Lifespan adversity and later adulthood telomere length in the nationally representative US Health and Retirement Study

Eli Puterman[a,1], Alison Gemmill[b], Deborah Karasek[c], David Weir[d], Nancy E. Adler[e], Aric A. Prather[e], and Elissa S. Epel[e,1]

[a]School of Kinesiology, University of British Columbia, Vancouver, BC, Canada V6T 1Z3; [b]Department of Demography, University of California, Berkeley, CA 94720-2120; [c]Division of Epidemiology, School of Public Health, University of California, Berkeley, CA 94720-7360; [d]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48106; and [e]Department of Psychiatry, University of California, San Francisco, CA 94118

Edited by Kathleen Mullan Harris, The University of North Carolina at Chapel Hill, Chapel Hill, NC, and approved August 2, 2016 (received for review December 30, 2015)

Stress over the lifespan is thought to promote accelerated aging and early disease. Telomere length is a marker of cell aging that appears to be one mediator of this relationship. Telomere length is associated with early adversity and with chronic stressors in adulthood in many studies. Although cumulative lifespan adversity should have bigger impacts than single events, it is also possible that adversity in childhood has larger effects on later life health than adult stressors, as suggested by models of biological embedding in early life. No studies have examined the individual vs. cumulative effects of childhood and adulthood adversities on adult telomere length. Here, we examined the relationship between cumulative childhood and adulthood adversity, adding up a range of severe financial, traumatic, and social exposures, as well as comparing them to each other, in relation to salivary telomere length. We examined 4,598 men and women from the US Health and Retirement Study. Single adversities tended to have nonsignificant relations with telomere length. In adjusted models, lifetime cumulative adversity predicted 6% greater odds of shorter telomere length. This result was mainly due to childhood adversity. In adjusted models for cumulative childhood adversity, the occurrence of each additional childhood event predicted 11% increased odds of having short telomeres. This result appeared mainly because of social/traumatic exposures rather than financial exposures. This study suggests that the shadow of childhood adversity may reach far into later adulthood in part through cellular aging.

cellular aging | telomeres | lifespan adversity | childhood adversity

Aging cells play a crucial role in the pathogenesis of noncommunicable diseases, and telomere shortening in cells plays a part of this aging process (1, 2). Telomeres are DNA–protein caps at the ends of chromosomes that protect genetic material from degradation, and their lengths indicate cellular aging (2, 3). Experiments in rodents implicate shortened telomeres and lower activity of telomerase, the enzyme that lengthens telomeres, as causes of mitochondrial and tissue damage associated with disease pathogenesis (4–6).

Telomere length is linked cross-sectionally and prospectively with human disease states in many studies. A recent meta-analysis suggests that individuals with observed short leukocyte telomeres are at an ∼80% increased risk of concurrent reports of cardiovascular disease and an ∼40% increased risk of developing cardiovascular disease in the future (7). Other recent meta-analyses support the concurrent associations between short telomeres and diabetes (8) and several cancers (9, 10). Several studies indicate that short telomeres from varied sources, including leukocytes and saliva, are related to early mortality (11–17), including a study with >60,000 adults (18), although null studies also exist (19–22).

Although these studies suggest that telomere length plays a role in disease, they are observational, and studies directly linking genetics of telomere length to disease would allow a more substantive inference of a causal role in disease pathogenesis. Recently, in humans, there were two such Mendelian randomization studies. These studies examined ∼80,000 participants from 15 mostly population-based genome-wide association cohort studies. They showed that common sequence variants of seven genes that directly regulate telomere maintenance, summed as a genetic risk score, significantly increase risks for cardiovascular, pulmonary (23), and Alzheimer's diseases (24).

As our understanding of the complexities of telomere biology and its consequences continue to deepen, increasing research is attending to the antecedents of telomere shortening. Telomere length is moderately to highly heritable; estimates range from 36% to 84% heritable (25). In light of this variable heritability, environmental risk factors that may accelerate telomere shortening have been widely studied. Considerable attention has been placed on discrete experiences of psychosocial adversities at different periods in the lifespan.

Exposure to adversity can degrade cell function and accelerate aging of the immune system (26–28). Adversity at different periods in the lifespan includes prenatal exposure to maternal stress, repeated experiences of abuse during childhood, and adulthood stressors such as exposure to financial and life stressors associated with poverty or caregiving. Some evidence, with exceptions (29, 30), indicates that adversity in childhood (31) and adulthood (32–37) are not only cross-sectionally related to short telomeres, but that childhood (38) and adulthood (39) adverse experiences can accelerate shortening over time. The vast majority

Significance

The gradual aging of the immune system is partly marked by shortened telomeres, the DNA–protein caps at the ends of chromosomes that protect genes from degradation. This study undertakes a lifespan approach to stress and leukocyte telomere length in a nationally representative sample of US residents. By using data from 16 y of the Health and Retirement Study, childhood and adulthood life stressors were examined for their individual and combined associations with increased odds of having short telomeres. Accumulated adverse experiences in childhood significantly predicted an increased likelihood of having short telomeres later in life, suggesting a potential pathway through which childhood experiences have been previously shown to predict adulthood morbidity and mortality.

Author contributions: E.P. and D.W. designed research; E.P., A.G., D.K., D.W., and A.A.P. performed research; A.G. and D.K. analyzed data; and E.P., A.G., D.K., N.E.A., and E.S.E. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

Data deposition: Our database is provided as Dataset S1.

[1]To whom correspondence may be addressed. Email: eli.puterman@ubc.ca or elissa.epel@ucsf.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1525602113/-/DCSupplemental.

