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# Lifetime socioeconomic status and early life microbial environments predict adult blood telomere length in the Philippines

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**Abstract**

**Objectives:** Psychosocial stress is postulated to hasten senescence in part by accelerating the shortening of telomere length (TL). One pathway through which this may happen is via increasing inflammation and innate immune system activation—a pathway which recent studies suggest acts more strongly for those who grew up in low microbial environments. Thus, we hypothesized that: (1) Psychosocial stress will be inversely associated with TL, (2) early life microbial environments will predict TL, and (3) microbial environments will moderate the association between psychosocial stress and TL.

**Methods:** We utilized data from the Cebu Longitudinal Health and Nutrition Survey based in the Philippines ($N = 1410$). We determined early life microbial environments by season of birth and exposure to animal feces. Psychosocial stress measures included perceived stress in adulthood, lifetime socioeconomic status (SES), and parental instability in childhood. TL was measured in blood from young adults by qPCR.

**Results:** Contrary to predictions, we found that higher SES was associated with shorter TL and no association of TL with the other stress variables. Individuals born in the higher microbial exposure season had shorter TL, but early life microbial environments did not moderate the association between psychosocial stress and TL.

**Conclusions:** The unexpected inverse association between SES and TL suggests that higher SES, while indexing lower psychosocial stress, may impact TL more strongly through nonstress factors in the Philippines, such as unhealthy behavior. The inverse association between microbial environments and TL is consistent with other evidence connecting early life infections to decreased life expectancies.

## 1 | INTRODUCTION

Psychosocial stress is thought to increase morbidity and mortality in part by accelerating the shortening of telomeres, nucleotide repeats which cap the ends of chromosomes and shorten with cell replication and age (Price, Kao, Burgers, Carpenter, & Tyrka, 2013). Telomere length (TL) shortening eventually leads to cellular apoptosis or replicative senescence and is associated with, and possibly contributes to, age-related health decline (Aviv et al., 2008; Hamad, Walter, & Rehkopf, 2016).

Over the past decade, studies in the United States and Europe have demonstrated that individuals reporting high

  

levels of psychosocial stress have shorter blood and saliva TL, particularly when stress is experienced early in life (Drury et al., 2012; Hartmann, Boehner, Groenen, & Kalb, 2010; Needham, Fernandez, Lin, Epel, & Blackburn, 2012; O'Donovan et al., 2011; Parks et al., 2009; Shalev et al., 2013). However, meta-analyses of adult stress and TL have only found a weak, negative association with considerable heterogeneity across studies (Mathur et al., 2016; Schutte & Malouff, 2014), and investigations of early life stress and adult TL are similarly inconsistent (Glass, Parts, Knowles, Aviv, & Spector, 2010; Jodczyk, Fergusson, Horwood, Pearson, & Kennedy, 2014; Oliveira et al., 2017; Price et al., 2013).

Potentially contributing to this heterogeneity are inflammation and innate immune system activation, which have been shown to be heightened among stressed individuals. In high-income, low microbial contexts in Europe and the United States, increased psychosocial stress is associated with an upregulation of inflammatory markers, such as C-Reactive Protein, and prolonged innate immune system activation (Segerstrom & Miller, 2004). There is further evidence that experiencing adversities, such as low social class, in early life is associated with increased inflammation in adulthood regardless of current adult stress (Miller et al., 2009). These elevated immune responses increase mitotic proliferation of white blood cells (WBCs) while also increasing oxidative stress. Both processes are expected to accelerate the shortening of TL and hasten the pace of functional decline in processes dependent on proliferation (Epel et al., 2004; Oikawa & Kawanishi, 1999; von Zglinicki, 2002). Thus, researchers have hypothesized that these pathways may explain the broader negative associations between psychosocial stress and TL in blood and saliva (Epel et al., 2004; Kawanishi & Oikawa, 2004; Manoliu, Bosch, Brakowski, Brühl, & Seifritz, 2017; Osler, Bendix, Rask, & Rod, 2016).

