INTRODUCTION

Mutations in genes that provide a selective advantage early in life often have pleiotropic adverse effects late in life (Byars & Voskarides, 2020; Williams, 1957) and the genetic changes that suppress telomerase activity in somatic cells of long-lived animals to limit their replication potential are no exception (Lansdorp, 2022). Limits to cell proliferation late in life are expected to impact cells of the immune system and cardiovascular system in particular. Of all leukocytes, NK cells and memory T cells show the most rapid decline in telomere length with age (Aubert et al., 2012) and replicative exhaustion of these and other immune cells is likely to impair immune responses in the elderly. Indeed, short telomeres have been linked to adverse COVID-19 outcomes, independent of known risk factors for COVID including age (Wang et al., 2021). Short telomeres in leukocytes have also been associated with cardiovascular disease (Scheller Madrid et al., 2016; Xu et al., 2020) and telomere erosion in endothelial cells has been linked to vascular pathology (Chang & Harley, 1995). Infectious diseases and cardiovascular diseases are leading causes of death, and a link between telomere length and age-related mortality is supported by several studies (Cawthon et al., 2003; Codd et al., 2021).

Most studies agree that the average leukocyte telomere length is between 0.1 and 0.3 kb longer in females than in males (Gardner et al., 2014). The telomere length in umbilical cord blood leukocytes
was found to be longer in females compared with males by Q- 
FISH (Mayer et al., 2006), flow FISH (Aubert et al., 2012), and by 
telomere restriction fragment (TRF) analysis (Factor-Litvak et al., 
2016) (Table 1 and Figure 1a,b). The rate of telomere attrition in 
adult human leukocytes was measured by TRF is 26 bp/year (Daniali 
et al., 2013), whereas by flow FISH, telomeric DNA is lost in adult 
lymphocytes at a rate of 43 bp/year (Aubert et al., 2012). By 
comparing the average telomere length and telomere attrition rate in 
adults with the average telomere length at birth, sex differences 
in telomere length correspond to a difference in average life ex-
pectancy between 5 and 8 years (Table 1 and Figure 1a,b), in close 
agreement with reported sex differences in average lifespan (Baum 
et al., 2021).

Currently, the sex difference in telomere length at birth is un-
explained. On average, boys are typically heavier at birth than girls 
(Jelenkovic et al., 2018) and the male conceptus seems to grow not 
only more, but also earlier than the female (de Zegher et al., 1999).
The telomere length in leukocytes declines most rapidly in the first 
few years of life in support of a mitotic clock ticking in blood form-
ing stem cells and lymphocytes (reviewed in Lansdorp, 2022). In 
view of these observations, both gestational age and birth weight 
are expected to correlate with the telomere length in neonatal 
leukocytes. Such a correlation was indeed found in a small study 
(Sibert et al., 2021) but not in the large study that reported sex 
differences in leukocyte telomere length at birth (Table 1, Factor- 
Litvak et al., 2016). Further studies of the telomere length in dif-
ferent pre- and post-natal cells are needed to clarify the role of 
accumulated cell divisions in the sex-specific difference in telomere 
length shown in Table 1. Given the shortcomings of all current telo-
mere length measurements (Lansdorp, 2022), such studies should 
aim to measure the average as well as the distribution of telomere 
length values in cells.

Sex hormones provide another possible explanation for the sex 
differences in telomere length. Androgens are known to benefit pa-
tients with telomere biology disorders (Townsley et al., 2016), and 
the rate of telomere attrition in adult leukocytes is slightly higher 
in males than females (Figure 1a,b). Among other explanations, 
these observations could reflect the effect of sex hormones on 
TERT expression (Calado et al., 2009). Differences in the type and 
level of hormones secreted by the fetus and the placenta could also 
contribute to sex differences in average telomere length at birth. 
Alternatively, or in addition, differences in the expression of telo-
merase during early embryogenesis could also play a role. In a study 
of gene expression in single cells from human embryos, it was found 
that many X chromosome genes maintain bi-allelic expression prior 
to embryo implantation and lineage specification (Petropoulos et al., 
2016). During this time males, with only one copy of the X chro-
mosome, express lower levels of X chromosome genes including the 
DKC1 gene that encodes the dyskerin protein (Figure 1c,d and 
Table 2). Telomerase RNA is sandwiched between two copies of dys-
kerin in the telomerase holoenzyme (Ghanim et al., 2021) and dys-
kerin is critical for folding and stabilizing primary telomerase RNA 
transcripts, telomerase assembly, and telomerase activity (Wong 
& Collins, 2006). Whereas in most somatic cells, TERT expression is 
limiting telomerase levels, telomerase RNA is limiting the telomerase 
activity in embryonic stem cells (Chiba et al., 2015). Higher dyskerin 
levels in female embryo cells could increase telomerase levels by in-
creasing the capture efficiency and stability of telomerase RNA prior 
to assembly with TERT, producing higher levels of active telomerase. 
Reduced telomerase levels were found in murine cells with reduced 
dyskerin levels (Ruggero et al., 2003) and allelic differences in DKC1 
are a plausible explanation for the reported X-linked inheritance of 
telomere length in humans (Nawrot et al., 2004). Higher telomerase 
activity in female embryo cells before the random inactivation of 
one DKC1 allele could result in longer telomeres in female compared 
with male embryos prior to embryo implantation. Longer telomeres 
in female embryo cells could explain why leukocytes from females 
are a plausible explanation for the reported X-linked inheritance of 
telomere length in humans (Nawrot et al., 2004). Higher telomerase 
activity in female embryo cells before the random inactivation of 
one DKC1 allele could result in longer telomeres in female compared 
with male embryos prior to embryo implantation. Longer telomeres 
in female embryo cells could result in shorter telomeres undergo either 
apoptosis or replicative senescence.

The relationships between sex, telomere shortening, and lifes-
pan found in humans are not ubiquitous throughout the animal king-
dom (Barrett & Richardson, 2011). The telomere length in several 
tissues from mice (Mus spretus) was found to be longer in females

**TABLE 1** Average telomere length in different umbilical cord blood cells is longer in female compared to male newborns

| Technique (year) | Cell type | Location | TL female (n) | TL male (n) | Δ TL | Δ lifespan |
|-----------------|-----------|----------|---------------|-------------|-----|-----------|
| Q-FISH T-C 2006 (Mayer et al., 2006) | Cultured T cells blood | Germany | 12.03 kb (53) | 11.81 kb (55) | 0.22 kb | 5.1 years |
| Flow FISH 2012 (Aubert et al., 2012) | Naive T cells blood | Canada | 11.24 kb (29) | 10.92 kb (29) | 0.32 kb | 7.4 years |
| TRF 2016 (Factor-Litvak et al., 2016) | Leukocytes | USA | 9.58 kb (216) | 9.44 kb (274) | 0.14 kb | 5.3 years |

Note: Results from three independent studies using three different techniques. Assuming a telomere attrition rate in cells from adults of around 26 bp/year for leukocytes (Factor-Litvak et al., 2016) and 43 bp for lymphocytes (Aubert et al., 2012), telomere length differences at birth could account in principle for a sex difference in life expectancy between 5.1 and 7.4 years.
compared with males (Coviello-McLaughlin & Prowse, 1997). In general, the mouse model has been extremely useful to identify genes that regulate telomere length (Ding et al., 2004). However, possible correlations between lifespan and telomere length are only expected in long-lived species in which telomerase activity is suppressed to limit the replication potential in somatic cells and suppress tumor growth (Lansdorp, 2022). To test the hypothesis that embryonic dyskerin and telomerase levels are connected to human life expectancy represents an enormous challenge. Both the large variation in average telomere length between human individuals as well as the indirect role of telomeres in life expectancy represent major hurdles. Even if enough human embryos could be made available for study, telomere length measurements by either TRF or flow FISH would be unsuitable given the numbers of cells required for such studies. While novel techniques promise to overcome some of the limitations of current telomere length measurements (Lansdorp, 2022), further studies of the relation between telomere length and life expectancy are expected to strengthen correlations, not establish causality. For these reasons, the proof that higher levels of dyskerin and telomerase in early embryos are a major contributor to the sex difference in average human life expectancy is not expected in the near future.
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CONFLICT OF INTEREST
The author is a founding shareholder of Repeat Diagnostics Inc., a company specializing in clinical telomere length measurements since 2006.

AUTHOR CONTRIBUTIONS
Peter Lansdorp is the sole author of this paper.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES
Aubert, G., Baerlocher, G. M., Vulto, I., Poon, S. S., & Lansdorp, P. M. (2012). Collapse of telomere homeostasis in hematopoietic cells caused by heterozygous mutations in telomerase genes. *PLoS Genetics*, 8(5), e1002696. https://doi.org/10.1371/journal.pgen.1002696
Barrett, E. L., & Richardson, D. S. (2011). Sex differences in telomeres and lifespan. *Aging Cell*, 10(6), 913–921. https://doi.org/10.1111/j.1474-9726.2011.00741.x
Baum, F., Musolino, C., Gesesew, H. A., & Popay, J. (2021). New perspective on why women live longer than men: An exploration of power, gender, social determinants, and capitals. *International Journal of Environmental Research and Public Health*, 18(2), 661. https://doi.org/10.3390/ijerph18020661
Byars, S. G., & Voskarides, K. (2020). Antagonistic pleiotropy in human disease. *Journal of Molecular Evolution*, 88(1), 12–25. https://doi.org/10.1007/s00239-019-09923-2
Calado, R. T., Yewdell, W. T., Wilkerson, K. L., Regal, J. A., Kajigaya, S., Stratakis, C. A., & Young, N. S. (2009). Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. *Blood*, 114(11), 2236–2243. https://doi.org/10.1182/blood-2008-09-178871
Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet*, 361(9355), 393–395.
Chang, E., & Harley, C. B. (1995). Telomere length and replicative aging in human vascular tissues. *Proceedings of the National Academy of Sciences of the United States of America*, 92(24), 11190–11194. https://doi.org/10.1073/pnas.92.24.11190
Chiba, K., Johnson, J. Z., Vogan, J. M., Wagner, T., Boyle, J. M., & Hockemeyer, D. (2015). Cancer-associated TERT promoter mutations abrogate telomerase silencing. *Elife*, 4. https://doi.org/10.7554/eLife.07918
Codd, V., Wang, Q., Allara, E., Musicha, C., Kaptoge, S., Stoma, S., Jiang, T., