# **Reproduction predicts shorter telomeres and epigenetic age acceleration among Filipino young adult women**

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## **Abstract (max of 250 words)**

Evolutionary theory predicts that reproduction entails costs that compete with somatic maintenance, accelerating aging. While studies in both humans and non-human animals broadly support this hypothesis, the pathways through which these costs manifest remain unclear. Telomere length (TL) and epigenetic age (DNAmAge) provide new opportunities to probe links between human reproduction and senescence. Telomeres are repeating DNA sequences that shorten with cell replication, oxidative stress and age. Telomere shortening eventually limits cell division, contributing to senescence. DNAmAge is also highly correlated with chronological age, is accelerated relative to chronological age in response to exposures such as infection and psychosocial stress, and when accelerated is predictive of age-related morbidity and mortality. Physiological changes accompanying pregnancy, including immune suppression, increased infection risk, cell proliferation, and oxidative stress could accelerate both telomere shortening and epigenetic age. We examined whether parity in 20-22 year old women in the Philippines predicted TL (n=811) and DNAmAge (n=397), and whether these effects were stronger among women of lower socioeconomic status (SES). With each additional pregnancy, TL showed ~0.34-3.72 years of accelerated aging (p=0.042) and DNAmAge 0.46 years (p=0.001). Neither aging biomarker predicted fertility over the subsequent 4 years (p>0.3 for both), supporting a causal effect of parity on aging. Contrary to expectations, the association between parity and TL and DNAmAge was not stronger for low SES women (p>0.3 for both). Consistent with prior work, TL and DNAmAge were not correlated, but appear to represent distinct aspects of senescence, both exhibiting patterns of premature aging with reproduction among these young adult women.

**Significance statement** [120-word-maximum statement about the significance of their research paper written at a level understandable to an undergraduate-educated scientist outside their field of specialty. The primary goal of the Significance Statement is to explain the relevance of the work in broad context to a broad readership. The Significance Statement appears in the paper itself and is required for all research papers.]

Evolutionary theories predict that reproduction consumes resources at the expense of bodily maintenance and repair, thereby accelerating aging. While ‘costs of reproduction’ have been demonstrated in other species, little is known about their biological underpinnings, and to what extent they apply to humans. Here, we test for costs of reproduction using telomere length and epigenetic age – two emerging biological markers of cellular aging that predict future health and mortality. Using data from female participants in a long-term study in the Philippines, we show that both markers show signs of accelerated aging with increasing parity. These findings provide insights into the biological links between reproduction and aging, and demonstrate that these costs are evident in early adulthood.

## **Introduction**

The ‘disposable soma’ theory for the evolution of senescence (Kirkwood 1977; Kirkwood and Rose 1991) makes predictions about the biological pace of aging based on antagonistic pleiotropy between early life fertility and late life functional decline (Williams 1957) and other key tenets of life history theory (Stearns 1992). A core principle of the disposable soma theory is that resources are finite, and can be devoted to either reproduction or somatic maintenance, but not both. Thus, the disposable soma model leads to the prediction that the “cost of reproduction” (CoR) results in a trade-off between fertility (i.e. reproductive effort) and lifespan (i.e. maintenance effort). Experimental tests for CoR in animal models show that reproduction hastens senescence (Reznick 1985; Dijkstra et al. 1990); conversely, selection for late life fecundity results in lifespan extension (Curtsinger et al. 1995; Rose et al. 2002). However, testing for CoR in humans is difficult due to the necessarily observational nature of such research. Past studies, primarily based on historical datasets, suggest that increased reproduction is associated with shorter lifespans (Westendorp and Kirkwood 1998; Doblhammer and Oeppen 2003; Penn and Smith 2007; Gagnon et al. 2008; Gagnon et al. 2009; Bolund et al. 2016; but see Le Bourg 2007), and that these costs are more evident among individuals with limited resources (Tracer 1991; Lycett et al. 2000; Dribe 2004). However, past studies primarily use mortality as an endpoint, and have generally not addressed underlying biological pathways by which reproduction might influence survival. A deeper understanding of these pathways may allow us to better understand the evolutionary constraints surrounding reproduction and possibly to mitigate negative health effects of reproduction.