Table 1. Characteristics and adversity experiences of telomere subsample and 2008 survey participants, HRS

	Unadjusted analysis sample		2008 sample	
Characteristic	*n*	%	*n*	%
Age (y)				
<60	876	25.7	3,465	27.1
60–70	1,423	36.7	5,163	36.7
70–80	1,538	24.0	5,303	22.0
80+	761	13.6	3,286	14.3
Gender				
Male	1,874	44.1	7,026	45.6
Female	2,724	55.9	10,191	54.4
Race/ethnicity				
Non-Hispanic white	3,600	84.3	12,725	81.5
Non-Hispanic black	507	7.3	2,439	9.1
Hispanic	428	7.0	1,757	7.6
Other	63	1.4	295	1.8
Missing			1	
Partnership status				
Married/partnered	3,099	66.5	11,011	64.7
Other	1,498	33.5	6,204	35.3
Missing	1		2	
Education				
<HS	855	15.1	3,733	16.7
HS or GED	1,680	34.8	6,077	34.4
Some college	1,051	24.8	3,774	23.8
College and above	1,011	25.4	3,629	25.2
Missing	1		4	
Father's education				
<8 y	1,050	22.9	4,207	24.0
8+ y	2,978	77.1	10,420	76.0
Missing	570		2,590	
BMI				
Underweight	57	1.0	304	1.5
Normal	1,316	28.3	5,052	28.3
Overweight	1,708	38.2	6,380	38.5
Obese	1,475	32.5	5,247	31.8
Missing	42		234	
CESD score (max = 8)				
0	2,229	49.6	7,329	46.9
1	1,023	21.4	3,560	21.9
2	465	9.9	1,779	10.6
3	290	6.1	1,099	6.5
4–8	591	13.2	2,308	14.1
Missing			1,142	
Smoking status				
Never smoked	1,973	43.1	7,410	42.8
Previous smoker	2,005	43.2	7,470	42.9
Current smoker	594	13.7	2,234	14.3
Missing	26		103	
Reported no. of medical conditions				
0	549	14.3	2,042	14.2
1	1,024	22.9	3,833	24.7
2	1,243	26.8	4,432	25.6
3	980	20.0	3,532	19.1
4 or more	802	16.0	3,378	16.4
Childhood adversities				
Relocated due to financial difficulties	836	17.2	3,161	17.7
Family received financial help	628	13.8	2,351	14.5
Father ever unemployed	934	19.8	3,472	20.1
Trouble with police before age 18	215	5.7	650	6.2
Repeated school	751	16.4	2,381	16.2
Physically abused	320	7.4	1,131	8.3
Parents used drugs or alcohol	707	16.3	2,465	18.2
Adult adversities				
Experienced the death of a child	794	15.0	2,664	15.1
Experienced the death of a spouse	1,282	23.9	4,949	23.0
Experienced a natural disaster (after age 17)	727	16.3	2,660	18.4
Fired a weapon in combat	290	6.7	1,025	7.3
Ever had a partner addicted to drugs or alcohol	918	18.7	2,966	20.1
Been a victim of a physical attack (after age 17)	281	6.0	1,059	7.6
Ever had a spouse or child with a serious illness	1,554	32.3	5,209	33.3
Ever received Medicaid	632	11.6	2,987	13.3
Ever received food stamps	540	10.1	2,212	10.8
Ever been unemployed looking for work or temporarily laid off	626	13.8	2,442	14.4

Unweighted *n* and weighted proportions are shown. For the unadjusted analysis sample, *n* = 4,598; for the 2008 sample, *n* = 17,217. CESD, Center for Epidemiological Studies Depression Scale; GED, general education development test; HS, high school.

of these previous studies have examined highly stressful experiences as predictors of telomere length within specific contexts of abuse, caregiving, low socioeconomic status, or unemployment, for example.

Rarely have researchers had the opportunity to examine a combination of adverse financial, social, and traumatic stressors and how they may accumulate over time from childhood through adulthood to predict short telomeres. Jodczyk et al. (40) prospectively examined the accumulation of childhood and early adulthood abuse and violence, mental health disorders, substance use, and other significant life stressors in a cohort of 677 New Zealand adults and found no association between the accumulation of childhood and early adulthood adversity with telomere length at age 30. Verhoeven et al. (41) also did not find a significant relationship between early adversity and adulthood telomere length in their sample of 2,936 Dutch adults with mean age 41 with a current or remitted diagnosis of a depressive or anxiety disorder and healthy controls. Conversely, in the European Prospective Investigation into Cancer, a nationally representative sample from the United Kingdom, Surtees et al. found a relationship (42). They measured telomeres in a subsample of 4,441 women aged 41–80 (median age 62) (42) and found that retrospectively reported childhood adverse life events accumulated to predict shorter adult telomeres. These events included separation from mother for more than 1 y, parental divorce, physical abuse, and parental unemployment, among others. These studies also examined associations between recent adulthood events and telomere length [measured over past the 5 y (41, 42) or between ages 16 and 25 (40)], and effects are mixed, with only Verhoeven et al. (41) demonstrating significant associations.

The present study examines the combined effects of adverse experiences during childhood and adulthood and their relationship to telomere length in the nationally representative US Health and Retirement Study (HRS). This study undertakes a lifespan approach on adversity and salivary telomere length in a large sample in the United States that does not limit adulthood experiences to recent events and that expands measured adversities to include financial, social, and traumatic experiences. We were specifically interested in examining the independent and combined associations of accumulated childhood and adulthood adversity with later-life telomere length. We also completed follow-up analyses to examine individual associations between each adverse experience and telomere length and whether financial or social/traumatic stressors drive any of the relationships.

Results

Our final study sample comprised 4,598 participants that had complete data for all adversity measures and telomere length. Table 1 shows the weighted covariate distributions in the telomere sample, as well as the full HRS sample, inclusive of the telomere sample (n = 17,217). The covariate distributions appear similar across the study sample and full HRS sample. Father's education data were missing for 570 respondents (12% of our sample). Other covariates contained few or no missing values.

Childhood adversity included whether before the age of 18, the respondent's (*i*) family received help from relatives because of financial difficulties, (*ii*) family ever had to relocate due to financial difficulties, (*iii*) father ever lost his job, and (*iv*) parents' substance or alcohol use caused problems in the home. Childhood adversity also included whether the respondent (*v*) had ever experienced physical abuse before age 18, (*vi*) had to repeat a year of school, and (*vii*) had gotten into trouble with police. The first three childhood adversity items are considered financial in nature, whereas the final four are social or traumatic. Adulthood adversity included whether, at any measurement point over the course of the biannual assessments from 1992–2008, the respondent (*i*) received Medicaid coverage, (*ii*) received food stamps, and (*iii*) was unemployed and looking for work or temporarily laid off. Adulthood adversity also included whether the respondent had experienced, at any age after 17, (*iv*) the death of a child, (*v*) the death of a spouse, (*vi*) a natural disaster, (*vii*) being wounded in combat, (*viii*) a partner addicted to drugs or alcohol, (*ix*) being victim of a physical attack, and (*x*) a spouse or child with a serious illness. The first three adulthood adversity items are considered financial in nature and the final seven social and traumatic. Table 1 presents the weighted proportions of each childhood and adulthood adversity item, and Table 2 presents weighted distributions of the cumulative scores. Individual childhood adversity items ranged in prevalence from 6% to nearly 20%, and adulthood adversity items ranged in prevalence from 6% to >30%. Total number of childhood adversity ranged from zero to seven in our sample and adult adversity ranged from zero to eight. Cumulative lifespan adversity (the total of all childhood and adulthood items) ranged from 0 to 11. More than three-quarters of the sample experienced at least one measure of lifetime adversity, and more than half experienced two or more. Childhood and adulthood adversities were significantly correlated (r = 0.18; P < 0.001).