Interestingly, high early life microbial environments may attenuate the degree to which psychosocial stress is associated with chronic inflammation and innate immune activity (Bilbo & Schwarz, 2009; McDade, Hoke, Borja, Adair, & Kuzawa, 2013). Previous studies in Cebu, the Philippines, have shown that the immune systems of individuals exposed to high microbial environments in early life show increased physiological investment in acquired immunity over innate immunity (Georgiev, Kuzawa, & McDade, 2016) and reduced inflammation outside of active infections (McDade et al., 2012). Further, McDade et al. (2013) demonstrated that associations between psychosocial stress and inflammation were apparent only in individuals with low microbial environments in early life. That is, individuals with early life environments with lower microbe exposure showed increased inflammation with increased psychosocial stress while those with high microbial exposure did not. Similar results have been shown in a longitudinal cohort study in China (Yazawa et al., 2015). Experimental studies in rodents parallel these findings, demonstrating that exposure to immune challenges in early life lead to lower levels of innate immune cell proliferation (Olszak et al., 2012) as well as reduced associations between psychosocial stress and inflammation, WBC proliferation, and oxidative stress (Harbuz, Chover-Gonzalez, Gibert-Rahola, & Jessop, 2002; Shanks et al., 2000). Through its potential impacts on psychosocial stress-immune system associations, early life microbial environments might reduce the strength of the association between psychosocial stress and blood TL.

Building on this, we examine whether higher early life microbial environments predict reduced associations between psychosocial stress, experienced throughout childhood and young adulthood, and blood TL in adulthood. We use data from a long-term prospective birth cohort study in metropolitan Cebu, the Philippines, to test three hypotheses. First, we hypothesized that individuals with higher exposure to psychosocial stress throughout childhood and early adulthood would have shorter adult TL. Second, we hypothesized that proxies for early life microbial environments would predict TL in adulthood (due to contrasting results with microbial exposure and immune function, we did not hypothesize a specific direction, see Georgiev et al., 2016). Lastly, we hypothesized that individuals who grew up in lower microbial environments would show a stronger association between exposure to psychosocial stressors and TL when compared to their peers with higher early life microbial environments.

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

Our sample consisted of young adult male and female participants of the Cebu Longitudinal Health and Nutritional Survey (CLHNS), a birth cohort study in metropolitan Cebu, the Philippines ($n = 1410$) (Adair et al., 2011). The survey began in 1983 with 3327 pregnant mothers randomly selected from rural and urban neighborhoods. The individuals included in the current analysis are the children (aged 20.8–22.5 years at telomere measurement) of these mothers who have been followed since birth. Due to loss from attrition, which is unavoidable in longitudinal studies, DNA was extracted from blood samples in 2005 from 1759 of the singletons from the original survey (Adair et al., 2011; Eisenberg, Kuzawa, & Hayes, 2015). Of these samples, we had 1410 individuals with all variables of interest. There were no differences in TL and the other covariates between those included and excluded (Supporting Information). Written informed consent was obtained from all participants, and data and sample collection were conducted with approval and oversight from the Institutional Review Boards of the University of North Carolina and Northwestern University.

Telomere measurement and analysis using de-identified samples and data were not considered human subject research by Northwestern University's Institutional Review Boards.

### 2.2 | Measures of stress

We included three putative measures of psychosocial stress: childhood parental instability, average lifetime socioeconomic status (SES), and current perceived stress. These measures cover childhood, adolescence, and young adulthood, potentially allowing us to simultaneously examine psychosocial stress throughout the lifespan in related yet distinct domains that may exert both independent and cumulative influences on physiology (Lupien, McEwen, Gunnar, & Heim, 2009; McLaughlin, 2016). We chose these specific variables because they have been associated with shortened TL in previous studies based in the United States and Western Europe (Drury et al., 2014; Mathur et al., 2016; Price et al., 2013; Ridout, Ridout, Price, Sen, & Tyrka, 2016). Importantly, we utilized versions of these variables that have also been associated with physiological changes relevant to our hypothesized pathway in the current cohort. In past studies in this cohort, our measure of SES has been associated with cortisol levels (Desantis, Kuzawa, & Adam, 2015), parental instability with immunophenotype and inflammation (Georgiev et al., 2016; McDade et al., 2013), and current perceived stress with inflammation (McDade et al., 2013).

Parental instability was coded as a dichotomous variable. Individuals classified as experiencing parental instability were those whose father or mother was deceased or absent at any point before age 11, whose mother was unmarried during their first year of life or beyond, or whose mother remarried during their childhood (for more see Gettler et al., 2015).

Average lifetime SES was coded as the mean of the combination of household income, parental education, and assets throughout the individual's life (collected at birth and again in the six survey waves between 1986 and 2005) (Desantis et al., 2015). Household income was adjusted for inflation then logged for each survey wave. Participants reported on whether they had, or did not have, 11 assets relevant to social class (described more fully in Desantis et al., 2015). Parental education was the average level of education for both parents at each wave or the level of education of the single parent or caregiver if one or both parents are missing. All values were rescaled to have a mean of zero and a standard deviation of one and then summed for each wave before being averaged together (Cronbach's α between SES variables within each wave range = 0.708–0.712).

Current perceived stress was assessed with a modified version of the 10-item Perceived Stress Scale (PSS) that measures psychosocial stress over the preceding month (Cohen, Kamarck, & Mermelstein, 1983; McDade et al., 2013). As described elsewhere (McDade et al., 2013): the PSS was administered in Cebuano after being translated from English and back-translated to confirm accuracy. Preliminary research with the questionnaire in Cebu led the research team to replace two questions (item 9, "how often have you been angered…"; item 10, "how often have you felt difficulties were piling up…") with "In the last 4 weeks, how often have you dealt successfully with irritating life hassles?" and "In the last 4 weeks, how often have you felt that you were effectively coping with important changes that were occurring in your life?" Scores on the PSS were centered on zero (0) before statistical analysis to reduce nonessential collinearity issues with interaction terms (Cohen, Cohen, West, & Aiken, 2003). The inter-correlations of all three psychosocial stress variables are below $r = 0.15$ and the variable inflation factors (VIFs), which is a measure of collinearity, are all below 3. Common cutoffs are 0.5 for pairwise correlations and 10 for VIFs (Supporting Information; Vatcheva, Lee, McCormick, & Rahbar, 2016).

### 2.3 | Microbial environments

We utilized two proxy measures of early life microbial environments: exposure to animal feces in the first two years of life and season of birth. Both have previously been associated with immune activity in adulthood in this cohort (Georgiev et al., 2016; McDade et al., 2013). Exposure to animal feces was defined as the total number of bi-monthly surveys, during the first two years of life, when the infant was observed crawling on the floor and animals were present in the home (range: 0–11). Exposure scores were then centered for statistical analysis. We classified infants by season of birth depending on whether they were born in the dry season (February-April) or wet season (May-January). Being born during the dry season was used as a proxy for microbial exposure in this population, because these individuals spend a greater proportion of their first year of life in the higher microbial wet season.

### 2.4 | Telomere measurement

Full description of the methods used for measuring blood TL have been published previously (Eisenberg, Hayes, & Kuzawa, 2012; Eisenberg et al., 2015). Briefly, DNA was extracted from the blood samples of 1753 singletons from the 1983 to 1984 CLHNS birth cohort, and TL (measured as the relative telomere to single copy gene ratio or "*T/S* ratio") was analyzed using a modified version the monochrome multiplex quantitative polymerase chain reaction (MMqPCR) method (Cawthon, 2009; Eisenberg et al., 2012,2015). A subsample of 190 CLHNS samples showed a correlation between MMqPCR measures and a southern blot of terminal restriction fragments ($r = 0.663$) that is on par with recent qPCR TL validation efforts (Eisenberg et al., 2015; Elbers et al., 2014). Since the coefficient of variation

(CV) has recently been recognized to be an invalid statistic to assess TL measurement reliability, we instead use the intraclass correlation coefficient (ICC) (Eisenberg, 2016; Verhulst et al., 2016) which estimates the percent of variation attributable to individuals versus to measurement error. Individual and average ICCs were calculated using a one-way random effects model to calculate absolute agreement between the averages of the same samples run in triplicate on different runs with the ICC command in Stata 14.1. Individual and average ICC values corresponded to ICC(1) and ICC(k) in McGraw and Wong (1996). Individual ICC gives an estimate of the reliability of measures of samples analyzed on one run (in triplicate), while average ICC gives an estimate of the reliability of the average TL estimate of a sample measured across multiple runs. While considerable numbers of samples in these analyses were included on multiple runs, these samples were re-run because of initially high intra-assay CVs. In all, 873 of the samples were run separately in triplicate on two separate runs and had an individual ICC of 0.81 (95% CI: 0.79–0.84) and average ICC of 0.89 (95% CI 0.88–0.91). Conventional rules of thumb suggest that these ICC values are good (Cicchetti, 1994). Since this ICC represents a subset of more noisy measures than the population measures, this ICC is an under-estimate of the true inter-run reliability. It is not surprising that it is slightly lower than the only other reports of ICC values in telomere biology coming from results from the lab which originated the qPCR assay (Eisenberg 2016).

