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

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**Abstract**

Evolutionary theory predicts that energy invested into reproduction comes at the expense of somatic maintenance, thereby accelerating aging. Despite support from studies in human and non-human animals, mechanisms linking costs of reproduction (CoR) to senescence remains scarce. Pregnancy entails massive physiological and immunological shifts capable of accelerating aging through mitotic or non-mitotic cellular pathways - or both. Telomeres are repetitive DNA sequences that cap chromosomes and shorten with cell replication, and telomere length (TL) provides an index of mitotic age. DNA-methylation age (DNAmAge) is marker of non-mitotic cellular aging correlated with chronological age, but is accelerated in response to physiological and immunological stress. Shorter TL and accelerated DNAmAge both predict age-related morbidity and mortality. To elucidate mechanisms underpinning CoR, we examined the relationship between parity, TL (n=821), and DNAmAge (n=397) in young (20-22 year-old) Filipino women. TL decreased (p=0.016) and DNAmAge increased (p=0.011) with parity, an effect that was not contingent upon resource availability. Neither biomarker predicted subsequent fertility, supporting a causal effect of parity on aging (p>0.4 for both). Consistent with prior work, TL and DNAmAge were uncorrelated, but appear to represent distinct aspects of senescence, both exhibiting patterns of premature aging with reproduction among these young women.**Introduction**

Evolutionary theory predicts that energy expenditure in the form of reproductive effort comes at the expense of somatic maintenance and lifespan (1). Because resources are finite and selection favors early life fecundity over late life functional decline (2), reproduction is expected to carry a ‘cost’ in the form of mortality risk, senescence, and functional decline (3). Direct ‘costs of reproduction’ (CoR) have been demonstrated among animal models, whereby reproduction hastens senescence (4, 5). Conversely, selection for late life fecundity results in lifespan extension (6, 7). In humans, CoR has been predominantly studied through the use of historical datasets. This research suggests that increased reproductive effort is often associated with a shortening of lifespan (8–12, but see 13), and that these costs are more evident when resources are limited (14–16). However, most studies of CoR in humans are restricted to the use of mortality as the only outcome, and are unable to address the underlying biological processes through which CoR might lead to functional decline and mortality in humans.

Among women, CoR likely arise predominantly from pregnancy and lactation (41, 42). Human pregnancy is relatively ‘invasive’ and energetically demanding (ref.), and requires massive physiological and immunological modifications capable of accelerating senescence. Pregnancy induced cellular senescence could occur through either mitotic and non-mitotic pathways, or both (ref.). Mitotic senescence is commonly measured using telomere length (TL). Telomeres are non-coding DNA sequences that cap chromosomes, and are required for cell division and survival (17, 18). Telomere length shortens with cell division and chronological age, placing a limit on the number of cell divisions (19–21). Shorter TL, controlling for age, in turn predicts higher morbidity and mortality rates (22–25).

A powerful and emerging marker of non-mitotic senescence in human cells is epigenetic age (DNAmAge). DNAmAge in human (27) and non-human genomes (refs) is calculated from methylation at a species-specific subset of cytosine-guanine dyads (CpGs), and is strongly correlated with chronological age (26). Independent of a host of associated risk factors in humans, accelerated DNAmAge relative to chronological age is associated with elevated risks for morbidity and mortality (28–30). Vital to capitalizing on epigenetic age as a marker of non-mitotic senescence, DNAmAge predicts senescence and mortality independently of TL in living humans (31, 32), and independently of both TL and the DNA damage response in vitro (27, 31).

Human pregnancy could generate costs to female health and lifespan by shortening TL (mitotic age), accelerating DNAmAge (non-mitotic age), or both. During pregnancy, blood cells proliferate to compensate for fluid volume expansion (43, 44), and the female body shifts towards a pro-inflammatory but immunocompromised state (45–47). Data from cell culture, rodent based experiments, and clinical studies show that inflammation and infection increase cell proliferation and DNA damage, both expected to accelerate the pace of telomere shortening (48–55). Accelerated DNAmAge relative to chronological age has been observed in other pro-inflammatory contexts (40, 56), and with menopause (57), 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 (57),m, suggesting that physiological and hormonal changes like those accompanying pregnancy could have profound effects on DNAmAge. While two studies have recently examined TL and pregnancy with mixed results (refs), none have attempted to test for CoR in humans using mitotic and non-mitotic measures of senescence simultaneously. While numerous studies do support CoR on human aging (ref. Ziomewics, Jasienska), examining multiple pathways of senescence simultaneously may be necessary.

Here, we test for human CoR using mitotic (TL) and non-mitotic (DNAmAge) measures of cellular senescence. We test three inter-related hypotheses in a relatively young cohort (age 20-22) of women in the Philippines. First, we ask whether pregnancy history increases mitotic or non-mitotic measures of cellular senescence, or both (H1). We also ask whether any associations between pregnancy history and senescence are stronger among women for whom resources are constrained by socioeconomic status (H2). Finally, we test a more causal effect of TL and DNAm on pregnancy history by examining the effect of both measures on fecundity over the subsequent 4 years (H3).

