
Self-reported Poor Relationship Quality[1]	844	.11** (.04, .18)	.01 (-.07, .09)	.21*** (.14, .27)	.20*** (.13, .28)
Objectively-Measured Outcomes					
Physical Health					
Biomarker-derived Poor Health	920	.11** (.04, .17)	.09* (.02, .16)	.08* (.02, .15)	.04 (-.03, .11)
Cognitive Health					
Poor Tested Working Memory	938	.15*** (.09, .22)	.15*** (.08, .23)	.07* (.01, .13)	.00 (-.07, .07)

Note. The table shows that both prospective and retrospective ACEs are related to poorer outcomes by midlife (white columns). Prospective ACE associations with all self-reported outcomes dropped to non-significance after adjusting for retrospective ACE counts while the associations with the objectively measured outcomes remained (first gray column). Retrospective ACE associations with all self-reported outcomes remained after adjusting for prospective ACE counts while the associations with the objectively measured outcomes dropped to non-significance (second gray column). *p < .05, **p < .01, ***p < .001. [1] Relationship quality was not obtained for 105 Study members who had no partner within the past year. All analyses were conducted controlling for sex. 95% confidence intervals for the effects are reported in parentheses.

3.1.4.3 Do beliefs about childhood adversity predict outcomes regardless of what adversities were prospectively recorded?

We used multivariate linear regressions to test associations between retrospective ACE counts and adult outcomes while controlling for prospective ACE counts (Table 9). For subjectively measured outcomes, retrospective ACEs remained a statistically significant predictor even after accounting for prospective ACEs. In contrast, retrospective ACE associations with objectively measured outcomes dropped to non-significance after adding controls for prospective ACEs (Table 9, Column 4). This pattern of results suggested that, regardless of what prospective childhood records indicated, individuals' beliefs that they experienced adversity appeared to be strongly related to their appraisals of their current life outcomes. The belief that one has experienced childhood adversity did not, however, necessarily relate to outcomes that were objectively measured once prospective adversities were taken into account.

3.1.4.4 Do prospectively recorded adversities predict outcomes regardless of beliefs about childhood adversity?

We used multivariate linear regressions to test associations between prospective ACE counts and adult outcomes while controlling for retrospective ACE counts (Table 9). As column two in Table 9 shows, prospective ACE associations with all subjectively measured outcomes dropped to non-significance after controlling for retrospective ACE counts. In contrast, prospective ACEs remained a statistically significant predictor of objectively measured outcomes after adding controls for retrospective counts. This

pattern of results suggested two things. First, greater adversity in childhood was followed by poorer mid-life outcomes (e.g., poorer physical and cognitive health) regardless of whether or not the adversity was remembered. Second, individuals who did not recall their prospectively recorded adversities when interviewed as adults tended not to make negative appraisals of their life outcomes.

3.1.4.5 Were findings biased by potentially missing prospective ACEs?

As noted earlier, sexual abuse may have been under-recorded in the prospective ACE data. Sexual abuse is thought to be especially harmful. To evaluate whether this under-detection could have biased associations between prospective ACEs and adult outcomes, we repeated our analyses with sexual abuse removed from the count of total retrospective and prospective ACEs. If false negatives for sexual abuse biased the prospective ACE associations with outcomes, the strength of outcome-associations for the two ACE measures should become more similar after removing sexual abuse from total ACE counts. We then also iteratively removed each additional ACE type from our total count in turn and re-ran the analyses. These leave-one-out tests did not change the results, suggesting that the overall results were unlikely to have been biased by misclassification in any of the ACEs components.

3.1.4.6 Are personality factors linked to ACE reports?

Our analysis suggested that ACE associations with adult outcomes depended on what was remembered from childhood in the case of some outcomes but not others. For objectively measured adult outcomes (e.g. health measured using biomarker indices), prospectively recorded childhood adversity that was not recalled by participants in adulthood nevertheless predicted poor adult outcomes. In contrast, prospectively recorded adversities that were not recalled in adulthood were unrelated to adult outcomes measured by subjective self-reports. This suggested that self-reports of adult outcomes could be biased by some individuals taking an overly positive view of their childhood and adulthood. Further, adversity that was recalled but not prospectively recorded predicted self-reports of poor health and memory problems that were not confirmed by objective outcome tests. This suggested that self-reports of adult outcomes could also be colored by some individuals taking an overly negative view of their childhood and adulthood.

We next tested for the potential influence of personality factors on adult ACE recall and an individual's potential discrepancy between prospective and retrospective ACE counts. To quantify this discrepancy, we subtracted each participant's prospective ACE exposure score from their retrospective ACE score to create a measure of directional divergence ranging from -10 to +10. Results showed that three personality traits were significantly linked to the discrepancy between retrospective and prospective

data: Neuroticism (r=.10, p=.004), Conscientiousness (r=-.07, p<.05), and Agreeableness (r=-.09, p<.01). As illustrated in Figure 6, individuals scoring high on Neuroticism or low on Conscientiousness were likely to have recalled more ACEs than were prospectively recorded and individuals scoring high on Agreeableness were likely to have recalled fewer ACEs than were prospectively recorded.

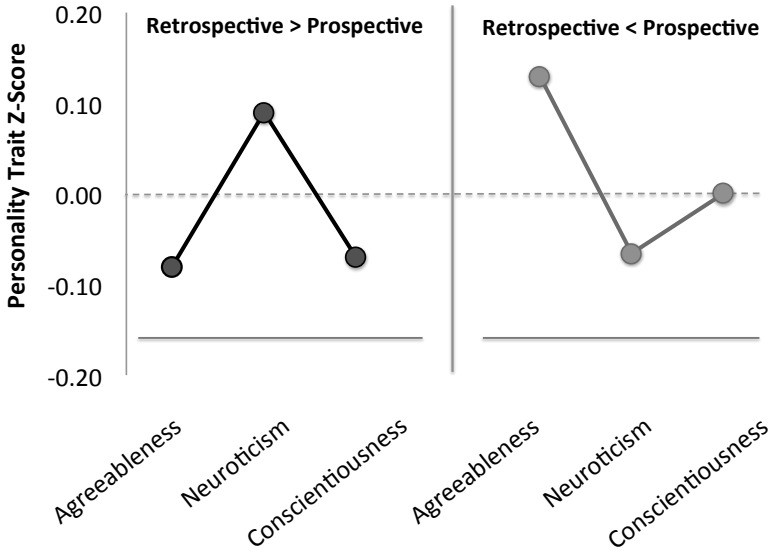

Figure 6. Personality characteristics of individuals who recall more or fewer ACEs than were recorded in their prospective records.

Note. "Retrospective > Prospective" represents individuals who recalled more ACEs than were prospectively recorded (N = 384) and "Retrospective < Prospective" represents individuals who recalled fewer ACEs than were prospectively recorded (N = 209). Analyses reported in the text are based on the complete distribution. Group means in the figure are adjusted for sex.

3.1.5 Discussion

Our longitudinal analysis of the association between ACEs and adult health outcomes revealed five findings. First, we replicated the association between retrospective ACEs and adult health outcomes reported in previous studies. In fact, when we compare our effect sizes in Table 9 to effect sizes reported in Felitti et al.'s[96] Table 8 (p.254-255) we find that they are very similar. For example, in individuals who recalled four or more ACEs, Felitti et al.[96] reported an increased risk of poor self-rated health on the order of *d* =.44 where we report *d*=.49. Second, consistent with observations from previous analyses of the agreement between prospective and retrospective measures of specific childhood adversities,[108,122] we found that prospective and retrospective ACE measures in the Dunedin cohort agreed only modestly. Such modest agreement may raise eyebrows, but it should be interpreted in context. For example, it is common in the behavioral sciences to observe modest levels of agreement between different reporters (e.g., mother and teacher reports of child ADHD symptoms typically correlate around .[123] Rather than suggesting that one reporter's information is invalid, this finding is interpreted to reflect that different reporters have access to complementary sources of information. By extension, it is possible that retrospective and prospective ACE measures may share something in common *and* also contain unique information. Modest agreement here may thus suggest that retrospective ACE measures be viewed as complementary to prospective measures, rather than as potentially invalid.

Third, notwithstanding low agreement with the retrospective measures, both retrospective and prospective ACEs predicted adult outcomes. Fourth, retrospective ACE measures, in comparison to prospective measures, more strongly predicted adult outcomes when outcomes were measured subjectively (through self-report). Fifth, prospective ACE measures, in comparison to retrospective measures, more strongly predicted adult outcomes when outcomes were measured objectively (through tests and biomarkers).

These results suggest that, relative to prospective ACE measures, retrospective ACE measures *underestimate* the influence of childhood adversity on "objective" adult outcomes and *overestimate* the influence of childhood adversity on "subjective" outcomes. This is consistent with a recent review of the limitations of retrospective recall of childhood adversity, which noted that adult psychopathology is more strongly associated with retrospective self-reports of childhood abuse than with official records of abuse.[110] The authors concluded that, "the most plausible interpretation [for this phenomenon] is that people who have more problems in adulthood look back on childhood and report more problems" **(**p.674). Our data support this conclusion across domains as diverse as physical, cognitive, mental and social health but also suggest that the opposite is true: people who do not recall problems in childhood also do not see themselves as having problems in adulthood. In our study, adult individuals with documented childhood adversity that they did not recall had objectively poorer physical

health and cognitive ability but surprisingly were unlikely to self-rate their health or memory as poor. Thus, strong associations between recalled adversity and poor self-rated health may result both from individuals who over-recall ACEs and under-rate health *and* from individuals who under-report ACEs and over-rate health. This suggests caution for interpretation; for domains where self-reports are the only means of measurement and no "objective" diagnostic tests are available, a downward correction factor may be desirable for interpreting health risks based on adult recollections of childhood adversity.

There is precedent for this finding. Past studies have found that negative mood or existing psychological dysfunction at the time of recall results in negative recollection bias[124,125] But "healthy" individuals may create biases of their own. In a comparison of clinical records with adult recollection of adversity, Robins et al.[126] found that healthy adults were "more likely to deny adverse information about early home life" than those with mental illness (p.31). The authors suggested that "those who are without current problems tend to forget and forgive." In a review of similar findings, Hardt and Rutter[108] concluded that recall bias can sometimes show "a tendency for people with good functioning in adult life to forget early parental negativity" (p.267). Colman et al.[109] asked 7,466 young adults to report on childhood adversity on two occasions separated by a twelve-year delay. They found that most participants forgot some episodes of adversity that they had originally recalled –but those with the most psychological

distress at the time of second testing "forgot" the least. Perhaps "forgetting and forgiving" can be both willful and adaptive.[127]

Our data suggest that trait-level personality may influence the process of "forgetting and forgiving." For example, we found that more neurotic individuals tend to recall more ACEs than their prospective records indicate and that more agreeable individuals tend to recall fewer ACEs than their prospective records indicate. Further, we found that an individual's recollection of their youth relates to their self-appraisals but not necessarily to their actual performance on objective tests once prospective ACE records are taken into account. Taken together these findings suggest that "grey" and "sunny" dispositions could be biasing both memories of childhood and self-appraisals of adulthood in a manner that exaggerates the predictive capacity of retrospective ACE measures**.** Further research on this phenomenon is warranted, however, as our analysis on this point was only suggestive. First, the effect sizes for personality associations with divergent ACE counts in our study were very small. Second, our design, which measured Study member personality factors potential exposure to ACEs, did not allow for the evaluation of cause-and-effect in the relationship between childhood adversity and adult personality (e.g., we are unable to disentangle the extent to which negative emotionality in adulthood is caused by childhood adversity or merely relates to the recall of adversity).

An additional contribution of our study is the finding that the imprint of childhood adversity maintains even when adversity is not recalled. We found that prospectively recorded adversity that an individual does not recall still results in demonstrable detriments to their physical and cognitive health. Critically, these detriments were only detected through "objective" tests that do not rely on self-evaluation of abilities or self-awareness of poor functioning.

We acknowledge limitations. First, we only examined ACEs as defined in the original ACE study,[96] and not "Expanded ACEs."[128,129] Second, our aggregation of ACE events across the first 15 years of life precluded testing the influence of developmental timing or duration of adversity. Third, our findings may not be representative of the recall reliability of elderly populations, who often evidence poor memory[107] and positive-event recall bias.[130] Finally, it is possible that our prospective ACE measures under-detected events of child harm, particularly sexual abuse. Our comparison of prospective and retrospective ACEs was not, therefore, a perfect one, because the mapping of the retrospective and prospective assessment was not exact. Yet, as far as we are aware, it was as complete as any other yet reported. Importantly, evidence suggests that most prospective records of childhood sexual abuse, including official court records, tend to under-detect events[108] and could benefit from the addition of retrospective measures.[131]

3.1.5.1 Conclusion

Notwithstanding its limitations, our study holds several implications. Experienced adversity, whether it is recalled or not, increases risk for poor physical and cognitive health at midlife. Psychological resilience to adversity thus may not confer physiological resilience,[132] and primary care clinics using retrospective ACE reports to screen for high-risk patients may overlook individuals at-risk from ACEs that they experienced but do not remember. Meanwhile, the strong association between recalled adversity and self-rated health and social outcomes suggests a bias of both under- and over-reporting. Future studies on the influence of recalled childhood adversity on later-life outcomes should take pains to include outcome measures that are obtained objectively. Sometimes objective measures are not available. This is especially true in the case of mental health. We would not advise clinicians to respond to reports of childhood adversity or perceived current malaise with suspicion –or for researchers to dismiss such valuable data. But neither would we advocate for uncritical acceptance of recollections of childhood as having purely causal implications for health.