### 2.5 | Statistical analyses

In addition to our measures of psychosocial stress, we included two potential mediator variables and a series of control variables that have been associated with TL in previous studies. Body mass index (BMI) at time of sample collection and smoking status ("never", "former", or "current") were included as potential mediators because they may lie within our hypothesized pathway of interest. Individuals with increased psychosocial stress are often more likely to smoke and have higher BMI (e.g., Ng & Jeffery, 2003), and increased BMI and smoking have been associated with shorter TL (reviewed in Eisenberg, 2011).

Our control variables lie outside of our hypothesized pathway of interest and include age, sex, age*sex interaction, the urbanicity of an individual's barangays (or neighborhoods) averaged for all waves of data collection (Dahly & Adair, 2007), and 10 principle components (PCs) of genome-wide genetic variation to control for possible population substructure (Croteau-Chonka et al., 2011,2012). Older age and being male are commonly associated with shorter TL (reviewed in Eisenberg, 2011). Further, the age-related TL shortening is thought to be accelerated in men compared to women (Mayer et al., 2006). Urbanicity is a community-level composite variable indicating the population size and density of an individual's neighborhood as well as the presence of available communications services (e.g., phone service, mail, internet), transportation (e.g., paved roads and public transportation), educational facilities (e.g., primary and secondary schools, colleges), health services (e.g., hospitals, clinics, community health centers), and markets (e.g., small retail shops, drug stores, grocery stores) (Dahly & Adair, 2007). It has previously been associated with TL in our cohort (Bethancourt et al., 2015) and lies outside of our pathway of interest, so it is included as a measure of access to community-level, shared resources. The 10 PCs of genome-wide genetic variation were included to minimize the potential effects of subpopulations within our cohort which could systematically vary for both our stress variables and TL (Croteau-Chonka et al., 2011,2012). We tested our null hypotheses with minimally controlled models where only age and sex were included as well as with maximally controlled models where all mediator and control variables were included.

We performed regression analyses, first testing the main effects of stress on TL (Table 1: Models 1 & 2) and microbial environments on TL (Models 3 & 4). Then we built on these to include the interactions between stress and microbial exposure (Models 5 & 6). To address multiple-testing, Wald joint-significance tests were utilized (Cohen, Cohen, West, & Aiken, 2003). These tested the null hypotheses that: (1) all stressor measures are not associated with TL, (2) all microbial exposure measures are not associated with TL, and (3) all stressor*microbial exposure interactions are not associated with TL and were performed for each appropriate regression model. In addition to these *a priori* tests, we conducted a series of sensitivity analyses that involved removing or adding variables in these *a priori* tests to explore potential causal pathways and examine the robustness of our findings.

## 3 | RESULTS

Descriptive statistics of key variables are displayed in Table 2. Eleven percent of participants experienced parental instability in childhood. The mean PSS score was 17.22 with a standard deviation of 4.48. While this mean is comparable to similarly aged adults in the United States (Roberti, Harrington, & Storch, 2006), the distribution is more concentrated—standard deviations for US populations have been reported around 6.1 to 6.86 (Cohen & Janicki-Deverts, 2012; Roberti et al., 2006). This may limit our ability to discern associations with TL, but, as mentioned in the Methods, this measure of PSS has been associated with physiological markers in Cebu in the past (McDade et al., 2013). Further, our sample size is much larger than previous studies demonstrating associations between PSS and TL (Mathur et al., 2016). About twenty percent of our participants were born in the dry season.

**TABLE 1** Regression models of psychosocial stress, pathogen exposure, and interactions predicting TL in 1410 young adults

| Line | Variable | Model: | 1 | 2[a] | 3 | 4[a] | 5 | 6[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | Perceived Stress Scale (PSS) | | 0.000 | 0.000 | | | 0.000 | 0.000 |
| 2 | Parental Instability | | 0.003 | −0.001 | | | 0.000 | −0.003 |
| 3 | Average SES | | 0.000 | **−0.0062**** | | | −0.001 | **−0.0072**** |
| 4 | Feces Exposure | | | | 0.000 | 0.002 | −0.001 | 0.002 |
| 5 | Season of Birth | | | | **−0.065***** | **−0.053***** | **−0.062***** | **−0.049***** |
| 6 | Feces Exposure*PSS | | | | | | 0.000 | 0.000 |
| 7 | Feces Exposure*Parental Instability | | | | | | **0.0077+** | 0.006 |
| 8 | Feces Exposure*SES | | | | | | −0.001 | −0.001 |
| 9 | Season of Birth*PSS | | | | | | 0.000 | 0.000 |
| 10 | Season of Birth*Parental Instability | | | | | | −0.043 | −0.043 |
| 11 | Season of Birth*SES | | | | | | **0.0092+** | **0.012*** |
| 12 | Joint sig. of variables 1-3 | | 0.99 | **0.048** | | | 0.97 | **0.035** |
| 13 | Joint sig. of variables 4-5 | | | | **0.0000** | **0.00010** | **0.00010** | **0.0010** |
| 14 | Joint sig. of variables 6-11 | | | | | | 0.23 | 0.13 |

Values on lines 1-11 are $\beta$ coefficients; + $P < .10$, * $P < .05$, ** $P < .01$, *** $P < .001$; Lines 12-14 are $P$-values.