**Results**

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**Supplementary Information**

**Table S1. Comparison of TL across ethnicities.** qPCR measured TL does not permit comparisons across populations, but 190 samples from the population for which the samples from this paper come from have had southern blot TL measured (Eisenberg et al. 2015). The average age of this sample is 35.96 (± 15.83, range 21.02-68.33), with an average TL of 7.86 kb (± 0.76), and an estimated age related decline in TL of 21.98 bp/year (95% CI 15.81-28.15). This age related decline is non-significantly less than that found in other populations (African=27.7 bp/year; African Americans = 25.6 bp/year; Europeans = 27.3 bp/year) (Hansen et al. 2016). These three populations from Hansen et al. (2016) have an average age of 43.25. Adjusting the Cebu population TL for the 7.29 years younger they are by assuming the observed 21.98 bp/year attrition rates yields an interpolated TL of 7.70 kb if the mean age was 43.25, the same as the samples in Hansen et al. (2016). This suggests that the TL in Cebu is longer than that of European and African Americans, but slightly shorter than that of Africans (Table S1).

|  |  |  |  |
| --- | --- | --- | --- |
| **Ethnicity (N)** | **% Female** | **Age (years)** | **LTL (kb)** |
| Europeans (90)\* | 63.3 | 43.9 (18-78) | 7.21 (5.39-9.42) |
| African Americans (97)\* | 67.1 | 42.9 (21-79) | 7.45 (5.55-9.16) |
| Africans (100)\* | 68.0 | 43.0 (18-79) | 7.85 (5.64-10.13) |
| Cebu, Philippines (190) | 50.3 | 43.3~ | 7.70 (6.10-9.21) |

\* from Hansen MEB, et al. (2016) Shorter telomere length in Europeans than in Africans due to polygenetic adaptation. *Human Molecular Genetics*.

†from Eisenberg DT, Kuzawa CW, Hayes MG (2015) Improving qPCR telomere length assays: Controlling for well position effects increases statistical power. *Am J Hum Biol* 27(4):570–5.

~ interpolated to match mean age of other populations - see above text

**Table S2. Full model estimates for parity and telomere length and epigenetic age (DNAmAge) among young women in the Philippines.**