The conceptualization of childhood adversity as a risk factor for later disability represents a powerful tool for identifying individuals at risk and, potentially, for developing targeted interventions. Our study confirms that the maltreatment and deprivation of the child holds implications for the adult. However, an individual's

perception of the past and present, accurate or not, plays a role as well, potentially influencing both prophesies of risk and their fulfillment.

4. The Neighborhood Level: Greenery and Socioeconomic Disadvantage

Above the level of the family, a child's neighborhood environment is also understood to play a unique role in their physical, psychological, and cognitive development.[133] While a neighborhood's overall socioeconomic status is believed to effect a moderate influence on child developmental outcomes,[134] the actual characteristics of a neighborhood that support or hinder healthy child development remain poorly characterized.[135] This chapter presents two studies that investigate the later-life cognitive and mental health implications of neighborhood characteristics, focusing on topical and timely factors important to policy makers. The first investigates the relationship between neighborhood greenery, or the amount of leafy-green vegetation growing within a neighborhood, and children's cognitive ability across childhood and adolescence. The second integrates the genomic revolution into studies of place to ask if the socioeconomic conditions of a child's neighborhood trigger epigenetic changes that may alter disease trajectories later in life.

4.1 Residential neighborhood greenery and children's cognitive development.

The following original research report was published in Social Science & Medicine in 2019 with the title, "Residential neighborhood greenery and children's cognitive development." The authors were as follows: Aaron Reuben, M.E.M., Louise Arseneault, Ph.D., Daniel W. Belsky, Ph.D., Avshalom Caspi, Ph.d., Helen L. Fisher, Ph.D., Renate M. Houts, Ph.D., Terrie E. Moffitt, Ph.D., and Candice Odgers, Ph.D.

4.1.1 Abstract

Children who grow up in neighborhoods with more green vegetation show enhanced cognitive development in specific domains over short timespans. However, it is unknown if neighborhood greenery per se is uniquely predictive of children's overall cognitive development measured across many years. The E-Risk Longitudinal Study, a nationally representative 1994-5 birth-cohort of children in Britain (n=1658 urban and suburban-dwelling participants), was used to test whether residential neighborhood greenery uniquely predicts children's cognitive development across childhood and adolescence. Greenery exposure was assessed from ages 5 to 18 using the satellite imagery-based normalized difference vegetation index (NDVI) in 1-mile buffers around the home. Fluid and crystalized intellectual performance was assessed in the home at ages 5, 12, and 18 using the Wechsler Intelligence Scale, and executive function, working memory, and attention ability were assessed in the home at age 18 using the Cambridge Neuropsychological Test Automated Battery. Children living in residences surrounded

by more neighborhood greenery scored significantly higher, on average, on IQ measures at all ages. However, the association between greenery and cognitive measures did not hold after accounting for family or neighborhood socioeconomic status. After adjustment for study covariates, child greenery exposure was not a significant predictor of longitudinal increases in IQ across childhood and adolescence or of executive function, working memory, or attention ability at age 18. Children raised in greener neighborhoods exhibit better overall cognitive ability, but the association is likely accounted for by family and neighborhood socioeconomic factors.

4.1.2 Introduction

Children who grow up in more versus less affluent neighborhoods exhibit better physical, psychological, and cognitive outcomes.[133] Neighborhood socioeconomic status is one of the most frequently measured and consistent predictors of children's outcomes, even after family-level influences are taken in to account.[134] For the most part, the specific dimensions of neighborhoods that support healthy child development remain poorly characterized.[135] Prior research has focused primarily on the influence of negative features of children's built and social neighborhood environments, including physical decay, neighborhood disorder and crime, and a lack of social cohesion.[136–138] However, intriguing new findings are emerging regarding the potential role of positive features of children's built environments on cognition and health. A number of recent studies have

reported positive associations between neighborhood greenery, or the amount of leafy-green vegetation growing within a neighborhood, and children's scores on cognitive and academic tests in urban and suburban settings.[139–148]

These findings raise the exciting possibility that children may experience cognitive benefits from spending time in or near "greenery,"[149,150] and that "greening" vegetation-deprived urban neighborhoods may result in improved cognitive outcomes for children. However, before investing in neighborhood-level interventions based on these findings, we need to ensure that identified associations are due to neighborhood greenery per se rather than to other related features of the neighborhood, or due to the self-selection of individuals into greener neighborhoods.

A number of mechanistic theories have been proposed to explain the associations found between children's exposure to neighborhood greenery and their performance on cognitive and academic tests. Strictly bio-physical theories argue that ambient vegetation improves child cognitive development by reducing environmental stressors, such as noise, heat, and air pollution, which are known to interfere with cognitive performance and learning, particularly in urban spaces with high stressor loads.[139,151–154] Bio-cognitive theories argue that green vegetation, and vegetated areas, naturally lower emotional arousal through evolutionarily-determined pathways,[152,155,156] and may encourage the restoration of cognitive resources that are otherwise required when navigating built human environments, particularly executive functions.[149,156–159] Finally,

bio-social theories argue that neighborhood "greenness" simply reflects the presence of parks and open spaces, which appear to provide children with unique environments for physical activity, risk-taking, mastery, self-regulation, and social-interaction, each of which may boost cognitive development and learning.[149,151,160]

While several studies have linked higher levels of ambient greenery surrounding schools to better school-wide test performance and in-classroom child behavior for both primary and secondary school students,[143–148,161,162] few studies have examined individual child cognitive outcomes in relation to residential neighborhood greenness. Two studies from Spain have reported positive associations between residential neighborhood greenery (measured through satellite-imagery) and child performance on attention and working memory tests, assessed cross-sectionally at ages 4-5 and 7,[140] and longitudinally across one year around age 8.[139] An additional study in the UK recently reported positive associations between residential neighborhood greenery (assessed through land use data) and child performance on a single spatial working memory task, assessed cross-sectionally at age 11 years.[142]

Here we seek to extend the emerging evidence base on the relationship between neighborhood greenery and child cognitive development using the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally-representative sample of children born in 1994-1995 in England and Wales and followed to age 18 (N=2,232 in the full cohort; Moffitt and the E-Risk Study Team, 2002). We drew on objective measures of child

neighborhood greenery (using the satellite-imagery-derived normalized difference vegetation index, NDVI) and child cognitive ability, and extend what is known about the association between neighborhood greenery and child development in three ways. First, neighborhood greenery has been related to cognitive abilities only in the specific domains of working memory and attention. Here, we include tests of fluid and crystalized intellectual performance to ask if greenery exposure relates to child cognitive ability more generally using a short-form-derived measure of overall IQ, which captures a child's ability to reason, solve novel problems, and acquire and use knowledge and information.[163] While working memory and attention abilities contribute to child success in learning and school performance,[164] the IQ represents a more global measure of ability that is known to predict outcomes of interest to policy makers and parents, including job performance and occupational attainment, physical health and longevity, and general well-being.[4,165–168] In case IQ tests are too broad to detect subtle greenery effects, executive function, working memory, and attention ability were also measured at age 18 years. Second, while previous studies have reported neighborhood greenery associations with cognitive development outcomes at individual time points in childhood[140,142] and, in one study, across one year,[139] here we leverage the E-Risk Study's longitudinal design to test cognitive associations with neighborhood greenery across the school-age years up through adolescence, from ages 5 to 18 years. Third, most epidemiologic studies of neighborhood effects attempt to control for the self-selection of

wealthier families into greener neighborhoods by applying analytic models that adjust for measures of family and neighborhood-level socioeconomic status. Here we control for both family and neighborhood socioeconomic status while also adjusting estimates for possible self-selection into greener neighborhoods by families with greater genetic predisposition toward high educational attainment and rapid cognitive development, using a polygenic score for educational attainment derived from genome-wide association studies (GWAS).[169]

This study thus sought to determine whether residential neighborhood greenery is uniquely predictive of children's overall cognitive ability at multiple ages across childhood and adolescence or with longitudinal growth in children's cognitive abilities as they develop, using high-quality measures of genetic and socioeconomic factors to adjust for the potential self-selection of children with high cognitive ability into greener neighborhoods.

4.1.3 Methods

4.1.3.1 Sample

Participants are members of the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally representative sample of children born in 1994 and 1995 in England and Wales (N=2232). Details about the sample have been reported previously (Moffitt and the E-Risk Study Team, 2002). Briefly, the E-Risk sample was constructed in 1999–

2000, when 1116 families with same-sex 5-year-old twins (93% of those eligible) participated in home-visit assessments. The full sample comprised 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs; sex was evenly distributed within zygosity (49% male). Families were recruited to represent the UK population of families with newborns in the 1990s, based on residential location throughout England and Wales and mothers' age (teenaged mothers with twins were over-selected to replace high-risk families who were selectively lost to the register through non-response. Older mothers having twins via assisted reproduction were under-selected to avoid an excess of well-educated older mothers). The study sample represents the full range of socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighborhood-level socioeconomic index (ACORN [A Classification of Residential Neighborhoods], developed by CACI Inc. for commercial use).[170] E-Risk families' ACORN distribution closely matches that of households nation-wide: 25.6% of E-Risk families live in "wealthy achiever" neighborhoods compared to 25.3% nationwide; 5.3% vs. 11.6% live in "urban prosperity" neighborhoods; 29.6% vs. 26.9% live in "comfortably off" neighborhoods; 13.4% vs. 13.9% live in "moderate means" neighborhoods; and 26.1% vs. 20.7% live in "hard-pressed" neighborhoods. E-Risk underrepresents "urban prosperity" neighborhoods because such households are likely to be childless.

Follow-up home visits were conducted when the participants were aged 7 (98% participation), 10 (96%), 12 (96%), and, most recently, 18 (93%) years. Home visits at

ages 5, 7, 10, and 12 years included assessments with participants as well as their mother (or primary caretaker); the home visit at age 18 included interviews only with the participants. Each twin participant was assessed by a different interviewer. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed consent and twins gave assent between 5–12 years and then informed consent at age 18.

As there are, on average, significant differences between urban/suburban-dwelling and rural-dwelling families in terms of neighborhood greenery and general socioeconomic trends,[135,136,171,172] for this analysis we focused only on the urban and suburban-dwelling members of the E-Risk Study (n=1658 analysis sample; 74.3% of the full cohort; 52.0% female). This matches the sample characteristics of previous studies of child residential neighborhood greenery exposure (e.g., Dadvand et al. 2015, 2017; Flouri et al. 2018), and avoids potential confounding due to gross urban/suburban vs. rural differences. Urbanicity classification was based on responses from a postal survey sent to residents living alongside E-Risk families when children were aged 12. Residents reported whether their neighborhood was in "a city," "a town," "a suburb," "a small village," or "the countryside." Urbanicity was categorized as urban (1: city/town), suburban (2: suburb), and rural (3: small village/countryside); additional details on the classification of residences in the E-Risk Study are provided elsewhere.[173] The analysis sample's ACORN distribution is similar to that of the full cohort but represents slightly

fewer "wealthy achiever" neighborhoods (19.3% of the analysis sample live in “wealthy achiever” neighborhoods compared to 25.6% in the full cohort) and slightly more "hard pressed" neighborhoods (30.2% of the analysis sample live in “hard pressed” neighborhoods compared to 26.1% in the full cohort).

4.1.3.2 Measures

Childhood neighborhood greenery exposure.

Greenery exposure was calculated through a measure of the density of ambient leafy vegetation within a 1-mile radius of the child’s home: the satellite-image-derived NDVI. Each child received an NDVI score localized to their residence at ages 5, 7, 10, 12, and 18. NDVI scores describe the ratio of near-infrared / green light to visible / red and blue light detected in a satellite image. NDVI gives a standardized measure of the “greenness” of a patch of land, as near-infrared and green light are reflected by healthy, chlorophyll-rich vegetation while visible and red and blue light are absorbed. NDVI values range from -1 to +1. Negative values typically represent clouds, snow, or water, values close to zero represent barren areas (e.g., rock, sand, buildings), and values close to one represent dense vegetation zones, like rainforests. For each home assessment year (participant ages 5, 7, 10, 12, and 18), raw MODIS (MOD13Q1) satellite images were retrieved from the U.S.-National Aeronautics and Space Administration’s EarthData registry (https://earthdata.nasa.gov/) across 16-day time series during peak vegetation periods for the Study region (August) localized to the Study members home address at

those ages. Images were resampled to a 30x30m resolution. 1-mile home radius buffers were chosen to accommodate the neighborhood activity zone of primary school age children (approximately 800m) and adolescents (up to approximately 1600m).[174–176]

To examine associations between lifelong residential greenery exposure and cognitive outcomes at ages 5, 12, and 18, and across ages 5 to 12 and 12 to 18, NDVI scores were averaged up to each age point of IQ assessment to produce an average childhood NDVI score by that age comprised of at least half of the potential observation time points whenever data was missing. A cross-sectional NDVI score was available for 1,574 children at age 5 (94.9% of the analysis sample, 51.8% female, Mean=.57, SD=.09, Range=.14 to .85), and childhood average NDVI scores were generated for 1,656 children for ages 5-12 (99.9% of the analysis sample, 52.9% female, Mean=.58, SD=.08, Range=.21 to .82) and 1651 children for ages 5-18 (99.6% of the analysis sample, 51.8% female, Mean=.55, SD=.08, Range=.21 to .82).

Childhood Cognitive Ability.

Overall cognitive ability was assessed at age 5 years using a short form of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)[177] using standard testing procedure. Using two subtests, Vocabulary (measuring crystallized ability) and Block Design (measuring fluid ability), children's age-5 IQs were computed following the procedure described by Sattler[178] (Table H-7). Overall cognitive ability was assessed again at age 12 years using a short form of the Wechsler Intelligence Scale for

Children-IV (WISC-IV) using standard testing procedure. Using two subtests, Information (measuring crystallized ability) and Matrix Reasoning (measuring fluid ability), children's age-12 IQs were computed following the procedure described by Sattler[179] (Table A-9). Overall cognitive ability was assessed a final time at age 18 years using a short form of the Wechsler Adult Intelligence Scale–IV (WAIS-IV) using standard testing procedure. Using two subtests, Information (measuring crystallized ability) and Matrix Reasoning (measuring fluid ability), children's age-18 IQs were computed following the procedure described by Sattler[180] (Table A-11). The WPPSI-R, WISC-IV, and WAIS-IV use matched scales. Executive function, working memory, and attention ability were also measured, independently, at age 18 years using the Cambridge Neuropsychological Test Automated Battery (CANTAB; http://www.cambridgecognition.com/cantab/) using standard testing procedures. Executive function was assessed through the Spatial Span subtest, which assesses the ability to hold in active memory and manipulate information about variable spatial sequences. Working memory was assessed through the Spatial Working Memory subtest, which assesses the ability to hold information about spatial location in active memory while searching for information. Attention was assessed through the Rapid Visual Information Processing subtest, which assesses sustained attentional vigilance for a target sequence within an on-going stream of digits.

Covariates.

Covariates measured at the child-genetic, family, and neighborhood level were used to account for selection effects that may influence both child cognition and exposure to greenery.

The Polygenic Score for Educational Attainment

To adjust for possible self-selection into greener neighborhoods by families of children carrying genes associated with more rapid cognitive development and higher levels of cognitive function, we turned to a polygenic score derived from a recent genome-wide association study (GWAS) of educational attainment. GWAS are large-scale data mining studies that scan common genetic variants across the entire human genome. GWAS of educational attainment have identified hundreds of variants associated with educational attainment and cognitive ability.[169] A composite measure derived from these GWAS results, called a polygenic score ,[181] can predict attainment in school, at work, and in the accumulation of wealth across life, including differences between siblings in the same family (Belsky et al. 2016, 2018). This polygenic score is also predictive of the rate of cognitive development in childhood.[182] There is also emerging evidence that this polygenic score is associated with family and neighborhood socioeconomic status.[183,184] Polygenic scores for educational attainment were created for each child of European descent (90% of full cohort, 88% of analysis sample) using the methods described below.

Genotyping – We used Illumina HumanOmni Express 12 BeadChip arrays (Version 1.1; Illumina, Hayward, CA) to assay common single-nucleotide polymorphism (SNP) variation in the genomes of cohort members. We imputed additional SNPs using the IMPUTE2 software (Version 2.3.1; https://mathgen.stats.ox.ac.uk/impute/impute_v2.html)[185] and the 1000 Genomes Phase 3 reference panel.[186] The resulting genotype databases included genotyped SNPs and SNPs imputed with 90% probability of a specific genotype among the European-descent members of the E-Risk cohort (N=1,999 participants in 1,011 families). We analyzed SNPs in Hardy-Weinberg equilibrium ($p > .01$).

Polygenic scoring – Polygenic scoring was conducted following the method described by Dudbridge [181] using the PRSice software.[187] Briefly, SNPs reported in the most recent GWAS results released by the Social Science Genetic Association Consortium [169] were matched with SNPs in the E-Risk database. For each SNP, the count of education-associated alleles was weighted according to the effect estimated in the GWAS. Weighted counts were summed across SNPs to compute polygenic scores. We used all matched SNPs to compute polygenic scores irrespective of nominal significance for their association with educational attainment.

Additional details on genotyping, imputing, and polygenic scoring are available in the Supporting Information and in Wertz et al.[188]

Family Socioeconomic Status

To adjust for possible self-selection into greener neighborhoods by families with greater socioeconomic status, family socioeconomic status (SES) was measured via a composite of parental income, education, and occupation that was divided into tertiles (i.e., low, middle, high-SES) (Trzesniewski et al. 2006). 37.15%, 32.93%, and 29.92% of the analysis sample were classified as low, middle, and high-SES respectively.

Neighborhood socioeconomic status

To adjust for possible confounding of greenery-IQ associations by socioeconomic aspects of the neighborhood environment, which may be related to the density of greenery within the neighborhood, neighborhood socioeconomic status was calculated for each Study member based on their address at ages 5, 7, 10, and 12 using the U.K. Government's 2015 Index of Multiple Deprivation (IMD; https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015) score for the address. The IMD is a linear combination of a set of relative measures of deprivation for small areas ("Lower-layer Super Output Areas") across the U.K., which are based on seven different domains of deprivation: 1) Income Deprivation, the proportion of the population experiencing deprivation relating to low income; 2) Employment Deprivation, the proportion of the working age population in an area involuntarily excluded from the labour market; 3) Education, Skills and Training Deprivation, the lack of attainment and skills in the local population; 4) Health Deprivation and Disability,

measures the risk of premature death and the impairment of quality of life through poor physical or mental health; 5) Crime, measures risk of personal and material victimization; 6) Barriers to Housing and Services, measures the physical and financial accessibility of housing and local services; and 7) Living Environment Deprivation, measures the quality of the local environment, with indicators for the 'indoors' living environment (containing measures of the quality of housing) and indicators for the 'outdoors' living environment (containing measures of air quality and road traffic accidents).

The Index of Multiple Deprivation ranks every small area in England (so-called Lower-Layer Super Output Areas, LSOA, containing approximately 650 households or 1,500 individuals) from 1 (most deprived area) to 32,844 (least deprived area). Rankings are published alongside deciles, which were used in this analysis, and were available for 2007, 2010, and 2015. There was high correlation among IMD rank scores at each available year: for example, the 2007 and 2015 IMD measures for the children's home address correlate at $r=.975$, $p<.005$. Consequently, only the 2015 IMD data, which contained a built-in postcode-to-LSOA conversion tool, were used for this study.

2015 IMD decile scores falling within a half-mile radius surrounding the child's home were averaged across ages 5, 7, 10, and 12 to create a childhood average neighborhood socioeconomic status score. The half-mile radius was chosen to match the most commonly used metrics of neighborhood poverty in the UK and the US, the Super

Output Area and the Census Block Group, respectively (each containing between 600 and 3,000 people). Average IMD scores were then used to control for neighborhood socioeconomic status in regression models examining associations between residential greenery and IQ scores at ages 12 and 18. For tests examining associations between residential greenery and IQ scores at age 5, only the age 5 IMD score was used.

4.1.3.3 Statistical analysis

Our analysis followed three steps. First, in a cross-sectional analysis, we tested the association between childhood greenery exposure and child cognitive ability measured at ages 5, 12, and 18 using full information maximum likelihood (FIML) estimated regression models to account for missing data. In an initial model, the outcome was regressed on childhood greenery exposure and sex. Each cognitive outcome was then examined using four covariate-adjusted models, including: (1) a "genetics-adjusted" model in which the outcome was regressed on childhood greenery exposure and the covariates of sex and the child's educational-attainment polygenic score, (2) a "family-adjusted" model in which the outcome was regressed on childhood greenery exposure and the covariates of sex and family socioeconomic status, (3) a "neighborhood-adjusted" model in which the outcome was regressed on childhood greenery exposure and the covariates of sex and residential neighborhood socioeconomic status, and (4) a "fully-adjusted" model in which the outcome was

regressed on childhood greenery exposure and the covariates of sex, the child's educational-attainment polygenic score, family socioeconomic background, and residential neighborhood socioeconomic status. Analyses were conducted with Mplus, Version 8.[190] Childhood average greenery exposure scores were utilized for tests involving age 12 and age 18 outcomes in order to examine the influence of cumulative greenery exposure up to that age, matching previously used methodology.[139] As a sensitivity test, these analyses were also run using cross-sectional greenery exposure scores at age 12 and 18. These tests produced similar results to those run with the cumulative childhood average exposure scores, with generally smaller effect sizes found. Only cross-sectional greenery exposure scores were available at age 5.

Second, in a longitudinal analysis, we tested the association between childhood greenery exposure and longitudinal change in child IQ from ages 5 to 12 and from ages 12 to 18 using an analysis of covariance model of IQ change. Age 5 and age 12 child IQ scores were added as covariates to each of the models specified in the first step that predicted age 12 and age 18 IQ scores, respectively. In this way greenery-IQ associations were adjusted for past IQ scores, providing a test of the relationships between cumulative greenery exposure and change in IQ between the two time-points. Additionally, to test the potential influence of longitudinal change in child greenery exposure across assessment waves, we created greenery and IQ change scores from ages 5 to 12 and from ages 12 to 18. These were calculated by subtracting age 5 greenery and

IQ scores from their corresponding age 12 scores and by subtracting age 12 greenery and IQ scores from their corresponding age 18 scores. Associations between longitudinal change in greenery exposure and longitudinal change in child IQ were examined using correlation tests.

Third, we tested the association between childhood greenery exposure and executive function, working memory, and attention ability at age 18 years, using the same initial and covariate-adjusted regression models specified in the first step.

Because the E-Risk Study contains a sample of twins, the non-independence of children within families was accounted for at each analysis step by adjusting the standard errors using the Mplus Cluster command. All results are presented in standard deviation units.

Comparing cases with present versus missing greenery exposure data. 100% of the E-Risk Study cohort was seen at age 5, 96% at age 12, and 93% at age 18. In order to best replicate past studies on greenery associations with child cognitive development[139,140,142] this study considered only urban and suburban members of the E-Risk Study; children who were rural dwelling by age 12 (n=494) or who had missing data on the measure of urbanicity (n=80) were removed from the analysis sample. Of the remaining 1,658 children, a minimum of 95% had present greenery data for each analysis. There were no statistically significant differences between those with and without greenery measurement in terms of children's cognitive abilities, their

educational-attainment polygenic scores, or their social class origins, but those children without greenery data did have lower neighborhood socioeconomic status scores (Mean neighborhood socioeconomic status for children with greenery data =.175 z-score standardized units, Mean for children without =-.335, p<.001).

All urban and suburban dwelling children were included in the analyses. FIML was used to adjust model estimates for information known to relate to the probability of missingness on study variables. FIML is a widely accepted technique for dealing with missing data[191,192] that, in most simulation studies, performs equally well to or better than multiple imputation techniques with respect to correcting bias in estimates and recovering known parameters.[193] For sensitivity tests, FIML analyses were also conducted after removing urban and suburban study members who were missing information on greenery; this did not change the results.

4.1.4 Results

4.1.4.1 Do children who grow up in greener neighborhoods score higher on overall cognitive ability tests?

Results from the multiple linear regression models testing associations between child greenery exposure and the cognitive outcomes are displayed in Table 10. Children living in greener neighborhoods tended to score slightly higher on measures of cognitive ability at ages 5, 12, and 18 (Table 10, first column), with larger associations found for crystallized cognitive ability (which measures a child's level of acquired knowledge)

than for the fluid cognitive ability (which measures a child's ability to reason and solve novel problems), at least at ages 12 and 18; overall, effect sizes were smaller for outcomes measured in adolescence (age 18) than for those measured earlier in childhood (age 5 and age 12). Differences among effect sizes were not statistically significant.

Table 10. Association of child cognitive ability with neighborhood greenery exposure measured from age 5 up to the age of IQ testing.

	Unadjusted		Adjusted for child genotype		Adjusted for family socioeconomic status		Adjusted for neighborhood socioeconomic status		Fully adjusted	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Age 5 overall IQ	.09 (.03, .16)	.006	.09 (.02, .15)	.009	.05 (-.01, .12)	.095	.02 (-.05, .09)	.560	.03 (-.04, .09)	.417
Age 5 crystallized ability	.06 (-.01, .13)	.069	.06 (-.01, .12)	.082	.03 (-.04, .09)	.379	.01 (-.06, .08)	.841	.01 (-.05, .08)	.730
Age 5 fluid ability	.09 (.03, .15)	.003	.09 (.03, .15)	.005	.06 (.00, .12)	.043	.03 (-.04, .09)	.407	.03 (-.03, .10)	.289
Age 12 overall IQ	.09 (.02, .15)	.007	.09 (.03, .15)	.004	.02 (-.04, .07)	.553	-.001 (-.07, .07)	.975	<.0001 (-.06, .06)	.999
Age 12 crystallized ability	.11 (.04, .17)	.001	.11 (.05, .18)	.001	.03 (-.02, .09)	.255	.01 (-.06, .08)	.771	.01 (-.05, .07)	.708
Age 12 fluid ability	.04 (-.02, .09)	.178	.04 (-.02, .10)	.151	-.01 (-.06, .05)	.814	-.01 (-.08, .05)	.653	-.01 (-.07, .04)	.664
Age 18 overall IQ	.06 (-.003, .12)	.062	.05 (-.01, .12)	.077	-.02 (-.07, .04)	.538	-.06 (-.12, .01)	.117	-.05 (-.11, .01)	.100
Age 18 crystallized ability	.07	.028	.07	.024	-.01	.742	-.04	.306	-.03	.292

	(.01, .14)		(.01, .14)		(-.06, .04)		(-.11, .03)		(-.09, .03)	
Age 18 fluid ability	.02	.430	.01	.662	-.03	.287	-.05	.096	-.05	.105
	(-.03, .08)		(-.03, .06)		(-.08, .02)		(-.01, .01)		(-.11, .01)	

Note. 95% confidence interval (CI) reported in parentheses. Neighborhood greenery exposure was measured by taking the average of NDVI scores within a 1-mile radius of the child's home assessed from age 5 years up to the age of IQ assessment for each outcome in the table. Neighborhood socioeconomic status was measured using the UK Government's Index of Multiple Deprivation. All models adjusted for sex. Covariates in the fully adjusted model include sex, child polygenic score for educational attainment, family socioeconomic status, and neighborhood socioeconomic status. Analyses were conducted using full information maximum likelihood (FIML) estimated regression models to adjust estimates for missing data. 205 children (12.4% of the analysis sample) lacked the educational-attainment polygenic score, 38 children (2.3%) were missing the measure of neighborhood socioeconomic status, and no children were missing the measure of family socioeconomic status. On study outcomes, 16 children (1.0% of the analysis sample) were missing the age-5 outcome variables, 84 (5.1%) were missing the age-12 outcome variables, and 136 (8.2%) were missing the age-18 outcome variables.