All models control for age in 2005, sex, and age × sex.

[a] Maximally controlled model additionally controls for smoking status, urbanicity over the lifetime, body mass index at sample collection, and the first ten principal components of genetic variation. Complete regression statistics including for control variables are included in Supporting Information Table S1.

### 3.1 | Association between stress and TL

First, we tested whether increased psychosocial stress was associated with shorter TL by evaluating whether our putative measures of stress during development (parental instability in childhood), adulthood (perceived stress), and cumulatively over the life course (average lifetime SES) jointly contributed to explaining variation in TL (using a Wald test; Table 1, Line 12). These tests revealed a significant association between the stress variables and TL in the maximally controlled models (Model 2: $P = .035$; Model 6: $P = .0481$). Wald tests of our stress variables were not significant in minimally controlled models (1 & 5). Examining the regression results shows that, out of our three psychosocial stress variables, only SES is significantly associated with TL (Table 1, Line 3; Figure 1). However, this association is in the opposite direction of expectations: higher average SES is associated with shorter TL ($\beta = -0.0072$; $P = .004$). An increase of one standard deviation in SES is associated with telomeres that are approximately 48 base pairs shorter, which is comparable to an increase in 3.5 years of telomeric aging in mid-adulthood in this population (Eisenberg et al., 2012,2015).

We conducted a series of sensitivity analyses in which we investigated whether this unexpected association was driven by a particular sub-component of SES or specific time period. Overall, we found that associations were in the same direction as the original findings regardless of specific sub-component or time period. However, associations were stronger with our original composite measure averaged over the lifetime (see Supporting Information for details).

Since SES only has a significant association in our maximally controlled models (2 & 6), we also reran these regressions while removing mediator and control variables, one at a time. This allowed us to explore how the association between SES and TL changes with the exclusion of individual covariates, possibly providing insights into its relationship with TL. Completing these analyses, we found that average SES has a significant effect only when average urbanicity, a measure of the urban development of an individual's community and the presence of public goods such as schools and hospitals, is included in the regression model. Average urbanicity is positively associated with TL ($\beta = 0.0030$; $P < .0001$ in both models) and its addition to the regression model strengthens the effect size of average SES in model 4 from −0.00050 to −0.0072. Average SES and average urbanicity are positively correlated ($r = 0.4098$; $P < .00010$), meaning that individuals in more urbanized settings tend to have more income, parents with higher education levels, and more assets. The implications of this are briefly commented on below.

**TABLE 2** Descriptive statistics of independent variables

| Variable | Mean (%) | SD |
|---|---|---|
| Age | 21.67 | 0.35 |
| Sex (Male) | 54.96% | - |
| BMI in 2005 | 20.7 | 3.17 |
| Average Urbanicity | 35.33 | 12.40 |
| Current Smoker | 30.14% | - |
| Former Smoker | 24.68% | - |
| Perceived Stress Scale | 17.22 | 4.48 |
| Parental Instability (% unstable) | 10.99% | - |
| Average SES | 0.03 | 2.14 |
| Feces Exposure | 3.96 | 3.04 |
| Season of Birth (% dry) | 19.57% | - |
| T/S ratio (unadjusted) | 0.78 | 0.16 |

Full regression results are available in our Supporting Information.