|  | **Telomere Length~** | | | | **DNAmAge~** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) |
| **Age** | -0.047 | -0.028 | -0.027 | -0.028 | 0.485 | 0.667 | 0.629 | 0.618 |
|  | p = 0.004\*\* | p = 0.080+ | p = 0.086+ | p = 0.079+ | p = 0.293 | p = 0.157 | p = 0.179 | p = 0.188 |
| **No.Pregnancies** | -0.013 | -0.012 | -0.016 | -0.018 | 0.363 | 0.326 | 0.437 | 0.491 |
|  | p = 0.030\* | p = 0.044\* | p = 0.016\* | p = 0.010\*\* | p = 0.026\* | p = 0.049\* | p = 0.011\* | p = 0.007\*\* |
| **PC1** |  | -0.426 | -0.437 | -0.438 |  | -11.623 | -10.481 | -10.457 |
|  |  | p = 0.060+ | p = 0.054+ | p = 0.054+ |  | p = 0.084+ | p = 0.117 | p = 0.118 |
| **PC2** |  | -0.155 | -0.144 | -0.131 |  | 5.098 | 4.679 | 4.207 |
|  |  | p = 0.499 | p = 0.530 | p = 0.568 |  | p = 0.458 | p = 0.494 | p = 0.540 |
| **PC3** |  | 0.013 | 0.002 | 0.008 |  | 8.510 | 9.075 | 8.853 |
|  |  | p = 0.955 | p = 0.992 | p = 0.972 |  | p = 0.202 | p = 0.172 | p = 0.183 |
| **PC4** |  | -0.024 | -0.015 | -0.022 |  | 11.991 | 11.495 | 11.551 |
|  |  | p = 0.917 | p = 0.949 | p = 0.922 |  | p = 0.069+ | p = 0.080+ | p = 0.078+ |
| **PC5** |  | -0.252 | -0.251 | -0.244 |  | -14.123 | -14.441 | -14.157 |
|  |  | p = 0.277 | p = 0.279 | p = 0.291 |  | p = 0.023\* | p = 0.020\* | p = 0.022\* |
| **PC6** |  | -0.293 | -0.304 | -0.294 |  | -4.002 | -3.125 | -3.748 |
|  |  | p = 0.205 | p = 0.189 | p = 0.204 |  | p = 0.548 | p = 0.637 | p = 0.574 |
| **PC7** |  | -0.497 | -0.529 | -0.531 |  | 18.513 | 19.744 | 20.019 |
|  |  | p = 0.034\* | p = 0.025\* | p = 0.024\* |  | p = 0.008\*\* | p = 0.005\*\* | p = 0.004\*\* |
| **PC8** |  | 0.426 | 0.428 | 0.433 |  | 3.987 | 3.796 | 3.691 |
|  |  | p = 0.062+ | p = 0.061+ | p = 0.058+ |  | p = 0.534 | p = 0.552 | p = 0.563 |
| **PC9** |  | -0.457 | -0.476 | -0.481 |  | -1.730 | -1.521 | -1.534 |
|  |  | p = 0.042\* | p = 0.035\* | p = 0.033\* |  | p = 0.789 | p = 0.813 | p = 0.812 |
| **PC10** |  | 0.559 | 0.548 | 0.541 |  | -2.701 | -1.976 | -1.672 |
|  |  | p = 0.020\* | p = 0.022\* | p = 0.024\* |  | p = 0.690 | p = 0.769 | p = 0.804 |
| **SES-score** |  | -0.006 | -0.006 | -0.004 |  | -0.180 | -0.190 | -0.271 |
|  |  | p = 0.140 | p = 0.158 | p = 0.395 |  | p = 0.146 | p = 0.123 | p = 0.075+ |
| **Urbanicity-score** |  | 0.002 | 0.002 | 0.003 |  | 0.015 | 0.016 | 0.015 |
|  |  | p = 0.00000\*\* | p = 0.00000\*\* | p = 0.00000\*\* |  | p = 0.270 | p = 0.260 | p = 0.275 |
| **Currently Pregnancy** |  |  | 0.038 | 0.038 |  |  | -1.223 | -1.211 |
|  |  |  | p = 0.080+ | p = 0.079+ |  |  | p = 0.018\* | p = 0.019\* |
| **No.Pregnancies\*SES-score** |  |  |  | -0.004 |  |  |  | 0.111 |
|  |  |  |  | p = 0.354 |  |  |  | p = 0.365 |
| **Intercept** | 1.816 | 1.315 | 1.303 | 1.314 | 14.818 | 10.319 | 11.177 | 11.422 |
|  | p = 0.00000\*\* | p = 0.0002\*\* | p = 0.0002\*\* | p = 0.0002\*\* | p = 0.138 | p = 0.318 | p = 0.276 | p = 0.266 |
| Observations | 824 | 824 | 824 | 824 | 397 | 397 | 397 | 397 |
| R2 | 0.017 | 0.080 | 0.083 | 0.084 | 0.016 | 0.075 | 0.089 | 0.091 |
| Adjusted R2 | 0.015 | 0.064 | 0.066 | 0.066 | 0.011 | 0.041 | 0.053 | 0.052 |
| Residual Std. Error | 0.161 (df = 821) | 0.157 (df = 809) | 0.157 (df = 808) | 0.157 (df = 807) | 3.165 (df = 394) | 3.117 (df = 382) | 3.098 (df = 381) | 3.098 (df = 380) |
| F Statistic | 7.089\*\* (df = 2; 821) | 5.007\*\* (df = 14; 809) | 4.892\*\* (df = 15; 808) | 4.639\*\* (df = 16; 807) | 3.220\* (df = 2; 394) | 2.214\*\* (df = 14; 382) | 2.475\*\* (df = 15; 381) | 2.371\*\* (df = 16; 380) |

**Table S3. Predictive effect of Telomere Length (TL) or Epigenetic Age (DNAmAge) on parity over the subsequent 4 years in young women in the Philippines.** Models derived from Poisson generalized linear regression meeting assumptions of equidispersion.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Parity 2005-2009** | | | |
|  | **Age Adjusted TL~** | | **Age Adjusted DNAmAge**~ | |
|  | (1) | (2) | (3) | (4) |
| Measurement time bt. 2005-2009 (Days) | -0.003 | -0.003 | -0.002 | -0.002 |
|  | p = 0.004\*\* | p = 0.009\*\* | p = 0.058+ | p = 0.068+ |
| Parity in 2005 |  | 0.252 |  | 0.123 |
|  |  | p = 0.000\*\* |  | p = 0.016\* |
| Age Adjusted Telomere Length in 2005 | 0.059 | 0.148 |  |  |
|  | p = 0.835 | p = 0.601 |  |  |
| Age Adjusted DNAmAge in 2005 |  |  | -0.011 | -0.016 |
|  |  |  | p = 0.483 | p = 0.325 |
| Intercept | 4.457 | 3.777 | 3.460 | 3.265 |
|  | p = 0.006\*\* | p = 0.022\* | p = 0.062+ | p = 0.082+ |
| Observations | 743 | 743 | 397 | 397 |
| Log Likelihood | -836.740 | -818.205 | -485.276 | -482.433 |
| Akaike Inf. Crit. | 1,679.481 | 1,644.411 | 976.552 | 972.866 |
| *Note:* | +p<0.1;\*p<0.05;\*\*p<0.01;\*\*\*p<0.001 | | | |