To test whether detected associations may be explained by the self-selection of families into greener neighborhoods, a series of adjusted models were fit to the data. First, controls for children's genetics were entered using the educational-attainment polygenic score. We have previously shown that, in the full E-Risk sample, children with higher educational-attainment polygenic scores exhibit greater overall IQ at age 5 (r=.14, 95%CI: .09, .19, p<.001) [188]. Here we found that, in the analysis sample, children with higher educational-attainment polygenic scores also tended to have higher overall IQs at age 12 (r=.24, 95%CI: .18, .30, p<.001) and at age 18 (r=.23, 95%CI: .17, .29, p<.001). However, children's educational-attainment polygenic scores were not associated with their greenery exposures across childhood (r=.03, 95%CI: -.04, .10, p=.463 by age 18). Consequently, adding the educational-attainment polygenic score to the models testing the associations between cumulative greenery exposure and the cognitive outcomes did not alter the results (Table 10, second column).

Second, we tested whether children's family socioeconomic status may explain the observed associations between greenery exposure and the cognitive outcomes. Children from higher-status families tended to live in homes surrounded by more ambient greenery; the relationship between children's family socioeconomic status and their greenery exposure increased as the children aged and more greenery assessment waves were averaged into the cumulative measure of greenery exposure (r=.12, 95%CI: .06, .19, p<.001 for family socioeconomic status and greenery exposure at age 5 and r=.18,

95%CI: .12, .25, p<.001 for family socioeconomic status and greenery exposure by age 18). Adding family socioeconomic status to the multiple regression models reduced the associations between greenery exposure and all cognitive outcomes to non-significance except for those with age-5 fluid cognitive ability (Table 10, third column).

Third, we tested whether children's neighborhood socioeconomic status may explain the observed associations between greenery exposure and the cognitive outcomes. Higher socioeconomic status neighborhoods also tended to have greater levels of ambient greenery; the relationship between children's neighborhood socioeconomic status and their greenery exposure grew stronger as the children aged and more greenery assessment waves were averaged into the cumulative measure of greenery exposure (r=.38, 95%CI: .31, .45, p<.001 for neighborhood socioeconomic status and greenery exposure at age 5 and r=.49, 95%CI: .43, .55, p<.001 for neighborhood socioeconomic status and greenery exposure by age 18). Adding neighborhood socioeconomic status to the multiple regression models reduced associations between greenery exposure and all cognitive outcomes to non-significance (Table 10, fourth column).

Fourth, all child, family and neighborhood-level potential confounds were entered into the multiple regression models simultaneously. As expected, and shown in Table 10 (fifth column), all associations between cumulative greenery exposure and the cognitive outcomes were reduced to non-significance in the final model.

4.1.4.2 Do children who grow up in greener neighborhoods display greater longitudinal change in overall cognitive ability?

We next tested whether cumulative childhood greenery exposure predicted enhanced longitudinal change in cognitive ability for our Study children across childhood and adolescence by 1) predicting age-12 IQ scores while controlling for age-5 scores, and 2) predicting age-18 IQ scores while controlling for age-12 scores. When considering change across childhood, we found that children living in greener neighborhoods scored slightly higher on measures of crystalized cognitive ability at age 12 than they did at age 5 (Table 11, first column), reflecting enhanced acquisition of knowledge relative to children living in less green neighborhoods. Children living in greener neighborhoods did not, however, demonstrate significantly more growth in full-scale IQ or fluid cognitive ability across the same ages relative to peers living in less green neighborhoods. When considering change across adolescence, we found that children living in greener neighborhoods did not tend to show greater growth on any of the IQ measures from age 12 to 18 relative to peers living in less green neighborhoods (Table 11, first column).

To test whether the detected association between cumulative greenery exposure and accelerated longitudinal growth in crystalized cognitive ability from ages 5 to 12 may be explained by the self-selection of families into greener neighborhoods, we applied the same series of adjustments to the longitudinal statistical model as for the cross-sectional analyses. First, we adjusted for the child's genetic predisposition to high

educational attainment and rapid cognitive development using the educational-attainment polygenic score. This adjustment did not reduce the size of the original association, although the p-value changed from .042 to .055 (Table 11, second column). Second, we adjusted for family socioeconomic status. This adjustment reduced the original association to non-significance (Table 11, third column). Third, we adjusted for neighborhood socioeconomic status. This adjustment also reduced the original association to non-significance (Table 11, fourth column).

Finally, as levels of neighborhood greenery are not static across time, particularly for children who move residences, we also tested whether children who experience longitudinal change in greenery exposure across IQ assessment waves displayed corresponding longitudinal change in overall cognitive ability. To do so we created greenery change scores from age 5 to 12 (by subtracting age 5 greenery scores from age 12 scores) and correlated those with IQ change scores from age 5 to 12 (created by subtracting age 5 IQ scores from age 12 IQ scores). These tests were replicated for greenery and IQ change from ages 12 to 18. We found that children whose exposure to residential neighborhood greenery changed over time did not display corresponding changes in overall cognitive ability, either from age 5 to 12 ($r=0.03$, $p=.187$) or from age 12 to 18 ($r=-.01$, $p=.846$).

Table 11: Association of longitudinal change in child cognitive ability from age 5 to 12 and from age 12 to 18 with neighborhood greenery exposure measured from age 5 up to the highest age of IQ testing.

	Unadjusted		Adjusted for child genotype		Adjusted for family socioeconomic status		Adjusted for neighborhood socioeconomic status		Fully adjusted	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Change in overall IQ from age 5 to 12 years	.01 (-.04, .07)	.607	0.01 (-.04, .07)	.858	-.02 (-.06, .03)	.477	-.03 (-.09, .03)	.325	-.02 (-.08, .03)	.392
Change in crystallized ability from age 5 to 12	.06 (.002, .12)	.042	.06 (-.001, .11)	.055	.01 (-.04, .06)	.656	.001 (-.06, .06)	.982	.01 (-.05, .06)	.846
Change in fluid ability from age 5 to 12	-0.01 (-.05, .03)	.858	-0.01 (-.06, .04)	.816	-0.03 (-.08, .02)	.301	-0.03 (-.09, .02)	.240	-0.03 (-.09, .02)	.257
Change in overall IQ from age 12 to 18 years	-0.01 (-.05, .03)	.541	-0.01 (-.05, .03)	.518	-0.03 (-.07, .01)	.128	-0.03 (-.08, .01)	.142	-0.04 (-.08, .01)	.108
Change in crystallized ability from age 12 to 18	-0.01 (-.04, .03)	.735	-0.01 (-.05, .03)	.689	-0.02 (-.06, .01)	.193	-0.03 (-.07, .02)	.224	-0.03 (-.07, .01)	.186
Change in fluid ability from age 12 to 18	-0.01 (-.06, .03)	.611	-0.01 (-.06, .03)	.623	-0.03 (-.07, .02)	.277	-0.03 (-.08, .02)	.243	-0.03 (-.08, .02)	.211

Note. 95% confidence interval (CI) reported in parentheses. Neighborhood greenery exposure was measured by taking the average of NDVI scores within a 1-mile radius of the child's home assessed from age 5 years up to the highest age of IQ assessment for each outcome in the table. Neighborhood socioeconomic status was measured using the UK Government's Index of Multiple Deprivation. All models adjusted for sex. Covariates in the fully adjusted model include sex, child polygenic score for educational attainment, family socioeconomic status, and neighborhood socioeconomic status. Analyses were conducted using full information maximum likelihood (FIML) estimated regression models to adjust estimates for missing data.

4.1.4.3 Do children who grow up in greener neighborhoods show enhanced executive function, working memory, or attention ability by age 18?

As IQ tests capture individual variability across a broad range of cognitive domains, they may not be sensitive enough to detect the modest changes in ability hypothesized to result from exposure to green-space. Therefore, we also tested the relationship between childhood green-space exposure and child cognitive ability in the specific cognitive domains of executive function, working memory, and attention ability, which were measured at age 18 using the CANTAB Spatial Span, Spatial Working Memory, and Rapid Visual Information Processing subtests, respectively. We found that children living in greener neighborhoods tended to score higher at age 18 on the Spatial Span subtest (β =.08, 95%CI: 02, .14 *p*=.007), but not on the Spatial Working Memory (β =-.02, 95%CI: -.08, .04, *p*=.488) or Rapid Visual Information Processing subtests (β =.02, 95%CI: -.04, .07, *p*=.512).

To test whether the association between cumulative greenery exposure and the Spatial Span test of executive function at age 18 may be explained by the self-selection of families into greener neighborhoods, we applied the same series of adjustments to the executive-function-outcome statistical model as for the cross-sectional and longitudinal IQ-outcome analyses. First, we adjusted for the child's genetic predisposition to high educational attainment and rapid cognitive development using the educational-attainment polygenic score. This adjustment did not reduce the original association (β =.07, 95%CI: 02, .13 p=.014). Second, we adjusted for family socioeconomic status. This

adjustment did reduce the original association to non-significance (β =.03, 95% CI: -.03, .09 p=.272). Third, we adjusted for neighborhood socioeconomic status. This adjustment also reduced the original association to non-significance (β =.002, 95%CI: -.06, .07 *p*=.960).

4.1.5 Discussion

The integration of in-home cognitive testing and satellite imagery data within a well phenotyped and genotyped cohort of children followed across childhood and adolescence advanced our understanding of the relationship between residential neighborhood greenery exposure and child cognitive development in four ways. First, similar to prior studies, we found statistically significant positive associations between children's exposure to residential neighborhood greenery and their performance on cognitive tests yielding overall IQ scores and subscale measures of crystalized and fluid cognitive ability at ages 5, 12, and 18 years. It should be noted that, similar to other neighborhood-level research findings, these associations were small (β=.08 to .11). At age 5, for example, children in the top quartile of neighborhood greenery exposure tested, on average, 3.18 IQ points higher on their overall IQ than their peers in the bottom quartile of exposure.

Second, we found no evidence that the association between greenery exposure and higher IQ scores was confounded by children's genetic propensity for high educational attainment and rapid cognitive development. In this cohort there was no

relationship between children's genetics and their exposure to residential neighborhood greenery; children with a genetic propensity for high educational attainment were not more likely to live in greener neighborhoods.

Third, we found a consistent social gradient in greenery exposure; children growing up in higher socioeconomic status families tended to live in greener neighborhoods, and the magnitude of the family socioeconomic status – greenery exposure association increased as children aged into adolescence. Statistically adjusting the greenery-IQ associations for measures of socioeconomic status attenuated all original associations to such an extent that none remained statistically significant.

Fourth, we found that, after adjusting for socioeconomic factors, children's lifelong exposure to residential neighborhood greenery did not predict longitudinal change in their IQ scores across childhood or adolescence, nor their scores on executive function, working memory, or attention tests at age 18 years.

Collectively, these results suggest that children living in homes surrounded by more vegetation and vegetated areas may tend to outperform their peers from less green neighborhoods on cognitive tests assessing acquired knowledge and the ability to reason and solve novel problems. We found no evidence to support the hypothesis that this phenomenon is the result of children with greater genetic predispositions towards rapid cognitive development living in residences surrounded by more greenery. We did find evidence to suggest, however, that this phenomenon is likely confounded by the

unequal distribution of greenery across urban and suburban neighborhoods in the UK, where families living in less deprived areas, and who have high-performing children, tend to enjoy greener residential environments (correlation between neighborhood socioeconomic status and neighborhood greenery scores ranged from r=.38 to .49). Neighborhood greenery may not, in other words, directly improve children's overall cognitive function despite the appearance of positive associations.

While socioeconomic status of the family and neighborhood fully explained the associations found between neighborhood greenery and children's overall cognitive development in this sample, our findings do not preclude the possibility that targeted greening interventions may impact other important child health and development outcomes. Controlled experiments in classroom settings suggest that children taught outdoors,[144] or given views to nature,[161] may attend to their lessons better. Likewise, a randomized neighborhood greening intervention trial in Philadelphia recently reported that greening vacant lots significantly improved the mental health of nearby residents, with the greatest effects reported for neighborhoods with the most participants living below the poverty line.[194] Further research, including randomized intervention trials, is required to understand for whom and under what conditions greenery exposure may influence cognitive outcomes.