Average telomere length *t/s* ratio for the sample was 1.28 (SD = 0.27). Average telomere length *t/s* ratio for the lowest quartile was 0.96 (SD = 0.15) and for the other 75% was 1.39 (SD = 0.21). Non-Hispanic black participants were less likely than Non-Hispanic white and Hispanic participants to be categorized as having short telomeres (16.7%, 25.1%, and 23%, respectively) but reported more adverse events across the lifespan than non-Hispanic whites (means 3.04, 2.35, and 2.94, respectively).

Table 2. Weighted distributions of cumulative lifetime, childhood, and adult adversity (sum scores), HRS

Cumulative adversity sum score	Weighted (%)
Lifetime (mean 2.5)	
0	14.4
1	21.4
2	20.9
3	15.9
4	12.0
5	7.4
6	4.2
7	2.4
8	0.8
9	0.5
10	0.1
11	0.1
Childhood (mean 1.0)	
0	45.8
1	28.4
2	14.1
3	8.2
4	2.4
5	0.8
6	0.3
7	<0.1
Adulthood (mean 1.5)	
0	26.0
1	29.2
2	23.1
3	12.8
4	5.6
5	2.2
6	0.8
7	0.1
8	0.2

n = 4,598 weighted proportions.

Unadjusted and adjusted multivariate logistic regression models were completed for summary measures of (*i*) cumulative lifespan adversity (childhood and adulthood combined) and (*ii*) childhood and adulthood adversity in the same model. Cumulative lifespan adversity significantly predicted increases in odds of having short telomeres in both unadjusted [odds ratio (OR) = 1.09; 0.95 confidence interval (CI) = 1.04–1.14] and adjusted (OR = 1.06; 0.95 CI = 1.01–1.12) models. When lifespan adversity was separated into childhood and adulthood components, both childhood (OR = 1.10; 0.95 CI = 1.03–1.19) and adulthood adversity (OR = 1.08; 0.95 CI = 1.02–1.14), significantly predicted increased odds of having short telomeres in the same unadjusted model. In an adjusted model, only childhood adversity (OR = 1.11; 0.95 CI = 1.02–1.21) was related to increased odds of short telomeres, whereas adulthood adversity was not (OR = 1.03; 0.95 CI = 0.96–1.10). In other words, each childhood adversity predicted 11% increased odds of having short telomeres. There was no evidence of an interaction between cumulative childhood and cumulative adult adversity ($P = 0.59$). Sensitivity analyses for racial differences revealed a similar association among non-Hispanic whites as the pooled sample (OR = 1.08; 0.95 CI = 1.02–1.15). Models were nonsignificant among non-Hispanic blacks and Hispanics.

A series of follow-up analyses were completed to test whether category of exposure mattered. When adversity in childhood was split into social/traumatic and financial adversity, only the former showed a significant increase in the odds of having short telomeres later in life (adjusted OR = 1.19; 0.95 CI = 1.03–1.38). In adulthood, neither financial nor adult social/traumatic events significantly predicted increased odds of having short telomeres in adjusted models. All significant effects of the summary adversity measures (unadjusted and adjusted) held when corrected for multiple testing using the false discovery rate method (43, 44) (Table 3).

Follow-up analyses on individual adversity items demonstrated that only death of a spouse and receipt of Medicaid significantly predicted increased odds of having short telomeres in unadjusted models after correcting for the false discovery rate. After adjusting for all covariates and accounting for the false discovery rate, no individual adversity item's OR was significant. See Table 4 and Fig. 1 for each adversity item's independent OR.

Discussion

In the present study, adverse experiences throughout the life course predicted increased odds of falling into the lowest quartile in telomere length in late adulthood, even after adjustment for potential covariates. These findings appear to be driven most strongly by experiences during childhood in fully adjusted models. Participants were at 11% increased odds of being categorized as short in telomere length for each additional childhood adverse experience. These findings accounted for childhood and current socioeconomic status, adulthood adversity, and many other behavioral and health-related factors, such as smoking status, body mass index (BMI), and presence of health conditions. The set of childhood events that are emblematic of trauma or psychological issues in oneself or one's parents—such as having trouble with the police, having to repeat school, physical abuse, and parents with substance abuse problems—predicted shorter telomeres, whereas the index of financial problems (i.e., paternal unemployment, receiving financial help from a family member or friend, or relocation due to financial difficulties) did not.

Although poverty can provide a fertile context for experiencing traumatic events (28), financial stressors alone had little effect in the current study. These findings are consistent with a recent meta-analysis demonstrating that there is very weak or no evidence for associations between childhood or contemporaneous markers of socioeconomic status and telomere length in adulthood (45). The rich survey data from HRS allowed us to differentiate the social and traumatic adverse experiences from the financial ones, but these differences should be further investigated in other large samples and with other health outcomes. Our findings on social adversity are consistent with the majority of studies on early adversity and telomere length as reported in previous reviews of this area (31, 46, 47), although exceptions of individual studies exist in the literature (40, 41). These findings also support previous pilot work in the HRS that reported significantly elevated expressions of genes associated with proinflammation in adults who reported experiencing childhood social and traumatic adversity (48) and support an eco-biodevelopmental conceptualization of disease risk (49).