Here we test for CoR in humans using two recently described markers of aging: telomere length (TL) and epigenetic age (DNAmAge). Telomeres are non-coding DNA sequences that cap chromosomes, and are required for cell division and survival (Blackburn and Gall 1978; Meyne et al. 1989). Telomere length shortens with cell division and chronological age, placing a limit on the number of cell divisions (Olovnikov 1971; Watson 1972; Harley et al. 1990; Counter et al. 1992; Oikawa and Kawanishi 1999; Richter and Zglinicki 2007). Shorter TL, controlling for age, in turn predicts higher morbidity and mortality rates (Cawthon et al. 2003; Honig et al. 2004; Martin-Ruiz et al. 2006; Bakaysa et al. 2007; Kimura et al. 2008; Ehrlenbach et al. 2009; Fitzpatrick et al. 2011; Haycock et al. 2014). DNAmAge is an emerging measure of aging based on methylation levels at 353 distinct CpG sites, which are strongly correlated with chronological age (Horvath 2013). Individuals with accelerated DNAmAge relative to chronological age exhibit increased mortality rate independent of a host of associated risk factors (Marioni et al. 2015; Chen et al. 2016; Christiansen et al. 2016), including TL (Marioni et al. 2016). Both TL and DNAmAge are heritable (Hjelmborg et al. 2015; Honig et al. 2015; Horvath et al. 2015; Marioni et al. 2015), and exhibit signatures of accelerated aging with life exposures such as low income (Miller et al. 2015; Simons et al. 2016), psychosocial stress (Boks et al. 2015; Zannas et al. 2015) and HIV infection (Horvath and Levine 2015).

Among women, CoR are likely to accrue mainly during pregnancy and lactation (Speakman and Król 2005; Jasienska 2009), which both involve physiological changes that could accelerate senescence. During pregnancy, such changes include increased blood cell proliferation to compensate for fluid volume expansion (Hytten 1985; Hollowell et al. 2005; Lurie et al. 2008; Bauer 2014), a shift towards pro-inflammatory immunity (McDade 2003), and a reduction in immunocompetence that increases the rates of infection (Roberts et al. 1996; Lanciers et al. 1999; McDade 2003; Gray et al. 2005; Mugo et al. 2011). Data from cell culture, rodent based experiments, and observations in humans show that inflammation and infection increase cell proliferation and DNA damage, both expected to accelerate the pace of telomere shortening (Pommier et al. 1997; Aviv et al. 2006; Sampson et al. 2006; Adaikalakoteswari et al. 2007; Carrero et al. 2008; Hou et al. 2009; O’Donovan et al. 2009; Olivieri et al. 2009; Bendix et al. 2010; Farzaneh-Far et al. 2010; Salpea et al. 2010; O’Donovan et al. 2011; Solorio et al. 2011; Sanders et al. 2012). Accelerated DNAmAge relative to chronological age is a measure of ‘non-mitotic age’ and has been observed in other pro-inflammatory contexts (Horvath and Levine 2015; Kananen et al. 2015), and with menopause (Levine et al. 2016), an important physiological and life history transition in human females. DNAmAge acceleration arising from menopause, whether naturally-occurring or surgically-induced, was attenuated by hormone therapy (Levine et al. 2016),m, suggesting that physiological and hormonal changes like those accompanying pregnancy could have profound effects on DNAmAge. To our knowledge, no studies have examined the relationship between CoR and epigenetic age. However, two recent studies examining the relationship between parity and TL have yielded conflicting results, with one suggesting a positive effect of parity on TL (Barha et al. 2016), while the other reported no evidence for an effect of parity on TL (Lane-Cordova et al. 2017). Both findings are contrary to CoR and the predictions of the disposable soma theory of aging, arguing for additional research examining the relationship between parity and TL and new biomarkers such as DNAmAge.

### Here we use blood-derived TL and DNAmAge data collected from a cohort of young adult women (age 20-22) in the Philippines to test three inter-related hypotheses: we hypothesized that women with a greater number of pregnancies would have shorter TL (H1) and elevated DNAmAge (H2). We also hypothesized that any associations between number of pregnancies and TL shortening and DNAmAge increases would be stronger in women for whom resources are more constrained, as reflected in lower socioeconomic status (H3).

## **Results**

The women in our sample had a mean age of 21.7 (± 0.4) and a mean of 0.6 pregnancies (±0.9; Table 1). The 397 individuals in this sample with available DNAmAge data showed 3.94 year higher average DNAmAge (25.6 ± 3.2; Table 1) than their chronological age, although a commonly applied linear transformation to DNAmAge would have reduced this effect (Horvath 2013). In contrast, age-corrected TLs in this sample are longer than that of European and African American populations, but shorter than that of several African populations (details in Table S1). Perhaps related to the narrow age range in the sample, TL and DNAmAge showed no associations with each other (n=397, r=0.00, p=0.62), including when both measures had chronological age effects factored out (n=397, r=0.00, p=0.21).