What can explain this study's non-significant findings given the recent positive reports at the child-level from Spain[139–141] and the UK?[142] First, previous studies have

only considered the narrow cognitive domains of attention and working memory ability, using cross-sectional measures or those recorded across short time-spans. It is possible that children's residential exposure to neighborhood greenery does not fundamentally alter long-term outcomes in overall cognitive ability, even if short-term beneficial associations with subdomains of ability exist. The finding that, after adjustment for socioeconomic factors, cumulative greenery exposure did not predict executive function, working memory, or attention ability at age 18 years does suggest, however, that greenery associations with these specific cognitive abilities may not extend past the school-age years.

Second, previous child-level studies have tended to measure residential greenery exposure within smaller zones than those considered in the current study. Dadvand et al. assessed NDVI within a 250m radius of children's homes for those in living Barcelona, for example, and within 100, 300, and 500m home radii for those living in Valencia and Sabadell.[139–141] Our roughly 1600m buffer size, chosen to accommodate the neighborhood activity zone of older children,[174–176] likely gathered information about a larger geographical neighborhood space than these past studies would have. This could account for differential findings if greenery in the near-home environment exerts differential influence from greenery in the larger neighborhood, as would be the case if a view to trees matters more, for example, than the general presence of trees. Notably, a recent review of 47 studies and 260 analyses found that the likelihood of neighborhood

greenery predicting physical health increased as neighborhood buffer zone size increased, with peak associations found in buffers of between 1000-1999m in size.[195]

We acknowledge limitations. First, while NDVI is a consistently used measure of ambient vegetation exposure, it does not capture information about children's use of parks and open spaces. Measures of child park use would have improved our exposure estimates. However, this limitation is common to larger studies with sufficient power to test subtle effects, such as those on cognition. Second, while Study members' exposure to greenery was assessed repeatedly across childhood (from ages 5 to 18) we did not measure exposure before age 5. Thus, early-life greenery exposure may have been misestimated for those children who moved before age 5 or for whom residential neighborhood greenery was not stable year to year. Third, neighborhood greenery was only measured at one buffer radius (1 mile), which precluded testing for differential influence of greenery near the home versus in the wider neighborhood environment. Fourth, our measure of neighborhood socioeconomic status averaged deprivation scores across small areas in the UK, leading to possible misspecification of neighborhood status for areas with highly heterogeneous neighboring parcels. Notably, the results of the study do not change if a smaller-scale neighborhood status measure, such as ACORN, is utilized. Finally, we were not able to fully leverage the E-Risk Study's twin-pair sample to strengthen causal inference because Study twins tended to live in the same home during childhood. As the E-Risk twins move through adulthood, there will greater

opportunity to test the influence of neighborhood greenery on those who have discordant exposure – a design recently employed with participants from the University of Washington Twin Registry to identify a significant link between residential neighborhood greenery and mental health at midlife.[196]

Notwithstanding its limitations, our study may hold implications for research. First, our results indicate that childhood exposure to residential neighborhood greenery can be linked to subtle differences in overall cognitive outcomes across childhood and adolescence that are likely best explained as arising from shared relationships with family and neighborhood socioeconomic factors. While most previous studies of neighborhood greenery and cognition adjusted estimates for at least one measure of family or neighborhood-level socioeconomic status, a recent systematic review determined that few controlled for possible confounding at both levels.[150] Future research should describe the extent to which greenery exposure is entwined with participant social class and, further, attempt to adjust for possible confounding at both the family and neighborhood level whenever possible. More research that can decouple the association between affluence and greenery is particularly needed. Second, our findings suggest that child genotype, at least for rapid cognitive development and high educational attainment, may be unrelated to greenery exposure and thus unlikely to exert a confounding effect on associations with cognitive outcome tests. This suggests that while there is documented genetic selection into deprived neighborhoods for factors

related to educational attainment,[197] genetically related selection pressures may be weaker with respect to neighborhood greenery.

As conflicting findings on neighborhood effects on child cognitive ability emerge, the process of integrating these observations into a coherent theory will require an increasing focus on experimentally isolating active components and estimating causal impacts rather than simply documenting robust associations within observational studies. This study did not fully replicate the initial novel findings about neighborhood greenery and child cognitive development reported by others. Rather than a "failure to replicate," these findings can be viewed as an opportunity to explore the limits of generalizability.[198] Further research is now required to explore and experimentally test the contexts and conditions in which neighborhood greenery may be beneficial for children's cognitive development. It is appealing to believe that exposure to green vegetation and natural spaces may enhance our children's intellectual growth. Our findings highlight the need to exercise caution, however, when assuming that direct benefits arise from greenery per se, or that benefits from greenery may be uniform across populations and settings.

4.2. Childhood neighborhood socioeconomic disadvantage and DNA methylation.

The following original research report was published in JAMA Network Open in 2020 with the title, "Childhood neighborhood disadvantage and DNA methylation." The authors were as follows: Aaron Reuben, M.E.M., Karen Sugden, Ph.D., Louise Arseneault, Ph.D., David L. Corcoran, Ph.D., Andrea Danese, M.D., Ph.D., Helen L. Fisher, Ph.D., Terrie E. Moffitt, Ph.D, Joanne B. Newbury, Ph.D., Candice Odgers, Ph.D., Joey Prinz, B.A., Line J.H. Rasmussen, Ph.D., Ben Williams, B.Sc., Jonathan Mill, Ph.D., and Avshalom Caspi, Ph.D.

4.2.1 Abstract

Importance: DNA methylation has been proposed as an epigenetic mechanism by which the childhood neighborhood environment may influence the genome to compromise adult health.

Objective: To determine whether childhood neighborhood disadvantage is associated with differences in DNA methylation by age 18 years.

Design: Longitudinal-prospective study of a 1994-95 birth cohort, followed to age 18 years (until September, 2014; 93% retention). Data analysis was performed from March to June 2019.

Setting: United Kingdom.

Participants: The nationally representative Environmental-Risk Longitudinal Study (N=2,232).

Exposures: High-resolution neighborhood data (indexing deprivation, dilapidation, disconnection, and dangerousness) collected across childhood.

Main Outcomes and Measures: DNA methylation in whole blood was drawn at age 18. Neighborhood-to-methylation associations were tested using three prespecified approaches: (1) testing probes annotated to candidate genes involved in biological responses to growing up in disadvantaged neighborhoods and investigated in previous epigenetic research (i.e., stress-reactivity and inflammation-related genes), (2) polyepigenetic scores indexing differential methylation in phenotypes associated with growing up in disadvantaged neighborhoods (i.e., obesity, inflammation, and smoking), and (3) a theory-free Epigenome-Wide Association Study (EWAS).

Results: 1,619 participants (72.5% of cohort, 806[50%] female) had complete neighborhood and DNA methylation data. Children raised in disadvantaged neighborhoods exhibited differential DNA methylation in genes involved in inflammation (β=.12, 95%CI: .06, .19, p<.001) and exposure to tobacco-smoke (β=.18, 95%CI: .11, .25, p<.001) but not obesity (β=.05, 95%CI: -.01, .11, p=.123). EWAS identified multiple CpG sites at an array-wide significance level of $p< 1.16x10^{-7}$ in genes involved in the metabolism of hydrocarbons. Neighborhood-to-methylation associations were

small but robust to family-level socioeconomic factors and to individual-level tobacco smoking.

Conclusions and Relevance: Children raised in disadvantaged neighborhoods enter young-adulthood epigenetically distinct from their more advantaged peers. This may be one mechanism by which the childhood neighborhood environment influences adult health.

4.2.1 Introduction

Children raised in socioeconomically disadvantaged neighborhoods grow up to have worse health as adults than their peers from more affluent communities,[199–201] a phenomenon not fully explained by individual or family-level socioeconomic factors, or by the selection of families with more illness into poorer neighborhoods.[135,202,203] Environmentally induced alterations to the epigenome have been proposed as one potential mechanism linking early-life neighborhood environments to later-life disease and dysfunction.[204,205] While a number of studies have linked individual-level socioeconomic factors to differential DNA methylation patterns,[206–209] only a handful have evaluated whether characteristics of the wider *neighborhood environment* exert a corresponding—and independent—influence on the epigenome.

To our knowledge, seven studies have tested for DNA methylation differences among individuals living along neighborhood socioeconomic gradients.[210–215] Each reported associations between measured neighborhood characteristics and some DNA methylation targets, supporting the premise that the neighborhood environment may

influence the epigenome. These studies are not without limitations, however.[211] First, some were underpowered to detect subtle associations; of the seven studies, five had N<250. Second, most quantified DNA methylation at sites that, together, represent only a small subset of potential targets. Third, none were able to rule out the possibility that methylation differences resulted from the proximal influence of behaviors (e.g., smoking) or conditions (e.g., obesity) that characterize individuals living in disadvantaged neighborhoods.

Here we sought to replicate and expand initial reports about neighborhood characteristics and DNA methylation using the Environmental Risk (E-Risk) Study, a nationally-representative birth cohort of children born in 1994-1995 in England and Wales and followed to age 18 years.[216] This cohort was constructed to include children growing up in Britain's most disadvantaged local areas in ample numbers for research. We measured multiple aspects of the participants' neighborhoods across childhood and adolescence (indexing neighborhood deprivation, dilapidation, disconnection, and dangerousness, respectively). We then integrated neighborhood assessments with measures of DNA methylation in whole blood drawn at age 18 to test the hypothesis that children raised in more disadvantaged neighborhoods will show differential methylation patterns in young adulthood relative to their peers.

We preregistered three distinct approaches to studying neighborhood-to-methylation associations (Figure 7), including: 1) Methylation of probes annotated to

candidate genes putatively involved in biological responses to growing up in disadvantaged environments (e.g., to those involved in stress reactivity);[215] 2) Methylation of probes known to be differentially methylated in phenotypes that are associated with growing up in disadvantaged environments (e.g., obesity, inflammation, and smoking); and 3) Methylation of probes identified through an EWAS testing the association between neighborhood disadvantage and quantitative methylation measured at approximately 430,000 CpG sites on the Infinium Human 450K BeadChip.

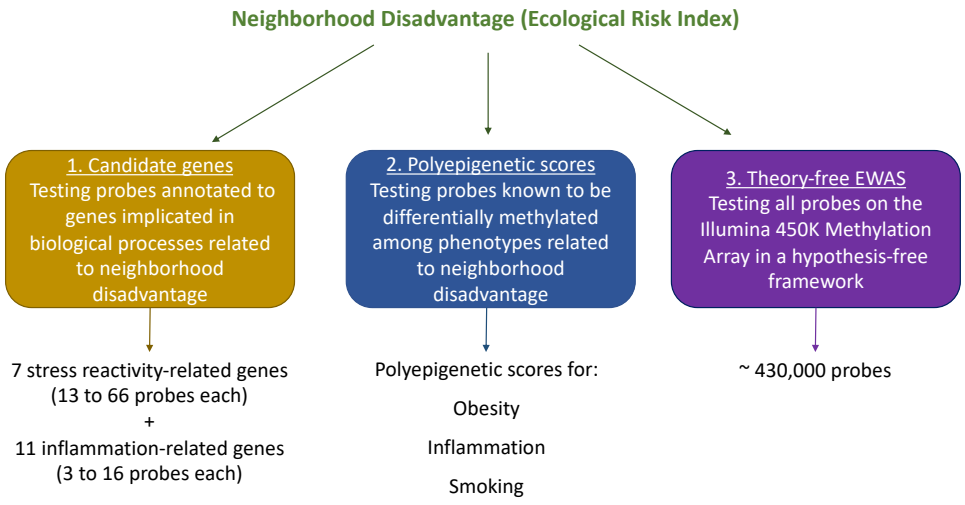

Figure 7: Analytic approach to testing the epigenetic correlates of growing up in disadvantaged neighborhoods.

4.2.2 Methods

4.2.2.1 Sample

Participants were members of the E-Risk Longitudinal Twin Study, which tracks the development of a nationally representative birth cohort of 2,232 twin children born in 1994-1995 in England and Wales and initially assessed at age 5. The full sample comprised 56% monozygotic and 44% dizygotic twin-pairs; sex was evenly distributed within zygosity (49% male). Follow-up home visits were conducted when participants were aged 7 (98% participation), 10 (96%), 12 (96%), and 18 (93%) years. The cohort's neighborhoods represent the full range of socioeconomic conditions in Great Britain. E-Risk families' addresses are a near-perfect match to the deciles of the UK government's 2015 Lower-layer Super Output Area Index of Multiple Deprivation, which ranks British neighborhoods in terms of relative deprivation at an area level of approximately 1,500 residents; approximately 10% of the E-Risk cohort fills each of the Index's 10% bands, indicating that the cohort accurately represents the distribution of deprivation in the UK. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed consent and twins gave assent between 5–12 years and then informed consent at age 18. Further details reported elsewhere.[216]

4.2.2.2 Measures

Neighborhood disadvantage (Ecological Risk Index).

Neighborhood disadvantage was measured through ecological risk assessment combining information from four independent sources of data: 1) geodemographic data from local governments; 2) official crime data from the UK Police; 3) Google Street View-based Systematic Social Observation (SSO); and, 4) surveys of neighborhood residents having the same postcode as each Study family, conducted by the E-Risk Study team (Figure 8).