Although adult adversity also predicted shorter telomeres with 8% increased odds of having short telomeres in unadjusted models in our study, the association was not significant in adjusted models and thus should be interpreted with caution. Childhood events may embed epigenetically and alter gene expression almost permanently (28, 49), although adulthood events are hypothesized to slowly wear down biological systems (50, 51). Perhaps the limited number and types of adulthood events available in HRS could explain the limited impact of adulthood adversity in this study. Typical life-events measures have a broader range and larger number of stressful events (for example, ref. 52), whereas our study only included 7 childhood and 10 adulthood stressors. The HRS does not

Table 3. Significance of each adversity item, correcting for multiple testing with false discovery rate method

Rank of *P* value	Adversity variable of interest	Model	*P* value from analysis	BH correction	Accept as significant?
1	Cumulative lifespan	Unadj	0.000	0.004	Y
2	Social/traumatic adulthood	Unadj	0.004	0.007	Y
3	Cumulative childhood	Unadj	0.008	0.011	Y
4	Cumulative adulthood	Unadj	0.008	0.014	Y
5	Cumulative childhood	Adj	0.012	0.018	Y
6	Social/traumatic childhood	Adj	0.015	0.021	Y
7	Social/traumatic childhood	Unadj	0.015	0.025	Y
8	Cumulative lifespan	Adj	0.02	0.029	Y
9	Financial childhood	Unadj	0.111	0.032	N
10	Financial adulthood	Adj	0.306	0.036	N
11	Financial childhood	Adj	0.307	0.039	N
12	Financial adulthood	Unadj	0.341	0.043	N
13	Cumulative adulthood	Adj	0.47	0.046	N
14	Social/traumatic adulthood	Adj	0.503	0.05	N

The Benjamini and Hochberg (BH) correction for the false-discovery rate requires listing the variables of interest within a set of analyses in rank order of their *P* value significance. To calculate the BH correction, each rank order of the *P* value is multiplied by 0.05 and divided by the number of variables of interest in the set of analyses. If the *P* value from the analysis is lower than the BH correction value, then the standard is to accept the rejection of the null hypothesis. Adj., adjusted; N, no; Unadj., unadjusted; Y, yes.

Table 4. Unadjusted and adjusted odds and 95% CI of shorter telomere length for individual measures of childhood and adult adversity, HRS

Adversity	Unadjusted OR	95% CI	Adjusted OR*	95% CI
Childhood adversities				
Relocated due to financial difficulties	1.15	(0.93, 1.43)	1.12	(0.88, 1.43)
Family received financial help	1.27	(1.00, 1.62)	1.28	(0.98, 1.68)
Father ever unemployed	1.13	(0.93, 1.39)	1.04	(0.84, 1.30)
Trouble with police before age 18	1.29	(0.89, 1.87)	**1.58**	(1.02, 2.43)
Repeated school	1.19	(0.95, 1.48)	1.13	(0.88, 1.44)
Physically abused	1.26	(0.91, 1.75)	1.28	(0.89, 1.85)
Parents used drugs or alcohol	1.25	(1.00, 1.56)	1.27	(0.99, 1.63)
Adult adversities				
Experienced the death of a child	1.19	(0.96, 1.48)	1.08	(0.84, 1.40)
Experienced the death of a spouse	**1.34**	(1.12, 1.59)	1.16	(0.90, 1.48)
Experienced a natural disaster (after age 17)	1.17	(0.94, 1.46)	1.12	(0.88, 1.42)
Fired a weapon in combat	1.20	(0.87, 1.65)	0.76	(0.52, 1.09)
Ever had a partner addicted to drugs or alcohol	1.01	(0.82, 1.24)	1.01	(0.80, 1.28)
Been a victim of a physical attack (after age 17)	0.92	(0.63, 1.35)	0.87	(0.56, 1.33)
Ever had a spouse or child with a serious illness	1.18	(0.99, 1.40)	1.08	(0.89, 1.30)
Ever received Medicaid	**1.43**	(1.14, 1.80)	**1.34**	(1.01, 1.77)
Ever received food stamps	1.17	(0.90, 1.52)	1.32	(0.93, 1.86)
Ever been unemployed/laid off	0.84	(0.66, 1.09)	0.84	(0.63, 1.12)

Bolded ORs include all significant associations. $P \leq 0.05$; only death of spouse and receipt of Medicaid were significant in unadjusted models when corrected for a false discovery rate. $n = 4{,}598$.

*Covariates include age, sex, race/ethnicity, partnership status, respondent's education, father's education, CESD score, smoking status, number of medical conditions, and BMI.

have information on some potentially relevant adversities in adulthood, such as bankruptcy, home foreclosure, and domestic abuse, and it does not differentiate between intensities of events. It is also possible that, beyond the type and number of events, the more recent the events, the greater the impact on cell aging. Two recent studies revealed that the accumulation of major life events over a 1-y period correlate with shorter telomeres (53) and prospectively predict shortening over this brief period (39) in adults. In the present study, recentness of the event was not studied. Finally, the lack of association in adjusted models between adulthood adversity and the odds of short telomeres may be partly a result of the covariates in the models, including the behavioral and health measures.

In the present study, telomere length is considered a marker of accelerated aging and disease development. Although telomere biology is widely accepted as a mechanism of aging and disease pathogenesis in animals, there remains some debate in epidemiological sciences about the importance of telomeres to human health and disease, with a range of perspectives on its significance as a marker (54), a mechanism (2, 55), or neither (56). Much of the inconsistent findings in previous studies may be attributed largely to methodological differences—for example, smaller sample sizes, a wider range of ages, and varied telomere length quantification. The effect size of telomere length predicting disease is likely small, so these differences in study design would easily obscure effects. Confidence that telomeres are important to disease pathogenesis is increasing with recent Mendelian randomization studies demonstrating that genetic variants associated with shorter telomeres are associated with cardiovascular, pulmonary, and Alzheimer's diseases (23, 24) and a recent meta-analysis that includes prospective associations between telomere length and cardiovascular disease (7). Considering the continued debate, however, there remains a significant need for more prospective, meta-analytic, and Mendelian randomization studies with nationally representative populations with other diseases and mortality as outcomes.

The present study has several strengths, including a large nationally representative sample, a wide range of childhood and adulthood events accumulated across multiple years of data, and the ability to adjust for critical factors known to affect telomere length. The randomly selected representative sample of older adults (age ≥50 y) in the HRS is especially valuable because it allows for generalization of how cumulative childhood adversity is related to telomere length among the aged population of the United States and avoids the bias associated with recruiting a clinical sample or those with a health condition who would be more likely to have both early adversity and shorter telomeres.

The present study also has several limitations. As mentioned previously, the HRS did not have information on some potentially relevant adversities in adulthood. Of concern is whether retrospective measurement of past events, especially of childhood events, is prone to reporting and recall error (57, 58). Previous studies on the validity of retrospective reporting from childhood (59, 60) suggest that people are more likely to underreport early abuse experiences than overreport them. Based on these studies, two questions that we used, parental substance abuse and physical abuse, may have been underreported (57). Hardt et al. (60, 61) concluded that recall bias, however, should have little effect in studies with clearly defined adverse experiences, which is the case with the rest of the selected adverse experiences in the current study (i.e., father unemployment, repeating a school grade, and getting in trouble with police). Furthermore, recent findings from large nationally representative studies, including HRS (62), Survey of Health, Aging, and Retirement in Europe (63), the Mainz Adverse Childhood Experiences Study, and the prospective British National Child Development Study (64) also support Hardt and Rutter's (60) general conclusion. These studies find that older adults recalled childhood health, economic, and traumatic experiences comparably to rates of experiences reported in either national data or to large prospective cohort studies that started in childhood with similar impact on outcomes in adulthood.

Study limitations only allowed the collection of DNA via saliva. Telomere length in saliva is not commonly studied. Although rich in immune cells, saliva also has other cell types, such as epithelial buccal cells, making it a less pure measure of immune cell telomere length. However, a recent study demonstrated a highly significant correlation ($r = 0.72$) between telomere length from saliva and blood (65). Additionally, a large study with 100,000 participants that used salivary telomere length as a marker of cell aging found that salivary

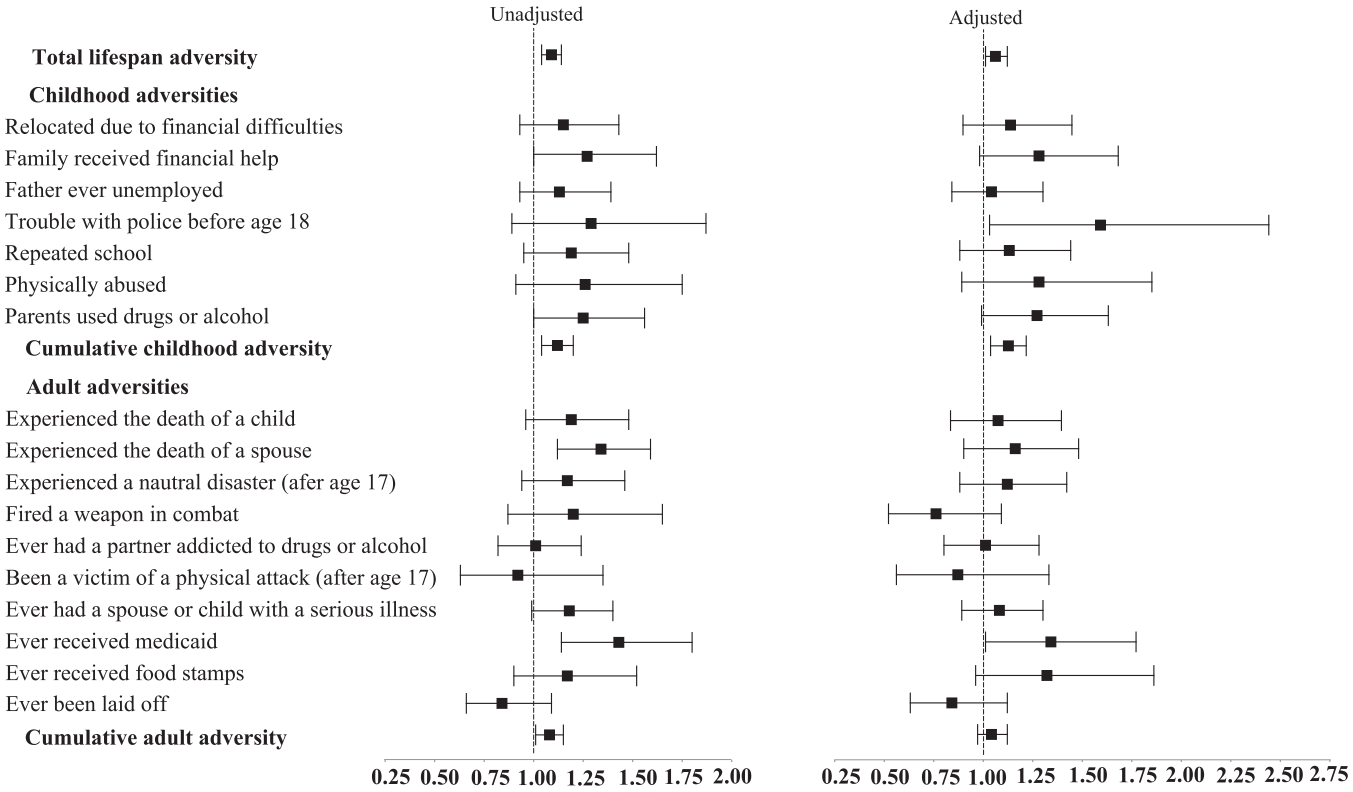

Fig. 1. ORs and 95% CI for total lifespan adversity, childhood adversities, adulthood adversities, and each independent item predicting odds of short telomeres (25th lowest percentile).

telomere length is associated with aging, health, and mortality (17). Finally, our results in the sample with all participants pooled across race and ethnicity were similar to those of the predominant racial/ethnicity group, non-Hispanic white participants, whereas results in non-Hispanic black and Hispanic participants were nonsignificant, perhaps limited by small sample sizes within each group. Considering these results and the racial and ethnic differences in telomere length and in exposures to adverse experiences that exist in our and other studies (66–69), we propose future studies with larger samples within minority communities to confirm or refute the uniqueness of our results to non-Hispanic whites.