**- [TABLE 1] -**

TL and DNAmAge showed the predicted (H1 & H2) evidence of accelerated aging with increasing number of pregnancies (Table 2; Figure 1; Table S2). After controlling for potential confounders, effect sizes of number of pregnancies on both TL and DNAmAge for most models increased (Table 2, Models 1 and 2 vs. 3 and 4 and Model 5 and 6 vs. 7 and 8). In contrast to total number of pregnancies, being currently pregnant was associated with a trend towards longer TL and significantly younger DNAmAge (Table 2, Models 3 & 7). However, these same models excluding current pregnancy slightly attenuated the associations of increasing numbers of pregnancies on TL and DNAmAge (Models 2 and 5). This suggests that controlling for what appears to be a transient protective effect of current pregnancy exposes more long-term costs of past pregnancies.

Each additional pregnancy was associated with a reduction in TL of 0.016 units (Table 2, Model 3), or an interpolated -50.6 bp/pregnancy based on previous southern blot measured TL in a subset of these samples (Eisenberg et al. 2015). The age related decline in TL in 36-69 year old women in this population was previously found to be 0.0043 relative TL units/year (n=1,845, p=7.19 x 10-16) (Eisenberg et al. 2012) or 13.6 bp/year, while the age related decline in TL within the younger and narrow age range in this sample is estimated between -0.027 and -0.047/year (Table 2, Models 1-4). In other populations the age-related decline in mid-late adulthood is approximately 25 bp/year (Hansen et al. 2016). This implies that one pregnancy is equivalent to between 0.34 and 3.72 years of telomere aging depending on the comparison population. Consistent with this calculation, each additional pregnancy was associated with 0.44-year increase in DNAmAge (Table 2, Model 7).

To test for reverse causation, we checked whether TL/DNAmAge at the time of measurement (in 2005) predicted the number of pregnancies over the subsequent four years (from 2005-2009). Controlling for the time elapsed between the 2005 and 2009 surveys, we found no effect of either TL (p = 0.835) or DNAmAge (p = 0.483) on subsequent parity, including after controlling for baseline parity in 2005 (Table S3).

Contrary to expectations (H3), there were no significant interactions between number of pregnancies and SES in predicting either TL (p=0.35; Table 2, Model 4) or DNAmAge (p=0.37; Table 2, Model 8). However, the main effect associations of number of pregnancies with TL and DNAmAge for these models increased slightly in magnitude with the inclusion of the interaction effect.

**- [TABLE 2] –**

**- [FIGURES 1A and 1B] -**

## **Discussion**

We found that women who had higher parity had shorter TL and accelerated DNAmAge. The effect sizes were dose-dependent and considerable, equivalent to between ~0.34 and 3.72 years of telomere aging and 0.44 years of DNAmAge aging per pregnancy. By and large, these findings were relatively robust to controls for potential confounders, which is particularly important in light of selection effects that frequently confound observational studies of the costs of reproduction. Intriguingly, women who were currently pregnant exhibited more youthful TL and DNAmAge. These results could reflect the suite of physiological shifts that occur during pregnancy, such as the protective effects of estrogens on TL and DNAmAge (Levine et al. 2016; Yeap et al. 2016), or perhaps even by the presence of fetal DNA in maternal circulation during pregnancy (Lo et al. 1997; Adams Waldorf et al. 2010). Current pregnancy status could therefore be important to control for in future studies investigating the costs of reproduction.

Contrary to our prediction that the costs of reproduction would be greatest among individuals with limited resources (Tracer 1991; Lycett et al. 2000; Dribe 2004), we found no evidence for an interaction between parity and SES in models predicting either TL or DNAmAge. It is unclear to what extent SES adequately captures resource limitations in this population, but given the relatively young age of the participants, a moderating effect of resource limitations might only emerge at more advanced ages. SES in this population may also index factors other than resource availability that contribute to accelerated aging, such as less healthful diets or decreases in physical activity.