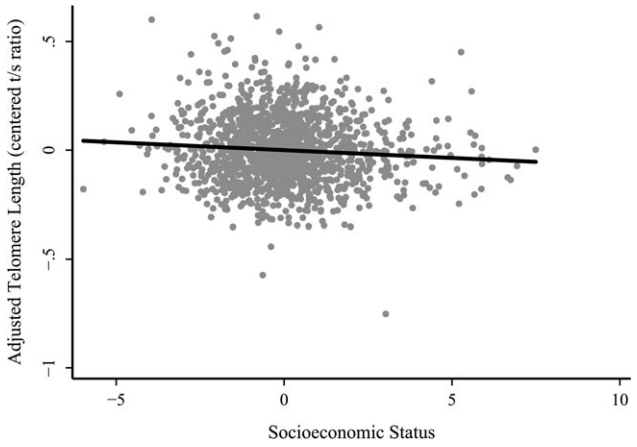


**FIGURE 1** Points are telomere length (t/s ratios adjusted for covariates from Table 1, Model 4) by average socioeconomic status; line represents linear best fit

### 3.2 | Association between microbial environments and TL

For our second hypothesis, we tested whether microbial environments in early life predict adult TL by evaluating whether both measures, season of birth and exposure to animal feces, jointly contributed to explaining variation in TL (Table 1, Line 13). These joint significance tests revealed significant associations between microbial environments and TL that is attenuated slightly in the maximally (Model 4: $\beta = -0.053$; $P < .0001$; Model 6: $\beta = -0.049$; $P = .001$) compared to the minimally controlled models (Model 3: $\beta = -0.065$; $P < .0001$; Model 5: $\beta = -0.062$; $P < .0001$). Examining the full regression results reveals that only season of birth is independently significant (Table 1, Line 5 and Figure 2). Being born in the dry season, which indicates greater infection risk in the first year of life, is associated with telomeres that are approximately 153 base pairs shorter, comparable to an increase in 11.3 years of telomeric aging in mid-adulthood in this population.

A recent analysis of this cohort by Eisenberg et al. (2016) found that infectious disease in early life, measured by diarrheal morbidity between 6 and 12 months of age, predicted TL in young adulthood. Since being born in the dry season is associated with higher chance of infectious disease in Cebu (McDade et al., 2013), it may be that infectious disease, and not microbial environments, leads to shortened adult TL. Increased rates of diarrheal morbidity between 6 and 12 months of age is associated with shorter TL ($\beta = -0.0488$; $P = .013$) when added to our regression model 6. However, the effect of being born in the dry season remains associated with shorter TL and is not substantially attenuated ($\beta = -0.0460$; $P = .001$ with diarrheal morbidity versus $\beta = -0.0486$; $P = .0004$ without in model 6).

### 3.3 | Moderation of stress and TL associations by microbial environments

Lastly, we tested whether microbial exposures moderate the association between psychosocial stress and TL by evaluating whether all microbial*stressor interaction variables jointly contributed to explaining variation in TL. These joint significance tests did not reveal any significant associations between the interaction variables and TL. Thus, we did not find support for this hypothesis. Further, our joint significance results were significant for our psychosocial stress measures with and without controlling for early life microbial exposures, and the SES-TL effect was only minimally increased when microbial exposures were included. Taken together, these results suggest it is unlikely that our SES effects were driven by microbial exposures. An exploratory examination of our regression models indicates that the interaction between season of birth and average SES was significant in our maximally controlled model 6 ($\beta = 0.0117$; $P = .0320$). That is, individuals born in the wet season (lower microbial exposure) display an association between SES and shorter TL while those born in the dry season (higher microbial exposure) do not. However, this regression result was not supported by our Wald tests and may be a spurious result of multiple testing.

## 4 | DISCUSSION

We examined predictors of young adult blood TL to test three hypotheses: (1) that increased exposure to psychosocial stress is associated with shorter TL, (2) that early life microbial environments predict adult TL, and (3) that microbial environments in early life moderate the association between psychosocial stress and adult TL. Using prospectively

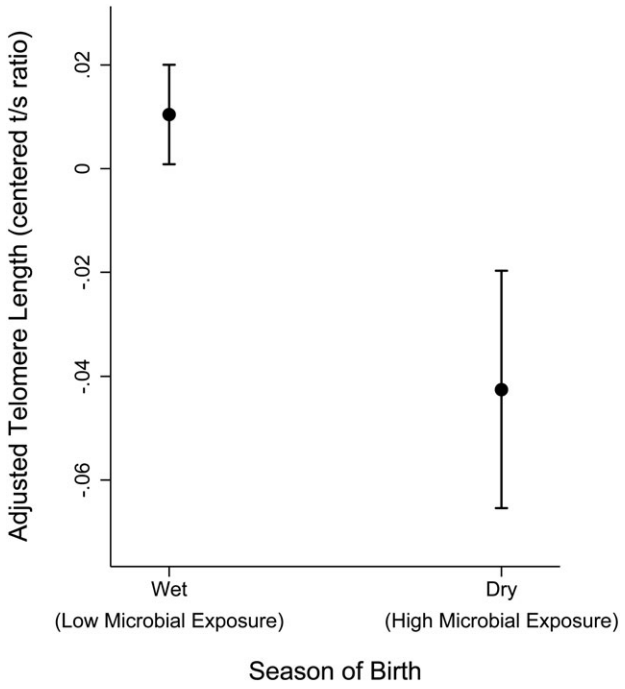


**FIGURE 2** Telomere length by season of birth. Points represent the predicted means of each group after adjusting for all covariates from Table 1, Model 4 constant. Error bars represent 95% confidence intervals for these means