The HRS is a unique, longitudinal dataset that can allow for the study of the effect of adverse events across the life course on health status and behavioral engagement in adulthood. Children may be set on trajectories of health, in part through the behavioral habits they formed and in part through the accumulation of exposures that may cause epigenetic alterations of gene expression and protein synthesis. Adopting an eco-biodevelopmental framework allows us to understand the long reach of adversity, well into later adulthood, as evidenced by the present study. Our findings, if replicated with other biological and health outcomes, suggest that childhood social adversity—beyond indices of socioeconomic position (parental income, employment, and education)—are especially salient to adulthood health and should be considered as targets for interventions. For example, our results add to the growing importance of intervention strategies to reduce parental substance abuse for lifespan health of children.

Not all children who experience adversity are at similar risk (28, 70), and investigating resiliency within the context of adversity is emerging as a new frontier in adversity research (71). Researchers have identified genetic, psychosocial, and behavioral factors that may mitigate or potentiate vulnerability to adverse experiences, and understanding their complex interplay will allow us to optimize policy initiatives for interventions for families, as proposed elsewhere (28, 49, 72), that target those most at risk for excessive early morbidity and mortality.

Methods

Data. The HRS is an ongoing longitudinal, nationally representative sample of >26,000 US residents over 50 y of age and their spouses, with survey assessments every 2 y since 1992. The study is supported by the National Institute on Aging (NIA; U01 AG009740) and the Social Security Administration. HRS is under Institutional Review Board approval at the University of Michigan and the NIA, and under no conditions have data been provided to researchers with individual identifiers or links to individual identifiers. The purpose of the study is to explore changes in health as individuals transition from employment to retirement and into old age. Since 1992, HRS has collected information related to financial health (income, employment, assets, pension plans, and health insurance) and physical health (disability; health, physical, cognitive, and psychological functioning; health behaviors; and some lifespan stressors). In 2004, HRS researchers started collecting biological data, and in 2008, a subsample of 5,808 subjects consented to provide saliva samples (Oragene) for DNA extraction. This DNA was assessed for telomere length. Sampling weights account for the probability of respondent selection and cooperation with the DNA request (73).

Lifespan Adversity. Major childhood and adulthood adversity items were asked across the survey modules. After examining all HRS measures from all waves, we identified measures that objectively qualified as highly stressful events, such as those indicative of severe financial difficulties, as well as social and traumatic events. We considered seven measures of childhood adversity that occurred before the age of 18, which we summed for childhood adversity (possible range 0–7). We also divided the index into childhood financial adversity (possible range 0–3) and social/traumatic childhood adversity (possible range 0–4). The three items of childhood financial adversity were asked during survey years 1996–2008. Respondents could skip these questions if they had already answered in a previous round. Each measure was coded as a binary variable if the respondent ever answered (yes/no). For experiences of father's unemployment, respondents who never lived with their father or whose father never worked were coded as no. Measures of social and traumatic childhood adversity were collected in survey years 2006, 2008, and 2010, although the police question was not asked in 2006. Respondents could skip these questions if they had answered in a previous

round. Each item was coded as a binary variable (yes/no). We also created a cumulative index of adult adversity (maximum 10) and divided these into adult financial and social/traumatic adversity. Adult financial adversity was constructed from all available surveys from 1992 to 2008, whereas the social and traumatic adult adversity items from years 2004–2008. Any report of "yes" at any year of available data were scored as a 1.

Telomere Length. Mean telomere length was assayed by Telome Health (Telomere Diagnostics, www.telomehealth.com/) using quantitative PCR (qPCR). Telomere data were available from 5,808 respondents who provided a saliva sample during the 2008 wave. We excluded observations with telomeres >2.0 *t/s* ratio ($n = 289$), because these high values are likely to be artifactual in salivary samples. We chose a binary outcome comparing the lower quartile of telomere length to all higher values for several reasons. First, we preferred to be consistent with previous large epidemiological cohort studies examining the association between telomere length with disease or mortality that use the qPCR method for telomere assays and categorize telomere length values into dichotomous variables (7, 11, 18). Second, research on qPCR compared with the flow-FISH method for telomere length measurement further demonstrates reduced qPCR sensitivity (40%) and specificity (63%) to detect accurate telomere length at the lowest decile (74). Finally, statistical analyses for normality using the Shapiro–Wilk test on random subsamples of 500 participants suggested nonnormality of data for the full sample ($n = 5,808$), for the reduced sample with the 289 participants excluded for artificially high values ($n = 5,519$), and after log-transformation of the full and reduced data.

Covariates. Covariates were selected for their identification in previous studies as related to lifespan adversity or telomere length. Demographic characteristics included a continuous measure of respondent's age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), sex, level of education (less than high school vs. high school and above), and current partnership status in 2008 (married or partnered vs. other). Health measures, assessed in 2008, included a continuous measure of BMI, history of smoking (never vs. ever smoked), and number of medical conditions ever reported (zero, one, two, three, and four or more). Medical conditions included high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems, and arthritis (i.e., a sum of indicators for whether a doctor has ever told the respondent that he or she has ever had the condition). Depressive symptoms were measured by using the modified Center for Epidemiological Studies Depression Scale (CESD), which ranged from 0 to 8 in depression severity. Lastly, we included a measure of father's education (<8 and ≥8 y), as a proxy of childhood socioeconomic status.

Statistical Approach. We used multivariate logistic regression to investigate the relationships between the (*i*) sum scores of cumulative lifespan adversity, and the differential effects of (*ii*) childhood and adulthood adversities, (*iii*) childhood financial and social/traumatic adversity, and (*iv*) adulthood financial and social/traumatic adversity with the odds of shortened telomere length. All analyses were corrected for multiple testing by using the false discovery rate (43, 44). Interactions between childhood and adulthood cumulative adversity were also examined. All analyses used the *svy* command prefix in Stata (v12.1, StataCorp) to adjust for survey weights in the HRS. Because there are known differences in telomere length by race and ethnicity (66–68), we conducted a sensitivity analysis to examine the association within each race/ethnic group. In a separate series of unadjusted and adjusted analyses corrected for the false discovery rate, we used multivariate logistic regression to investigate the relationship between each individual adversity item with the odds of shortened telomere length. Although we present results for only observations with telomeres 2.0 *t/s* ratios and shorter, we completed analyses including the 289 participants originally excluded, and results were unaltered. Dataset S1 contains all data used in the current study.