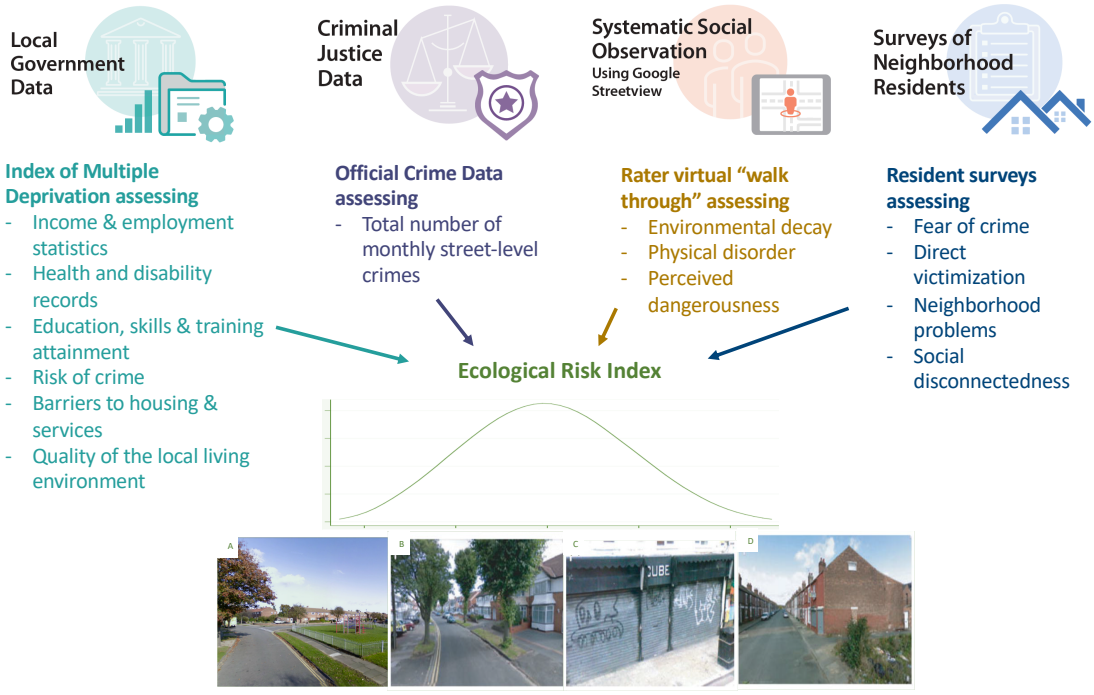

Figure 8: Assessing neighborhood disadvantage in the Environmental Risk Longitudinal Study.

Note. The figure describes the four independent data sources utilized to create the composite measure of neighborhood disadvantage, the Ecological Risk Index. Images at bottom are Google Street View demonstrations of rated neighborhood characteristics, including: (A) A well-kept neighborhood with amenities visible and sidewalks in good condition. (B) A comfortably-off residential area, with roads and sidewalks in good condition and no signs of litter or graffiti. (C) A poorly-kept neighborhood, with evidence of graffiti and street and sidewalk in only fair condition. (D) A deprived residential area, with a vacant lot in poor condition, heavy amounts of litter, and sidewalks and road in poor condition.

We used these data sources to measure four neighborhood characteristics across childhood (from ages 5 to 17 years): deprivation, dilapidation, disconnection, and dangerousness. These measures have been previously described.[217]

For each of these four characteristics, we constructed a measure of ecological risk as follows. First, variables with skewed distributions were log-transformed. Second, values were standardized to have M=50, SD=10. Finally, scores were averaged across measurement method within each domain. The resulting scales of deprivation, dilapidation, disconnection, and dangerousness were approximately normally distributed. Neighborhoods' ecological risk levels on these four measures were moderately to strongly correlated (Pearson's r=0.5-0.7). We computed the composite Ecological Risk Index by summing values across the four measures. Ecological-Risk Index values were generated for n=2,172 children (97% of the cohort).

Genome-wide quantification of DNA methylation.

Our epigenetic study used DNA from a single tissue: blood. At age 18, whole blood was collected from 82% (N=1700) of the participants in 10mL K_2EDTA tubes and assayed for 1669 participants (31 samples were not useable due to low DNA concentration). DNA methylation was quantified using the Illumina Infinium HumanMethylation450 BeadChip ("Illumina 450K array") run on an Illumina iScan System (Illumina, CA, USA). Samples from 1,658 E-Risk participants passed our QC pipeline.

4.2.2.3 Statistical analysis

We preregistered three approaches to studying neighborhood-to-methylation associations (Figure 7).

1. Candidate genes: First, we interrogated 18 candidates genes that have been studied in the most detailed report about neighborhood disadvantage and DNA methylation.[215] These include seven stress-reactivity-related genes and 11 inflammation-related genes (Table 12), with 3-66 probes annotated to each. Details about probe sequences are in the Supplementary Material. We tested associations between neighborhood disadvantage (assessed via the Ecological Risk Index) and probes annotated to these 18 candidate genes using generalized estimating equations following three steps: 1) A "basic" model in which probe methylation was regressed onto the

neighborhood Ecological Risk Index predictor and covariates of sex, methylation-array control probe principal components indexing technical variation, and cell-type proportion estimates. A gene-wide significance threshold was derived for each gene by applying a Bonferroni correction to the nominal alpha of 0.05, adjusting for number of probes tested (between 3-66) (Table 12, column 3). 2) Probes identified as gene-wide significant in the basic model were subjected to a "smoking-adjusted" model that controlled for known influence of smoking on methylation data by adding information about the 18-year-olds' tobacco pack-years-smoked.[218] 3) Probes identified as gene-wide significant in the "smoking-adjusted" model were subjected to a "family socioeconomic status-adjusted" model that added information about family social class (measured via a composite of parental income, education, and occupation).[189]

Table 12: Replication candidate stress-reactivity and inflammation-related genes, from Smith et al (2017).

Domain	Gene	# of Probes	Codes for
Involved in stress response / stress reactivity	NR3C1	42	Glucocorticoid receptor
	FKBP5	33	Regulator of the glucocorticoid receptor network
	BDNF	66	Brain-derived neurotrophic factor
	AVP	17	Neuropeptide vasopressin
	CRHR1	31	Corticotropin-releasing hormone receptor
	SLC6A4	16	Serotonin transporter gene
	OXTR	13	Oxytocin receptor
Involved in immune response / inflammation	CD1D	16	Glycoprotein lipid antigen CD1
	CCL1	8	Glycoprotein inflammatory cytokine
	F8	7	Factor VIII anti-hemophilic blood-clotting protein
	IL8	3	Interleukin 8 chemokine signaling protein
	KLRG1	8	Killer cell lectin-like receptor transmembrane protein
	LTA4H	9	Leukotriene A4 aminopeptidase bifunctional enzyme
	NLRP12	9	Cytoplasmic proteins involved in activation of inflammatory caspases
	PYDC1	13	Pyrin domain-containing protein 1, involved in suppression of kinase activity
	SLAMF7	6	Signaling lymphocytic activation molecule F7 immune cell receptor
	TLR1	11	Toll-like receptor 1, involved in identifying gram-positive bacterial infection
	TLR3.5	9	Toll-like receptor 3, involved in identifying viral infection

2. Polyepigenetic scores: Second, leveraging the observation that EWAS of DNA methylation typically identify multiple differently methylated CpG sites spread across multiple genes, we drew on previous EWAS reports about DNA methylation and obesity, inflammation, and tobacco-smoking to create composite "polyepigenetic" scores indexing the methylation correlates of these phenotypes. These phenotypes were

chosen because they represent substantial public health and economic burden, have been linked with neighborhood characteristics in prior studies, were prevalent among 18-year-olds in the UK at the time data were collected, and had been subject to large-scale EWAS. Polyepigenetic scores were calculated by averaging the product of CpG probe intensities in our data and estimated coefficients across each of the CpG probes identified as epigenome-wide significant in previous meta-analyses of obesity, inflammation, and tobacco-smoking. Scores were standardized to M=0 and SD=1. We tested associations between neighborhood disadvantage and the polyepigenetic scores using Ordinary Least Squares linear regression. Each score was examined using three models: 1) A "basic" model in which the polyepigenetic score was regressed onto the neighborhood Ecological Risk Index predictor with the covariate of sex. 2) A "phenotype-adjusted" model in which the polyepigenetic score was regressed onto neighborhood disadvantage and the covariates of sex and the age-18 phenotype relevant to the polyepigenetic score (obesity status, C-reactive protein level, and pack-years-smoked, respectively). This model was built to take into account the known influence of the phenotypes on the relevant polyepigenetic scores to determine whether neighborhood associations with the epigenome operate independently of individual health behaviors or conditions. 3) A "family socioeconomic status-adjusted" model in which the polyepigenetic score was regressed onto neighborhood disadvantage and the covariates of sex and family socioeconomic status.

3. EWAS: Third, in an EWAS, we tested the association between participants' childhood neighborhood disadvantage and their DNA methylation-status across the epigenome (i.e., on all ~ 430k probes included in our dataset from the Illumina array) using generalized estimating equations. Three modeling steps were used: 1) a "basic" model in which probe methylation was regressed on the neighborhood Ecological Risk Index predictor and covariates of sex, methylation-array control probe principal components indexing technical variation, and cell-type proportion estimates. An array-wide significance threshold of $p<1.16x10^{-7}$ was derived by applying a Bonferroni correction to the nominal alpha of 0.05, thereby adjusting for the 430,802 probes tested. 2) Probes identified as array-wide significant in the basic model were subjected to a "smoking-adjusted" model that added information about 18-year-olds' pack-years-smoked to the basic model. 3) Probes identified as array-wide-significant in the "smoking-adjusted" model were subjected to a "family socioeconomic status-adjusted" model that added information about family social class.

Because the E-Risk Study comprises twins, the non-independence of children within families was accounted for in all models by adjusting the standard errors, using the *gee* package for analyses conducted in R and the Robust Cluster command for analyses conducted in STATA. As a sensitivity test, all significant models were subjected to additional statistical adjustment for twin zygosity status (MZ vs. DZ); this did not change the results.

The premise and analysis plan for this project were pre-registered on https://sites.google.com/site/dunedineriskconceptpapers/documents. Findings reported here were checked for reproducibility by an independent data-analyst, who recreated the code by working from the manuscript and applied it to a fresh dataset.

Summary statistics of associations between neighborhood disadvantage and all DNA methylation probes on the Illumina 450K array can be downloaded and analyzed from a file available on Open Science Framework, https://osf.io/t4hkv/. Methylation values are modelled as Beta values, which reflect proportion of methylation, ranging from 0-1. The report of this study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for observational cohort studies, available at https://www.equator-network.org/reporting-guidelines/strobe/.

4.2.3 Results

The Ecological Risk Index measure of childhood neighborhood disadvantage was generated for 2,172 participants (97% of the full cohort). Blood was collected from 1,700 participants at age 18 (82% of cohort seen at that age); samples from 1,658 participants passed the QC pipeline. Statistical analyses were performed on N=1,619 participants (806[50%] female) with complete neighborhood and DNA methylation data (Table 13). There were no differences in socioeconomic background ($t(2230)=1.174$, $p=.24$) or neighborhood deprivation status (measured by the UK government Index of Multiple

Deprivation) (t(2154)=-0.893, p=.37) between participants with and without complete neighborhood and methylation data.

Table 13: Demographics of E-Risk study members with and without complete neighborhood disadvantage and DNA methylation data.

	Full Sample (N = 2,232)			With complete data (N = 1619)			Without complete data (N = 574)			Complete vs Not
Variable	No.	%	M (SD)	No.	%	M (SD)	No.	%	M (SD)	*P* Value
Sex										
Female	1,140	(51.08%)		806	(49.78%)		334	(54.49%)		
Male	1,092	(48.92%)		813	(50.22%)		279	(45.51%)		
Zygosity										
MZ	1,242	(55.65%)		916	(56.58%)		326	(53.18%)		
DZ	990	(44.35%)		703	(43.42%)		287	(46.82%)		
Family Socioeconomic Status										.24
Low	742	(33.24%)		550	(33.97%)		192	(31.32%)		
Middle	738	(33.06%)		532	(32.86%)		206	(33.61%)		
High	752	(33.69%)		537	(33.17%)		215	(35.07%)		
Neighborhood Deprivation Status	2,156		0.00 (1.00)	1564		0.01 (1.00)	592		-0.03 (0.99)	.37

Note. SD = standard deviation. Family Socioeconomic Status was measured via a composite of parental income, education, and occupation that was divided into tertiles (i.e., low(1), middle(2), high-SES(3)). Neighborhood Deprivation Status was measured via the UK government's 2015 Lower-layer Super Output Area Index of Multiple Deprivation, which ranks British neighborhoods in terms of relative deprivation at an area level of approximately 1,500 residents; approximately 10% of the E-Risk cohort fills each of the Index's 10% bands. The deprivation measure was scaled within the full cohort to M(SD)=1(0)

4.2.3.1 Is childhood neighborhood disadvantage associated with young-adult epigenetic variation in genes involved in inflammation and stress reactivity?

Children raised in more disadvantaged neighborhoods did not display gene-wide significant differences in DNA methylation on most probes annotated to stress reactivity or inflammation-related genes. Overall, across the 317 probes annotated to the 18 candidate genes, associations crossed the threshold for gene-wide significance for only one probe, annotated to the inflammation-related gene *NLRP12* (cg07042144, β=0.07, 95%CI: 0.03, 0.11, p=.001) . This association remained gene-wide significant (p<.0056) after adjustment for participants' pack-years-smoked (β=0.06, 95%CI: 0.02, 0.10, p=.003) but not after adjustment for family socioeconomic status (β=0.06, 95%CI: 0.01, 0.11, p=.02) .

4.2.3.2 Is childhood neighborhood disadvantage associated with young-adult epigenetic variation in polyepigenetic scores associated with inflammation, obesity, or smoking?