Although consistent with theoretical predictions and non-human animal work, our findings contrast with two recent studies of TL and parity in women. The first, conducted among 75 Guatamalan Maya women, found a positive association between TL and number of surviving offspring over a 13-year time period (Barha et al. 2016). Unfortunately, TL in that study was determined using a combination of saliva- and buccal-derived DNA samples, which do not show a consistent relationship with chronological age (O’Callaghan et al. 2008; Thomas 2008; Goldman et al. 2017). Unlike longitudinal assessments of blood TL (Benetos et al. 2013), the two measures of TL in this study were also uncorrelated within individuals between the two timepoints, making comparisons between the findings of that study and our own blood-derived TL findings difficult. More recently, a study among 620 participants of the US-based CARDIA study found no evidence for an effect of parity on TL (Lane-Cordova et al. 2017). The reasons for such contrasting findings are unclear, but may relate to pronounced differences in the age ranges and socio-ecological conditions in the different populations under investigation. TL attrition occurs more rapidly at younger ages (Frenck et al. 1998), suggesting that any impacts of reproduction on the pace of TL attrition could be amplified among young women, especially if reproduction overlaps with late stages of somatic growth (Stearns 1992; Hill and Kaplan 1999). Our large sample of blood-measured TL among young, similarly-aged women overcomes many of these limitations, and has the advantage of being free of confounding by concurrent secular trends in parity or other factors that might affect TL among women across a broader age range.

Telomere length and DNAmAge appear to reflect different underlying biological pathways linking reproductive effort with somatic senescence. Telomere length and DNAmAge measured in the same individuals have been independently associated with aging and mortality in prior studies (Lowe et al. 2016; Marioni et al. 2016), and were not associated with each other in this study – although the very narrow age range of our sample (<2 years) may have contributed to this finding. It is also notable that DNAmAge was slightly elevated relative to chronological age at Cebu, while TLs were on the long side and show evidence for a slightly slower attrition rate relative to other populations (Table S1). This finding further supports that TL and DNAmAge are independent markers of senescence in this population. Accelerated TL attrition – a measure of ‘mitotic age’ that is modified directly by cellular division – could stem from factors that modify cellular proliferation rates, such as the elevated inflammation, blood cell production, and cell-turnover rates, all of which that characterize pregnancy in this and other samples (Kuzawa et al. 2013).

In contrast to TL, DNAmAge is not considered a marker of mitotic age, as it captures chronological age even in immortal, non-dividing, and non-proliferative tissues and cells (Horvath 2013). DNAmAge is instead thought to reflect the integrity of an epigenetic maintenance system, itself responsible for maintaining dynamic regulatory stability (Horvath 2013). In light of the relationship between DNAmAge and epigenetic robustness, our findings are consistent with the prediction that reproduction comes at the expense of ‘maintenance’ – in this case at the scale of the integrity of regulatory stability. Exactly how parity might lead to cumulative changes in DNAmAge is unclear, but could involve tradeoffs between protein homeostasis and epigenetic stability arising from immune activation or buffering of oxidative stress (Feder and Hofmann 1999; Marshall and Sinclair 2010; Okada et al. 2014; Ryan et al. 2016). The fact that the functionally-distinct measures of TL and DNAmAge show similar associations with parity provides strong support for our prediction that reproduction accelerates senescence, at least among the young adult women represented by our sample.

The current study is not without limitations. While our models attempt to control for socio-ecological factors that could affect both parity and our biomarkers of aging, confounding arising from differences in health and/or resources remains a possibility. Although there was no evidence for powerful confounding effects in our data, confounding may explain the slight decrease in effect size of parity between models 1 and 2 (TL) and 4 and 5 (DNAmAge). Future studies employing a longitudinal design would minimize the potential effects of such confounders (Noordwijk and Jong 1986), while inclusion of lactation and other indices for reproductive effort would provide a more accurate estimate of the CoR (Gurven et al. 2016). Finally, the women in this study all fell within a relatively narrow age range during young adulthood (20-22 years old). Because both TL and DNAmAge ‘age’ more rapidly during early adulthood (Frenck et al. 1998; Horvath 2013), it is possible that both measures are particularly sensitive to reproduction at this time.

In sum, we find evidence that parity is associated with shorter telomeres and epigenetic among the young women in our sample. The consistent relationships between parity and aging in these two distinct pathways—one reflecting cellular turnover and genomic stability, and the second a marker of epigenomic stability—supports predictions for a cost of reproduction in humans.