ACKNOWLEDGMENTS. We thank Jordan Weiss for his contributions to the figure. We thank the Robert Wood Johnson Foundation Health & Society Scholars program for its financial support. This research was supported in part by the Canada Research Chairs program (E.P.); NIH National Heart, Lung and Blood Institute Award R00 HL 109247 (to E.P.); NIH National Institute on Aging Award R24 AG048024 (to E.S.E.); NIH National Institute on Aging Award T32-AG000246 (to A.G.); and NIH National Heart, Lung and Blood Institute Award K08 HL 112961 (to A.A.P.).

1. Blasco MA (2005) Telomeres and human disease: Ageing, cancer and beyond. *Nat Rev Genet* 6(8):611–622.
2. Armanios M, Blackburn EH (2012) The telomere syndromes. *Nat Rev Genet* 13(10): 693–704.
3. Blackburn EH (2000) Telomere states and cell fates. *Nature* 408(6808):53–56.
4. Jaskelioff M, et al. (2011) Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature* 469(7328):102–106.
5. Pérez-Rivero G, et al. (2006) Mice deficient in telomerase activity develop hypertension because of an excess of endothelin production. *Circulation* 114(4):309–317.
6. Sahin E, DePinho RA (2012) Axis of ageing: Telomeres, p53 and mitochondria. *Nat Rev Mol Cell Biol* 13(6):397–404.
7. Haycock PC, et al. (2014) Leucocyte telomere length and risk of cardiovascular disease: Systematic review and meta-analysis. *BMJ* 349(jul08_3):g4227.
8. Zhao J, Miao K, Wang H, Ding H, Wang DW (2013) Association between telomere length and type 2 diabetes mellitus: A meta-analysis. *PLoS One* 8(11):e79993.
9. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA (2011) The association of telomere length and cancer: A meta-analysis. *Cancer Epidemiol Biomarkers Prev* 20(6):1238–1250.
10. Ma H, et al. (2011) Shortened telomere length is associated with increased risk of cancer: A meta-analysis. *PLoS One* 6(6):e20466.
11. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA (2003) Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet* 361(9355):393–395.
12. Epel ES, et al. (2008) The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men. *Aging (Albany, NY)* 1(1):81–88.
13. Glei DA, Goldman N, Weinstein M, Risques RA (2015) Shorter ends, faster end? Leukocyte telomere length and mortality among older Taiwanese. *J Gerontol A Biol Sci Med Sci* 70(12):1490–1498.
14. Kimura M, et al. (2008) Telomere length and mortality: A study of leukocytes in elderly Danish twins. *Am J Epidemiol* 167(7):799–806.
15. Bakaysa SL, et al. (2007) Telomere length predicts survival independent of genetic influences. *Aging Cell* 6(6):769–774.
16. Deelen J, et al. (2014) Leukocyte telomere length associates with prospective mortality independent of immune-related parameters and known genetic markers. *Int J Epidemiol* 43(3):878–886.
17. Schaefer C, et al. (2013) Demographic and behavioral influences on telomere length and relationship with all-cause mortality: Early results from the Kaiser Permanente Research Program on Genes, Environment, and Health (RPGEH). *Clin Med Res* 11(3):146.
18. Rode L, Nordestgaard BG, Bojesen SE (2015) Peripheral blood leukocyte telomere length and mortality among 64,637 individuals from the general population. *J Natl Cancer Inst* 107(6):djv074.
19. Bendix L, et al. (2014) Longitudinal changes in leukocyte telomere length and mortality in humans. *J Gerontol A Biol Sci Med Sci* 69(2):231–239.
20. Svensson J, et al. (2014) Leukocyte telomere length is not associated with mortality in older men. *Exp Gerontol* 57:6–12.
21. Duggan C, et al. (2014) Change in peripheral blood leukocyte telomere length and mortality in breast cancer survivors. *J Natl Cancer Inst* 106(4):dju035.
22. Njajou OT, et al. (2009) Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a population-based cohort study. *J Gerontol A Biol Sci Med Sci* 64(8):860–864.
23. Codd V, et al. (2013) Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet* 45(4):422–7, e1–2.
24. Zhan Y, et al. (2015) Telomere length shortening and Alzheimer disease—A Mendelian randomization study. *JAMA Neurol* 72(10):1202–1203.
25. Aviv A (2012) Genetics of leukocyte telomere length and its role in atherosclerosis. *Mutat Res* 730(1-2):68–74.
26. McEwen BS (2004) Protection and damage from acute and chronic stress: Allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci* 1032:1–7.
27. Miller GE, Chen E, Cole SW (2009) Health psychology: Developing biologically plausible models linking the social world and physical health. *Annu Rev Psychol* 60:501–524.
28. Shonkoff JP, Boyce WT, McEwen BS (2009) Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. *JAMA* 301(21):2252–2259.
29. Fujishiro K, Diez-Roux AV, Landsbergis PA, Jenny NS, Seeman T (2013) Current employment status, occupational category, occupational hazard exposure and job stress in relation to telomere length: The Multiethnic Study of Atherosclerosis (MESA). *Occup Environ Med* 70(8):552–560.
30. O'Donovan A, et al. (2012) Stress appraisals and cellular aging: A key role for anticipatory threat in the relationship between psychological stress and telomere length. *Brain Behav Immun* 26(4):573–579.
31. Price LH, Kao H-T, Burgers DE, Carpenter LL, Tyrka AR (2013) Telomeres and early-life stress: An overview. *Biol Psychiatry* 73(1):15–23.
32. Damjanovic AK, et al. (2007) Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. *J Immunol* 179(6):4249–4254.
33. Epel ES, et al. (2004) Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA* 101(49):17312–17315.
34. Humphreys J, et al. (2012) Telomere shortening in formerly abused and never abused women. *Biol Res Nurs* 14(2):115–123.
35. Ala-Mursula L, et al. (2013) Long-term unemployment is associated with short telomeres in 31-year-old men: An observational study in the northern Finland birth cohort 1966. *PLoS One* 8(11):e80094.
36. Litzelman K, et al. (2014) Association between informal caregiving and cellular aging in the survey of the health of Wisconsin: The role of caregiving characteristics, stress, and strain. *Am J Epidemiol* 179(11):1340–1352.
37. Ahola K, et al. (2012) Work-related exhaustion and telomere length: A population-based study. *PLoS One* 7(7):e40186.

