Adverse Childhood Experiences (ACEs) and mRNA Aging Signature

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Abstract

Exposure to Adverse Childhood Experiences (ACEs) is linked to mortality and several forms of morbidity although the mechanism through which these associations emerge is still not well understood. Using recently-collected mRNA abundance data in Wave V of the National Longitudinal Study of Adolescent to Adult Health, this study examines how ACEs are related to gene expression markers of biological aging. We test the hypothesis that the experience of adversities early in life correlates with a mRNA expression marker of biological age. The analyses focus on social trajectory and cumulative exposure models, taking into account adult socioeconomic attainment and health behaviors. Preliminary results show an association between ACEs and mRNA aging signature. Accelerated aging is associated both with ever experiencing one of the ACEs as well as with the number of negative events. Further analysis will examine the pathways from ACEs to health in mid-adulthood through a differential gene expression analysis.

Introduction

Adverse Childhood Experiences (ACEs) are associated with poor health outcomes, including increased mortality in the United States and globally (Ferraro et al. 2016; Hughes et al. 2017). Among individuals who have experienced ACEs, diseases with higher incidence include cancer, diabetes, coronary heart diseases, and respiratory diseases. However, the social and biological pathways through which these harmful health outcomes emerge are still unclear. One hypothesis is that ACES alter genetic expression; ACES could also alter expression via social signal transduction pathways that results in changes in transcription factor binding motifs, which likely accounts for the majority of variance in gene expression patterns. The present analysis links ACEs and poor health in later life using one of the largest mRNA abundance datasets in United States (US). In this extended abstract we focus on an mRNA signature associated with biological ageing developed by Peters et al. (2015). Two models are used to elucidate the theoretical mechanisms through which the experience of adverse childhood conditions could affect later life health. First, the cumulative exposure model postulates that poor early life conditions affect both adult socioeconomic status and health. According to this perspective, we should observe both a direct and indirect pathway for the association between ACEs and accelerated aging. Second, the social trajectory model hypothesizes that early negative experiences affect health only through socioeconomic attainment and behavioral mechanisms. Hence, the relationship between ACES and the mRNA aging signature is completely mediated by socioeconomic status in the adulthood and health behaviors (such as smoking and BMI).

Thus, for the first research question, we test the hypothesis that mRNA ageing signature is associated to the exposure of ACEs in early life; and for the second research question, we explore whether the observed differences in mRNA aging signature between individuals exposed and not exposed to ACEs is explained by differences in socioeconomic attainment and health behaviors. We will examine this latter possibility using counterfactual mediation

methods. Finally, we will perform a differential gene expression analysis to determine which, if any, genes may be up- or down-regulated by ACEs, and what their functional significance is.

The study of gene transcription offers a strategic, mechanistic approach to how the organization of societies and systems biology combine to influence major forms of morbidity and mortality in populations. In contrast to GWAS, which focus on the invariant structure of the SNPs, gene expression data indicate how "active" genes are in synthesizing their products. Genes may be more or less active depending on, for example, regulatory elements that are upstream from the actual protein-coding region. The social and physical environment cause changes in gene expression that, in turn, foster physiological adjustments to a person's surroundings but may also initiate and maintain disease processes. Although the expression of the genome is regulated by many mechanisms, early studies identified genetic transcription—the rate at which messenger RNA is "written out" from the DNA—as highly responsive to "signals" originating in social settings (Cole 2014). That is, social experiences "get under the skin" and influence the rate at which coding regions of the DNA are transcribed to mRNA, which in turn begins biological cascades regulating virtually every biological process in the cell (Irwin & Cole, 2011).

Data and Method

Data for the preliminary analyses come from Wave V of Add Health, a nationally representative sample of adults aged 32 to 42 years. At Wave V, mRNA data were collected and analyzed from a random subsample of Add Health respondents (n=1132). ACEs are identified using previous analyses that have identified ACEs critical exposure in Add Health sample (Easterlin et al. 2019; LeTendre and Reed 2017). Eight different domains of early adversity are considered: experiencing physical abuse before age 18 (more than 2 times), emotional abuse before age 18 (more than 10 times), sexual abuse before age 18, parental alcohol abuse (5 drinks or more in the last month), parental incarceration, single parent household in wave I, parents as recipient of public assistance in Wave I or Wave II (such as Social Security or Railroad Retirement, Supplemental Security Income (SSI), Aid to Families with Dependent Children (AFDC), a housing subsidy or public housing), parents recipient of food stamps in Wave I. Table 1 below presents some basic descriptive statistics on the ACEs.

Table 1 – ACEs Descriptive Statistics in Add Health Wave V Sample I

	Non-missing observations	Missingness	Prevalence Count (Percent)
ACEs			
Physical abuse before age 18 (more than 2 instances)	1088	44	151 (13.8 %)
Emotional abuse before age 18 (more than 10 instances)	1089	43	149 (13.7 %)
Parental alcohol abuse at Wave I (more than 5 drinks)	918	214	50 (5.4 %)
Sexual abuse before age 18	1125	7	44 (3.9 %)
Parental ever being in jail	1079	53	170 (15.8 %)
Single parent household at Wave I	1132	0	286 (25.3 %)

Parent recipient of public assistance	1047	85	164 (15.6 %)
Parent recipient of food stamp	972	160	95 (9.8 %)
Any of the 8 ACEs	996	136	559 (56.1 %)
Just one ACE (ref. no ACEs	1132	0	275 (24.3 %)
More than 1 ACEs	1132	0	284 (25.1 %)

The gene expression signature constructed and analyzed is mRNA aging signature. The scores are constructed using an arithmetic mean of the expression scores for the genes the expression of which has been previously found to be associated with accelerated biological aging. We include as controls: birth year, biological sex, race/ethnicity, and region of residence. An extensive set of controls refers to the specifics of the blood draw: pregnancy status, an indicator variable for illnesses in the four weeks before interview, any illness in the two weeks before, smoking status at the time of blood draw, an indicator for normal kit condition, an indicator for normal tube conditions, number of hours spent fasting before the blood draw, month of collection, and time of day in two hours intervals. Two mRNA technical controls were also included: sample-specific quality control measures for mRNA and indicators for assay batch (since observations collected in the same plate are expected to be highly correlated due to the lab methodology).