## **Materials and methods**

*Data collection.* Data came from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a birth cohort study in Metropolitan Cebu, Philippines that began with enrollment of 3,327 pregnant mothers in 1983-1984 (Adair et al. 2011). Longitudinal data are available for download at https://dataverse.unc.edu/dataverse/cebu. In 2005 blood samples from overnight fasted subjects were collected into EDTA-coated vacutainer tubes. Automated and manual DNA extraction (Puregene, Gentra) was conducted on blood samples.

Informed consent was obtained from all participants and data collection was conducted with approval and oversight from the Institutional Review Boards of the University of North Carolina at Chapel Hill and Northwestern University.

*Telomere length.* TLs were measured using a modified form of the monochrome multiplex quantitative polymerase chain reaction assay that was externally validated. Details of the protocol and external validity can be found in (Eisenberg et al. 2015) and since the coefficient of variation (CV) has recently been recognized to be an invalid statistic to assess TL measurement reliability (Verhulst et al. 2015; Eisenberg 2016), intraclass correlation coefficient (ICC) statistics of measurement error can be found in (Eisenberg et al. 2017).

*Epigenetic age (DNAmAge).* 160ng of sodium bisulfite converted DNA (Zymo AZDNA methylation kit, Zymo Research, Irvine, CA, USA) was applied to the Illumina HumanMethylation450 Bead Chip using manufacturer’s standard conditions. Standard methods for background subtraction and color correction were carried out using default parameters in Illumina Genome Studio and exported into R for further analyses. Quality control involved first confirming participant sex and replicate status. This was followed by quantile normalization using *lumi* (Du et al. 2008) on all probes including SNP-associated and XY multiple binding probes. To maximize the number of sites available for the epigenetic age calculator, probes with detection p-values above 0.01 were called NA for poor performing samples only, and were otherwise retained. DNAmAge was calculated using an online calculator (http://labs.genetics.ucla.edu/ horvath/dnamage/), which is considered robust to cell-type differences associated with age (Horvath 2013). Background-corrected beta values were pre-processesed using the calculator’s internal normalization algorithms.

*Socioeconomic status (SES).* SES is measured as a combination of income, education, and assets. Participants reported their annual income from all sources, including in-kind services, and the sale of livestock or other products by household members during the prior year, which were summed to determine total household income. Incomes were deflated to 1983 levels, and log-transformed. Maternal education (in years) was also reported. Participants also reported on nine assets (coded 0, 1) that were selected to capture population-relevant aspects of social class, including electricity, televisions, refrigerators, air conditioners, tape recorder, electric fans, jeepneys, cars, and their residence. In addition, house construction type (i.e., light, mixed, permanent structure) was coded as 0,1, and 2, respectively. Thus, asset scores ranged from 0 to 11. A principal components analysis was run on log income and assets at birth (1983) and at sample collection (2005) along with maternal education in Stata (v. 14.1). The first component of variation accounted for 49% of the variation and individual scores for this component of variation were used as our measure of SES.

*Statistical methods.* The key predictor variable was the number of pregnancies (including stillbirths, miscarriages and live births, but not current pregnancies) the respondent reported having had in 2005 (at the time of blood sampling). Control variables included the measure of socioeconomic status (SES) described above, average urbanicity score between 1983 and 2005 (Dahly and Adair 2007), age in 2005 (when blood collection for TL and DNAmAge analysis occurred) and whether the respondent was pregnant at the time of blood collection. Principal components (PCs) of genome-wide genetic variation were considered to control for potential population structure effects. The derivation of these principal components have been described previously (Croteau-Chonka et al. 2011; Wu et al. 2011; Croteau-Chonka et al. 2012). As in previous analyses (Bethancourt et al. 2015; Eisenberg et al. 2017), the bivariate association between the first ten principal components and TL were tested. The top principal components up to and including the last one showing a significant bivariate association with TL (10 total) were retained as control variables, with the same 10 principal components used for DNAmAge models. Linear regression was used for analyses predicting TL and DNAmAge, while generalized linear models with a poisson family and log-link were used to test for reverse causation – that TL/DNAmAge predicted parity over the subsequent 4 years. The absence of collinearity in predictor variables was confirmed with variance inflation factors (VIFs) for all models falling below 1.1, while Poisson GLMs showed no signs of under- or over-dispersion (Kleiber and Zeileis 2008). All models were two-tailed with α = 0.05 and were run in R (R Core Development Team 2011) with ggplot2 (Wickham et al. 2013) and stargazer (Hlavac 2014) for figures and tables.

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