38. Shalev I, et al. (2013) Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: A longitudinal study. *Mol Psychiatry* 18(5):576–581.
39. Puterman E, Lin J, Krauss J, Blackburn EH, Epel ES (2015) Determinants of telomere attrition over 1 year in healthy older women: Stress and health behaviors matter. *Mol Psychiatry* 20(4):529–535.
40. Jodczyk S, Fergusson DM, Horwood LJ, Pearson JF, Kennedy MA (2014) No association between mean telomere length and life stress observed in a 30 year birth cohort. *PLoS One* 9(5):e97102.
41. Verhoeven JE, van Oppen P, Puterman E, Elzinga B, Penninx BWJH (2015) The association of early and recent psychosocial life stress with leukocyte telomere length. *Psychosom Med* 77(8):882–891.
42. Surtees PG, et al. (2011) Life Stress, emotional health, and mean telomere length in the European Prospective Investigation into Cancer (EPIC)-Norfolk population study. *J Gernotol A Biol Sci Med Sci* 66(11):1152–1162.
43. Glickman ME, Rao SR, Schultz MR (2014) False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol* 67(8):850–857.
44. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc B* 57(1):289–300.
45. Robertson T, et al. (2013) Is socioeconomic status associated with biological aging as measured by telomere length? *Epidemiol Rev* 35:98–111.
46. Oliveira BS, et al. (2016) Systematic review of the association between chronic social stress and telomere length: A life course perspective. *Ageing Res Rev* 26:37–52.
47. Shalev I, et al. (2013) Stress and telomere biology: A lifespan perspective. *Psychoneuroendocrinology* 38(9):1835–1842.
48. Levine ME, Cole SW, Weir DR, Crimmins EM (2015) Childhood and later life stressors and increased inflammatory gene expression at older ages. *Soc Sci Med* 130:16–22.
49. Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics (2012) The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* 129(1):e232–e246.
50. Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009) Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* 10(6):434–445.
51. Seeman T, et al. (2010) Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. *Am J Hum Biol* 22(4):463–472.
52. Brown G, Harris T (1989) Life events and measurement. *Life Events and Illness*, eds Brown G, Harris T (Guilford, London), pp 3–45.
53. Verhoeven JE, van Oppen P, Puterman E, Elzinga B, Penninx BWJH (2015) The association of early and recent psychosocial life stress with leukocyte telomere length. *Psychosom Med* 77(8):882–891.
54. Fyhrquist F, Saijonmaa O, Strandberg T (2013) The roles of senescence and telomere shortening in cardiovascular disease. *Nat Rev Cardiol* 10(5):274–283.
55. Aviv A, Kark JD, Susser E (2015) Telomeres, atherosclerosis, and human longevity: A causal hypothesis. *Epidemiology* 26(3):295–299.
56. Sanders JL, Newman AB (2013) Telomere length in epidemiology: A biomarker of aging, age-related disease, both, or neither? *Epidemiol Rev* 35(SI):112–131.
57. Maughan B, Rutter M (1997) Retrospective reporting of childhood adversity: Issues in assessing long-term recall. *J Pers Disord* 11(1):19–33.
58. Dube SR, Williamson DF, Thompson T, Felitti VJ, Anda RF (2004) Assessing the reliability of retrospective reports of adverse childhood experiences among adult HMO members attending a primary care clinic. *Child Abuse Negl* 28(7):729–737.
59. MacDonald K, et al. (2016) Minimization of childhood maltreatment is common and consequential: Results from a large, multinational sample using the Childhood Trauma Questionnaire. *PLoS One* 11(1):e0146058.
60. Hardt J, Rutter M (2004) Validity of adult retrospective reports of adverse childhood experiences: Review of the evidence. *J Child Psychol Psychiatry* 45(2):260–273.
61. Hardt J, Sidor A, Bracko M, Egle UT (2006) Reliability of retrospective assessments of childhood experiences in Germany. *J Nerv Ment Dis* 194(9):676–683.
62. Smith JP (2009) Reconstructing childhood health histories. *Demography* 46(2):387–403.
63. Havari E, Mazzonna F (2015) Can we trust older people's statements on their childhood circumstances? Evidence from SHARELIFE. *Eur J Popul* 31(3):233–257.
64. Hardt J, Vellaisamy P, Schoon I (2010) Sequelae of prospective versus retrospective reports of adverse childhood experiences. *Psychol Rep* 107(2):425–440.
65. Mitchell C, et al. (2014) Social disadvantage, genetic sensitivity, and children's telomere length. *Proc Natl Acad Sci USA* 111(16):5944–5949.
66. Hunt SC, et al. (2008) Leukocyte telomeres are longer in African Americans than in whites: The National Heart, Lung, and Blood Institute Family Heart Study and the Bogalusa Heart Study. *Aging Cell* 7(4):451–458.
67. Diez Roux AV, et al. (2009) Race/ethnicity and telomere length in the Multi-Ethnic Study of Atherosclerosis. *Aging Cell* 8(3):251–257.
68. Needham BL, et al. (2013) Socioeconomic status, health behavior, and leukocyte telomere length in the National Health and Nutrition Examination Survey, 1999-2002. *Soc Sci Med* 85:1–8.
69. Slopen N, et al. (2016) Racial disparities in child adversity in the U.S.: Interactions with family immigration history and income. *Am J Prev Med* 50(1):47–56.
70. Boyce WT, Ellis BJ (2005) Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* 17(2):271–301.
71. Puterman E, Epel E (2012) An intricate dance: Life experience, multisystem resiliency, and rate of telomere decline throughout the lifespan. *Soc Personal Psychol Compass* 6(11):807–825.
72. Shonkoff JP, Fisher PA (2013) Rethinking evidence-based practice and two-generation programs to create the future of early childhood policy. *Dev Psychopathol* 25(4 Pt 2):1635–1653.
73. Heeringa SG, Connor J (1995) *Technical Description of the Health and Retirement Study Sample Design* (Univ of Michigan, Ann Arbor, MI).
74. Gutierrez-Rodrigues F, Santana-Lemos BA, Scheucher PS, Alves-Paiva RM, Calado RT (2014) Direct comparison of flow-FISH and qPCR as diagnostic tests for telomere length measurement in humans. *PLoS One* 9(11):e113747.