Analyses begin with a linear model using the mRNA aging signature as dependent variables. Moreover, the role of adult socioeconomic conditions in mediating the association between ACEs and mRNA aging signature is analyzed. The analyses will also include a differential expressional analysis for a composite index of ACEs (both experiencing any of the ACEs as well as the cumulative number of ACEs). Finally, the timing of exposure to the adversity will be analyzed with the aim of understanding the presence of sensitive periods.

Preliminary results

Tables 2 present the results for a linear regression model which tests the presence of an association between ACEs and gene expression score related to aging. This analysis examines both the experience of any the listed ACEs as well as the cumulative number of ACEs. Preliminary results show that adverse childhood experiences are associated with an increase in the mRNA aging signature. With the inclusion of Wave V BMI and a composite adult socioeconomic indicator (including education, income and subjective social status), the estimates for the association between ACEs and mRNA stay significant in the case of any experience of ACEs whereas they seems partially mediated when the intensity of ACEs is taken into account. Moreover, adult BMI shows a strong association with mRNA signature for biological aging. Further analyses will explore the role of BMI for the accelerated aging signature.

Table 2 – Linear Regression Model for ACEs and mRNA Aging Signature

	mRNA Aging Signature			
Any of the 8 ACEs	0.016**		0.028**	
	(0.008)		(0.014)	
Just one ACE (ref. no ACEs		0.032**		0.030*
		(0.016)		(0.016)
More than 1 ACEs		0.028*		0.02
		(0.016)		(0.017)
Adult BMI			0.004***	0.005***
			(0.001)	(0.001)
Adult SES			-0.001	-0.003
			(0.003)	(0.003)
Parental Education (ref. High-school and less)				
Vocational	0.020	0.018	0.025	0.016
	(0.017)	(0.017)	(0.018)	(0.017)
College	-0.014	-0.015	-0.018	-0.011
	(0.019)	(0.019)	(0.02)	(0.019)
More than College	-0.032*	-0.033*	-0.018	-0.02
	(0.019)	(0.019)	(0.021)	(0.02)
Low Birthweight	0.020	0.020	0.021	0.026
	(0.023)	(0.023)	(0.024)	(0.023)
Race/ Ethnicity (ref. Non-Hispanic White)				
Black Non-Hispanic	0.041**	0.042**	0.041**	0.028
	(0.019)	(0.019)	(0.02)	(0.019)
Asian Non-Hispanic	0.008	0.006	0.031	0.028
	(0.035)	(0.035)	(0.04)	(0.035)
Other Non-Hispanic	-0.041	-0.045	-0.061	-0.06
	(0.069)	(0.069)	(0.068)	(0.068)
Hispanic	0.006	0.005	0.008	-0.005
	(0.021)	(0.021)	(0.022)	-0.021
Male	0.017	0.016	0.029**	0.016
	(0.013)	(0.013)	(0.014)	(0.013)
Birth Year	0.006*	0.006*	0.003	0.006*
	(0.004)	(0.004)	(0.004)	(0.004)
Region (ref. East)				
Midwest	-0.013	-0.013	-0.005	-0.008
	(0.019)	(0.019)	(0.02)	(0.019)
South	0.001	0.001	-0.002	0.0001
	(0.019)	(0.019)	(0.02)	(0.019)
West	-0.054**	-0.054**	-0.061**	-0.053**

	(0.023)	(0.023)	(0.024)	(0.023)
Constant	1.111**	1.087**	0.991*	0.949*
	(0.510)	(0.511)	(0.541)	(0.511)
Observations	1,095	1,095	949	1,075
R^2	0.393	0.394	0.431	0.413
Adjusted R^2	0.359	0.359	0.393	0.377
F Statistic	11.565*** (df = 58; 1036)	11.399*** (df = 59; 1035)	11.233*** (df = 60; 888)	11.667*** (df = 61; 1013)

Note: *p<0.1; **p<0.05; ***p<0.001

Preliminary Conclusions

Thus far, analyses have examined whether and by what mechanisms adverse childhood conditions are related to mRNA risk signatures aging. Preliminary results suggest that the experience of any adverse childhood experience as well as the number of such adverse experiences are significantly associated with accelerated aging in the context of a mRNA signature. Further analysis will use differential gene expression to better understand the biological pathways through which ACEs and health at mid-adulthood are linked. Understanding the biobehavioral pathways through which ACEs are associated with morbidity is essential in order to design effective policy interventions to reduce the impact of ACEs on public health outcomes. This work is not free from limitations. The design does not allow us to make causal statements about the associations presented. However, the present analysis is the first to examine associations between ACEs and a validated mRNA signature for aging in a representative population-based study.

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