collected data from the Philippines, we found support for the second hypothesis, that microbial environments in early life are associated with shorter TL in young adulthood. However, our findings do not support our first or third hypotheses.

While the stress variables in this study explain a significant amount of variation in TL when their effects are considered together, we found this was driven by higher SES being associated with shorter TL—contrary to our predictions and much of the existing literature (Cherkas et al., 2006; Needham et al., 2012,2013; Oliveira et al., 2016; Robertson et al., 2012). One previous study did find an inverse association between SES and TL in elderly men in Hong Kong (Woo, Suen, Leung, Tang, & Ebrahim, 2009). The authors of this study speculated that men with higher SES may have experienced more stress with retirement and shifting status in family and society, which may explain their shorter TL. However, it is unlikely that our finding is due to higher SES individuals experiencing higher levels of stress. In Cebu, higher SES is associated with lower scores on the PSS (Supporting Information), and higher SES adults show physiological profiles, such as cortisol secretion, consistent with lower stress (Desantis et al., 2015).

Interestingly, the association between SES and TL only becomes significant when adjusting for urbanicity, a measure of community-level urbanization and resources such as hospitals and markets. This suggests that the effects of SES are occurring on the individual- or household-level, because urbanicity is expected to track the impact of resources in the broader environment. Since urbanicity is positively associated with both SES and TL (Supporting Information), it is likely these relationships confound SES when not included in the analysis. Unfortunately, it is unclear what underlies urbanicity's relationship with TL. Urbanicity may be important in accessing healthcare, more diverse foods, improved social networks, decreased childhood and adolescent microbial exposure, or it may be the combination of these factors. Future studies should examine these components in more depth, testing the potential pathways linking broader social and physical environments to cellular health and TL. Lastly, while the SES association is surprising, the positive association between neighborhood measures and TL are in line with previous studies in the United States (Needham et al., 2014; Theall, Brett, Shirtcliff, Dunn, & Drury, 2013), suggesting that behaviors specific to higher SES in Cebu are driving our inverse association between SES and TL.

In studies of SES and health outcomes, higher SES is normally assumed to reflect lower stress, less material deprivation, and healthier behavior (Adler & Stewart, 2010). While this is broadly true in high-income populations, associations between health behaviors and SES may be more complicated in populations experiencing nutritional and epidemiological transitions. Previous studies in Cebu have found associations between higher SES and several negative health outcomes and behaviors including gains in BMI, increased central adiposity and overweight status, higher proportions of dietary fat, and decreased rates of breastfeeding (Colchero, Caballero, & Bishai, 2008; Dahly & Adair, 2005, 2010; Kelles & Adair, 2009; Schmeer, 2010).

Thus, higher SES may indicate less healthy lifestyles even while stress and material deprivation are lowered, and these less healthy lifestyles may be the key factors negatively impacting TL. Woo et al.'s (2009) study, that also found an inverse association between SES and TL, was performed in Hong Kong where higher SES is similarly associated with less healthy behaviors (Chan & Leung, 2015). This highlights the importance of critically assessing factors that vary with stress and adversity (e.g., health behaviors) before attributing causality of TL differences to psychosocial stress. These other factors may be more strongly tied to TL, and their varying relationships with stress may help explain the heterogeneity between previous studies of psychosocial stress and TL. Since we were originally interested in the role of psychosocial stress connecting SES and TL, we did not include many of these potential factors. We did assess both smoking status and BMI as potential mediators, but removing them from the regression models in our sensitivity analyses did not impact SES-TL associations (Supporting Information). While we present health behaviors as one potential factor to explain our findings, it is not the sole potential factor. For example, exposure to pollutants is often associated with SES and can differ on the household-level (Khan et al., 2017).