In this step we drew on published EWAS findings about three phenotypes of public-health importance that have been previously associated with neighborhood disadvantage (obesity, inflammation, and smoking). We constructed DNA methylation-based algorithms to capture manifold methylation differences in a single polyepigenetic score for each phenotype. Each resulting polyepigenetic score correlated significantly with its phenotype at age 18 in the E-Risk cohort (r=.35, 95%CI: .30, .39, p<.0001 for obesity; r=.23, 95%CI: .18, .28, p<.0001 for inflammation; and r=.45, 95%CI: .41, .49,

p<.0001 for smoking). We then tested the associations between neighborhood disadvantage and these polyepigenetic scores. Three findings stood out.

First, children raised in more disadvantaged neighborhoods did not display significantly greater obesity-related DNA methylation than their peers from less disadvantaged neighborhoods, as indexed by the obesity polyepigenetic score (β=.05, 95%CI: -.01, .11, p=.12). Second, children raised in more disadvantaged neighborhoods displayed greater inflammation-related DNA methylation than their peers from less disadvantaged neighborhoods, as indexed by the inflammation polyepigenetic score (β=.12, 95%CI: .06, .19, p<.001). Adjusting for the relevant phenotype, CRP level, did not alter the results (β=.13, 95%CI: .07, .19, p<.001). Adjusting for family socioeconomic status attenuated the effect size (to β=.07, 95%CI: .004, .15) but the association remained significant (p=.04). Third, children raised in more disadvantaged neighborhoods displayed greater smoking-related DNA methylation than their peers from less disadvantaged neighborhoods, as indexed by the smoking polyepigenetic score (β=.18, 95%CI: .11, .25, p<.001). Adjusting for the relevant phenotype, pack-years-smoked, attenuated the effect size (to β=.11, 95%CI: .05, .17), as did adjusting for family socioeconomic status (to β=.09, 95%CI: .02, .17), although the association remained significant in both cases (p<.05).

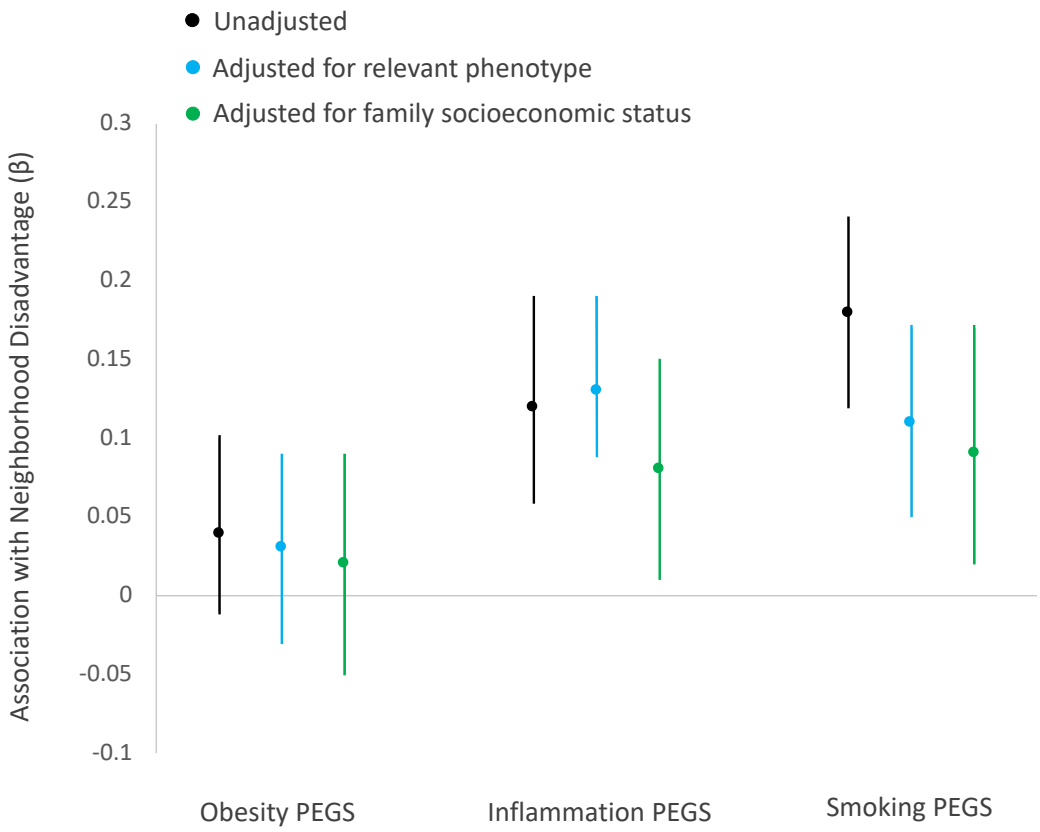

Figure 9: Association of childhood neighborhood disadvantage with polyepigenetic scores indexing the young-adult DNA methylation correlates of obesity, inflammation, and smoking.

Note. PEGS = PolyEpiGenetic Score. Error bars represent 95% confidence intervals. Polyepigenetic scores index putative DNA methylation signatures for obesity, inflammation, and smoking derived from meta-analyses of these phenotypes. All models adjusted for sex. Additional covariates in the phenotype-adjusted model included obesity status, plasma C-reactive protein level, and pack-years-smoked, respectively, for each of the relevant polyepigenetic scores. Family socioeconomic status was measured as a composite of parental income, education, and occupation.

4.2.3.3 Is childhood neighborhood disadvantage associated with young-adult epigenetic variation across the entire Illumina 450K array?

Children raised in more disadvantaged neighborhoods displayed array-wide significant differences ($p<1.16x10^{-7}$) in DNA methylation at age 18 at six positions (Figure 10, panel A) annotated to the *CNTNAP2*, *CYP1A1*, *AHRR*, and *OR4C13* genes. Of these six array-wide significant probes, three were annotated to *CYP1A1*. Notably, probes annotated to the *CYP1A1* gene accounted for eight of the top 20 most significant CpG sites, as ranked by p-value (all $<1.31x10^{-6}$). After adjustment for pack-years-smoked, three sites remained array-wide significant (Figure 10, panel B), two annotated to *CYP1A1* (cg13570656 and cg00213123) and one annotated to *CNTNAP2* (cg25949550). Two further *CYP1A1* sites (cg17852385 and cg12101586) approached the significance threshold with p-values of $1.23x10^{-7}$ and $1.37x10^{-7}$ respectively. These five probes remained significant after adjustment for family socioeconomic status, although effect sizes of the associations were attenuated. As *CNTNAP2* and *CYP1A1* have been previously associated with maternal smoking while pregnant,[219] we applied additional post hoc adjustment for maternal smoking to these five probes. The size of the associations with neighborhood disadvantage was attenuated but all probes remained significant.

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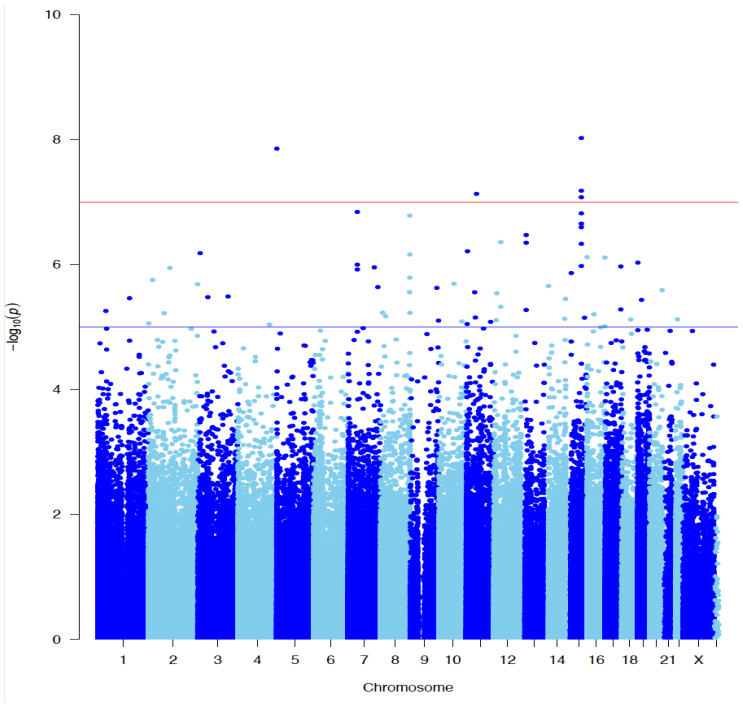
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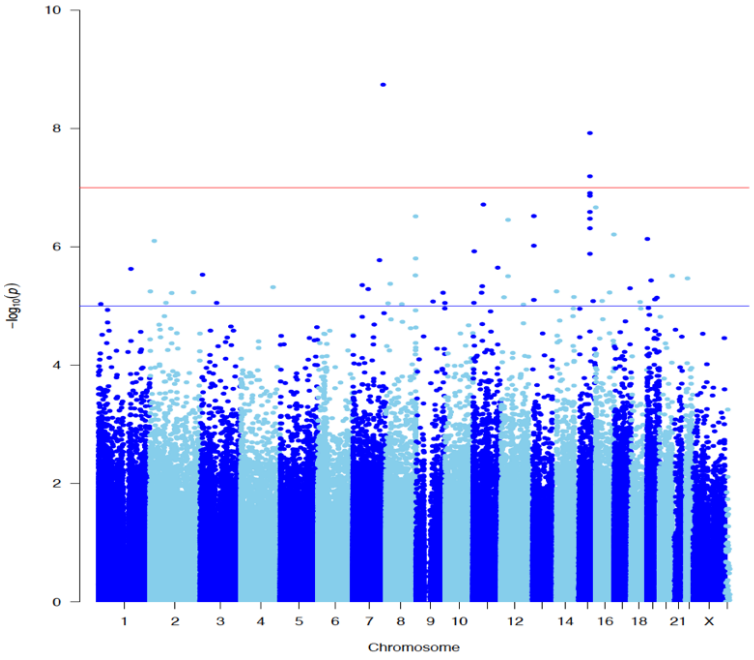
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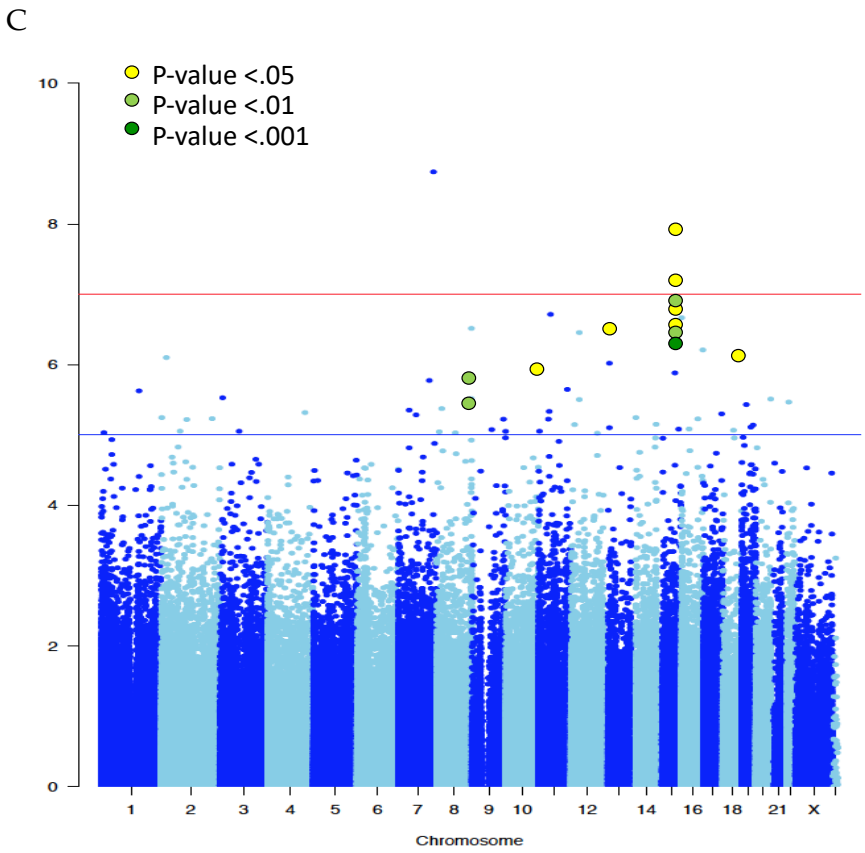

Figure 10: Association of childhood neighborhood disadvantage with epigenome-wide DNA methylation at age 18.

Note. In panel A, associations with six probes passed the array-wide multiple testing threshold ($p<1.16x10^{-7}$; red line), three of which were annotated to the *CYP1A1* gene on chromosome 15. 66 probes passed the "suggestive" significance threshold ($p<1.0x10^{-5}$; blue line). In panel B, associations with three probes remained significant after adjustment for smoking status, two annotated to *CYP1A1* and one annotated to *CNTNAP2*. A further two probes annotated to *CYP1A1* approached array-wide significance (p-values of $1.23x10^{-7}$ and $1.37x10^{-7}$ respectively) in the smoking-adjusted model. 59 probes passed the "suggestive" significance threshold, including 8 annotated to *CYP1A1*. Panel C presents the smoking-adjusted associations with additional notation about probe associations with air pollution exposure. Large circles notate the top probes that were also significantly associated with NO_x air pollution exposure, with darkening color indicating smaller p-values for the association. Of of the top 20 probes from the smoking-adjusted EWAS of neighborhood disadvantage, 12 were also significantly associated with NO_x air pollution exposure at the alpha=.05 level, four at the .01 level, and one at a level corrected for multiple testing of 20 tests, p<.0008.

4.2.3.4 Is air pollution implicated in young-adult epigenetic differences associated with neighborhood disadvantage? An exploratory secondary analysis.

The *CYP1A1* gene encodes a member of the cytochrome P450 superfamily of monooxygenase enzymes that is specifically involved in the metabolism of polycyclic aromatic hydrocarbons (PAH),[220] the toxic byproducts of organic material combustion found in cigarette smoke and emissions from residential heating, coke production, waste incineration, and internal combustion engines.[221] Following the primary EWAS finding of associations between neighborhood disadvantage and multiple probes annotated to the *CYP1A1* gene that survived adjustment for study members' tobacco-smoking and prenatal exposure to smoking, we designed post hoc exploratory follow-up analyses to test the hypothesis that toxic air pollutants other than cigarette smoke are associated with differential methylation in *CYP1A1* across neighborhoods.

We utilized two measures of annual air pollution exposure estimated for the E-Risk Study members at age 17: exposure to nitrogen oxides (NO_x), a regulated gaseous pollutant composed of nitrogen dioxide and nitric oxide, and exposure to fine particle pollution, $PM_{2.5}$, a regulated aerosol pollutant with suspended solid and liquid particles smaller than 2.5 microns in diameter. Hourly pollution exposure estimates were modeled down to individual streets on which E-Risk participants lived and spent the majority of their time and averaged to estimate mean pollutant level exposure across one year, 2012, preceding the age-18 assessment of E-Risk participants. While not direct measures of PAH, NO_x and $PM_{2.5}$ represent byproducts of the incomplete combustion of

organic material, with NO_x linked, in particular, to common PAH sources.[221] On average, Study member exposure to NO_x (mean annual level = 25.71μg/m^3, SD=16.28) fell within World Health Organization (WHO) guidelines for NO_2 (40μg/m^3), a component of NO_x, while exposure to $PM_{2.5}$ (mean annual level = 11.24μg/m^3, SD=2.18) exceeded WHO guidelines (10μg/m^3). Levels of both pollutants were higher in more disadvantaged neighborhoods (r=.32, p<.001 between neighborhood disadvantage and exposure to NO_x, and r=.22, p<.001 between neighborhood disadvantage and exposure to $PM_{2.5}$).

Using Ordinary Least Squares multiple regression, we tested the association of the top 20 differentially methylated probes identified in the smoking-adjusted EWAS of neighborhood disadvantage, as ranked by p-value, with estimates of participants' exposure to NO_x and $PM_{2.5}$. With NO_x, associations for 12 of the top 20 probes achieved significance at the alpha=.05 level, 4 at the .01 level, and one at a level corrected for multiple testing of 20 tests, p<.0008 (Figure 10, panel C). With $PM_{2.5}$, associations for 3 of the top 20 probes achieved significance at the alpha=.05 level, two at the .01 level, and none at a level adjusted for 20 tests, p<.0008.

4.2.4 Discussion

This longitudinal study of the association between childhood neighborhood disadvantage and young-adult DNA methylation revealed three findings. First, children raised in more disadvantaged neighborhoods did not, when compared to their peers,

display any significant pattern of differential DNA methylation among probes indexed to candidate genes tested in previous epigenetic research on neighborhood effects. This represents a failure to replicate in a young-adult sample a previous report about DNA methylation among older adults (aged 45-84 years) living in disadvantaged neighborhoods.[215] This failure may reflect differences in accumulated epigenetic burden between those who have lived in disadvantaged neighborhoods for a short time (18 years or less) versus multiple decades. It likely does not result from differences in power, as this study had a larger sample than Smith et al.[215]

Second, children raised in more disadvantaged neighborhoods displayed greater DNA methylation associated with inflammation and tobacco-smoking, but not to obesity. This represents a partial replication of previous reports.[215] Notably, these results held even after adjustment for inflammation and smoking phenotypes, respectively. Three hypotheses could explain this finding: 1) Epigenetic signatures of inflammation and smoking in the absence of elevated CRP-levels and smoking behavior could indicate the historical trace of a former phenotype that is no longer present; 2) It could indicate a future condition that is yet to emerge, to the extent that these epigenetic signatures are not outcomes but causes; 3) It could indicate the presence of phenotypes associated with inflammation and smoking that were not observed in this study, such as non-CRP-related inflammation and non-tobacco-smoke-related air pollutant exposure. We are unable to empirically adjudicate between these possibilities.

Third, in a hypothesis-free EWAS, 18-year-olds raised in more disadvantaged neighborhoods displayed differential methylation of probes annotated to the *CNTNAP2* and *CYP1A1* genes. Adjustment for tobacco-smoking, family socioeconomic status, and in utero exposure to maternal smoking reduced the size of these associations but did not account for them entirely. *CYP1A1* is putatively involved in the metabolism of PAH found in cigarette smoke and ambient outdoor air pollution. Exploratory follow-up tests using two measures of air pollutant exposure (NO_x and $PM_{2.5}$) identified significant associations between neighborhood disadvantage-related probes, particularly at the *CYP1A1* gene, and adolescents' exposure to air pollution. Air pollution may contribute to epigenetic differences among young adults raised in different neighborhoods. Notably, *CYP1A1* is believed to encode an enzyme specifically involved in the activation of PAH carcinogenic intermediates;[27220,222] the gene's activity has consequently been linked to risk for lung cancer following PAH exposure.[222–224] As there is evidence to suggest the EWAS-identified *CYP1A1* probes are located within a *CYP1A1* gene enhancer region,[225] differential expression of the *CYP1A1* gene may represent a pathway linking the childhood neighborhood environment to risk of disease in adulthood.

This study has a number of limitations. First, we used DNA only from blood. Our findings may not generalize to other tissues. Second, across all probes on the array, effect sizes were small. In the top 20 EWAS-identified probes, study members raised in the least disadvantaged neighborhoods (bottom 10% on the Ecological Risk Index)

displayed, on average, between one and four percent difference in DNA methylation from study members raised in the most disadvantaged neighborhoods (top 10% on the Ecological Risk Index). Differences of this size may not have practical biological effects, although small shifts in methylation can have meaningful influence at the cell level.[226] Third, while the availability of air pollution exposure data allowed for exploratory follow-up tests, there was no direct measure of PAH exposure or of air pollution exposure across childhood. Our air pollution findings should be considered suggestive. Fourth, this study took place in only one cohort in one country. To encourage replication in other settings, particularly among other longitudinal studies of children and adolescents, we have made our results available on Open Science Framework (https://osf.io/t4hkv/) and encourage replication. Finally, our study was observational and does not establish causation.

To our knowledge, this is the largest and most comprehensive test of the hypothesis that epigenetic regulation may be one biological pathway through which neighborhood disadvantage "gets under the skin" to engender long-term health disparities. If confirmed, our findings suggest that policy interventions at the neighborhood-level could influence long-term child health trajectories. We found evidence that neighborhood disadvantage is associated with DNA methylation differences in genes involved in inflammation, exposure to tobacco-smoke, and metabolism of toxic air pollutants. Collectively, these results suggest that children raised

in disadvantaged neighborhoods enter adulthood epigenetically distinct from their more advantaged peers.

5. Conclusion: Adult Disease May Begin in Childhood

This dissertation involving five empirical studies in two multi-decade longitudinal population-representative cohorts produced several novel findings. First, in support of the DOHaD hypothesis, we found that negative early life events at micro-physical, family, and neighborhood-levels associated, across a long-time span, with subtle and diverse poor outcomes later in life. In the studies comprising this dissertation's chapters, adults exposed to lead as children demonstrated mild cognitive deficits relative to their peers and lower social standing (Chapter 1), adults exposed to childhood adversity demonstrated poorer mental, cognitive, physical, and social health (Chapter 2), and young adults raised in socioeconomically disadvantaged neighborhoods demonstrated epigenetic differences from their more advantaged peers (Chapter 3).

Second, we found that some poor outcomes from negative early life events arrive contemporaneously and persist, while others appear to develop over time, only emerging later in life or else manifesting to a greater degree as time passes. This phenomenon was most pronounced in the studies of childhood lead exposure. In the Dunedin Study blood-lead levels were assessed at age 11 years. At this time, children with greater blood-lead levels tended to display more hyperactivity and inattention,[21] antisocial behavior, and internalizing problems – symptoms of mental disorder that persisted, with some heterogenous continuity, into adulthood (Chapter 1). Despite signs

of mental illness, lead-exposed Dunedin Study members did no demonstrate cognitive deficits relative to their peers at age 11 years.[21] By age 38, however, cognitive deficits had emerged on the order of several IQ points, on average, for the most lead-exposed children compared to the least. Longitudinal tests determined that these adult IQ deficits represented longitudinal decline from childhood.

Third, in evaluating hypotheses about cause and effect over many decades, we found that the style of exposure and outcome measurement matters. Adults exposed to adversity in childhood may be unable or unwilling to recall this adversity, for example, leading to potential exposure miss-classification. However, even the best prospective measures of childhood adversity exposure can potentially undercount events that are hard to detect or, as was the case in the Dunedin Study (Chapter 3), were not directly assessed (e.g., sexual abuse). After examining the results of tests predicting adult outcomes following childhood adversity, we determined that retrospective and prospective measures of childhood events may be complementary, sharing something in common *and* also containing unique information. Of relevance to the DOHaD hypothesis, both were found to be predictive of poor outcomes, although with different effect sizes based on the style of outcome measurement. The finding that retrospective and prospective measures may be complementary was echoed in the conclusions of a systematic review and meta-analysis on the same topic, which was conducted following the study reported in this dissertation.[227] Despite being complementary, however, we

also found that retrospective and prospective reports may be differentially influenced by personality factors, with individuals' personality traits potentially influencing their propensity to self-report adversity. This led to the additional conclusion that when forced to rely upon self-reported exposure data, epidemiological studies should strive to include objective outcome measures in order to avoid common-method bias inflated by the personality style of reporters.

Fourth, across this suite of observational studies, we found that the issue of socioeconomic confounding must never be overlooked, particularly when moving across micro-physical, family, and neighborhood-levels of measurement and analysis. On the one hand, the lack of a socioeconomic gradient in childhood lead-exposure found among members of the Dunedin Study (Chapter 1) made this cohort globally unique and uniquely well-positioned to test causal hypotheses about the long-term consequences of early life exposure.[228] On the other hand, the relatively large association between residential neighborhood greenery and family-level socioeconomic status found among members of the E-Risk Study (Chapter 3) made this cohort potentially ill-equipped to test causal hypotheses about green-space and cognitive ability. While we found that children raised in greener neighborhoods performed better on cognitive tests across childhood and adolescence than their peers raised in less green neighborhoods, statistical adjustment for measures of family and neighborhood-level socioeconomic status broadly attenuated these associations to practical and statistical non-significance.

This represented a failure to replicate several heralded studies from Spain,[229–231] where the contexts surrounding neighborhood greenery may be less entwined with social class (or, potentially, equally entwined and less well-controlled-for).

Finally, the outcomes found by the studies comprising this dissertation to follow from negative early life events – e.g., diminished cognitive capacity, increased symptoms of psychopathology, altered epigenetic controls, disadvantageous personality styles, and worse physical health – carry great costs to the individual and, collectively, to society.[4] A good deal of further evidence is still needed to inform questions about mechanisms of effect, potentially moderating individual, family, and neighborhood factors, and avenues for intervention. However, our results collectively reinforce the consideration, now growing among researchers from diverse disciplines, that the early life represents a profound window of vulnerability and opportunity, with potentially lasting implications for lifelong health, wealth, and happiness. If anything, these findings most reinforce the importance of taking a lifespan perspective towards health research, clinical practice, and public policy, as the diseases of the adult likely have roots in the life of the child.

6. References

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7. Biography

Aaron Reuben holds a bachelor's degree in Neuroscience & Behavior and English Literature from Wesleyan University (2007) and a Masters in Environmental Management from Yale University (2012). His research focuses on the link between environmental health and human psychology, cognitive health, and aging. He has worked as a study coordinator for Columbia University's Taub Institute for Research on Alzheimer's Disease and the Aging Brain, a science communications officer for the International Union for Conservation of Nature, a research associate at the Yale Center for Environmental Law & Policy, and a presidential policy intern at the White House Council on Environmental Quality. At Duke University Aaron has studied longitudinal observational research methods under the mentorship of Drs. Terrie E. Moffitt and Avshalom Caspi. He has published original empirical work in numerous academic journals including *JAMA*, *JAMA Psychiatry*, *JAMA Pediatrics*, *the Journal of Alzheimer's Disease*, *Atmospheric Environment*, *Social Science & Medicine*, and the *Journal of Child Psychology and Psychiatry*, among others. Aaron has also contributed new science writing about nature, psychology, and public health to magazines including *Scientific American*, *Outside Magazine*, *Wired*, and *the Atlantic*, among others. His work has been supported by the Berkley Conservation Program, Middlebury College's Environmental Journalism Fellowship Program, the James B. Duke Fund, the City University of New York's Journalism School, and the U.S. National Institute of Environmental Health Sciences. Aaron holds the Richard Merritt Jr. Memorial Award for Excellence in Science Journalism from Duke University and is a member of the International Society for Environmental Epidemiology, the American Psychological Association, and the National Association for Science Writers. He plans to pursue an academic research career in neuropsychology and environmental epidemiology.