With these points in mind, it is also important to note that the PSS has not been directly validated in Cebu. It is possible that we missed aspects of psychosocial stress that impact TL in Cebu even while PSS accurately assesses such stress in the United States (Kohrt et al., 2014; Tennyson, Kemp, & Rao, 2016). However, several questions were modified to improve local salience after pretesting with local participants. Further, prior work at Cebu has shown that PSS is associated with inflammation (McDade et al., 2013), suggesting that it is capturing relevant dimensions of psychosocial stress.

We also found that microbial environments in early life predict TL in young adulthood. This association is primarily driven by being born in the dry season, which is linked to increased microbial exposure in the first year of life (McDade et al., 2013). This finding extends the conclusions of a previous analysis in this cohort showing that infectious disease, assessed by diarrheal morbidity, between the ages of 6 and 12 months predicts shorter adult TL (Eisenberg, Borja, Hayes, & Kuzawa, 2017). The direction of causality of this past association was unclear. Increased proliferation of WBCs and increased inflammation due to infections is thought to shorten TL, but shorter TL also appears to increase risk of infection (Cohen et al., 2013). In contrast, season of birth is a more exogenous variable which is

unlikely to be influenced by TL. Thus, it is probable that being born in the dry season leads to increased infection risks which then cause accelerated TL shortening in early life.

Previous studies in the United States have found an association between SES and season of birth (Buckles & Hungerman, 2013), indicating that other important factors may be represented by season of birth—not solely microbial exposure. We do find an association between season of birth and parental instability in our dataset ($r = -0.059$; $P = .027$). However, since we do not find any other associations with season of birth, parental instability shows no significant association with TL, and the VIFs in our regressions are low, this association seems unlikely to have biased our results (Supporting Information). Thus, our findings, combined with previous studies showing that shorter TL predicts higher risk of mortality in adulthood (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003), may offer another biological pathway through which early life infectious disease impacts later life survival (Finch & Crimmins, 2004), particularly when considering that the effect size of this association is similar to 11.3 years of telomere aging in mid-adulthood. A survival analysis is not possible with our current data, but we would expect that this accelerated shortening could lead to decreased life expectancies. Existing studies in low and middle income countries have demonstrated associations between season of birth and increased adulthood mortality (e.g., Moore et al., 1997), but it is unclear whether these findings are related to TL.

Lastly, we failed to find evidence to support the hypothesis that microbial environments in early life moderate the association between psychosocial stress and TL. Our analysis was motivated, in part, by findings in this cohort that early life microbial exposures moderate the relationship between psychosocial stress and inflammation (McDade et al., 2013). Psychosocial stress is posited to impact TL through increasing levels of inflammation, so if early life microbial exposures moderate this relationship, we speculated, it may similarly moderate the relationship between psychosocial stress and TL. Past studies demonstrate considerable heterogeneity in stress-TL associations and our study only found an effect in a direction opposite to that expected. Thus, our inability to detect an interaction between stress and early life microbial environments could simply be due to there being no effect of stress on TL in Cebu. Despite past work at Cebu documenting a relationship between stress and inflammation in individuals exposed to low microbial environments in this cohort, the relationship may not be strong enough to lead to a measurable impact on TL. Individuals with low microbial exposure in Cebu likely still experience a higher immunological load than individuals living in Europe and the United States, so perhaps the threshold allowing for this pathway to lead to TL shortening is lower than what is experienced in Cebu. Cellular maintenance of TL increases during immune activation, so perhaps the differences in proliferation and oxidative stress between stressed and less stressed individuals have not outpaced these cellular processes in our sample. Future investigations could test direct associations between inflammatory markers and TL to examine whether the variation in inflammation in Cebu is indeed large enough to expect an impact on TL.

In conclusion, we found that higher lifetime SES and being born in the higher microbial exposure season are each associated with shorter TL. We did not find evidence that early life microbial environments moderate the relationship between psychosocial stress and adult TL. Our study suggests that measures of stress and adversity may have different associations with biology across contexts, and the nature of these differences may elucidate the pathways connecting stress and long-term biological change. Our finding that higher early life microbial environments predict shorter adult TL may also help to explain broader secular trends in improvements in life expectancy coincident with improved public health infrastructures and decreasing infectious disease loads.

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## AUTHOR CONTRIBUTIONS

RLT conducted the data analysis, participated in study design, and drafted the manuscript; LTG participated in study design and contributed to the manuscript; CWK participated in study design, contributed to the manuscript, and oversaw collection of 2005 field data; MGH participated in study design, oversaw lab work, and contributed to the manuscript; SSA had a key role in collection of field data and contributed to the manuscript; DTAE performed the telomere length analyses, participated in study design, contributed to the manuscript, and oversaw data analysis.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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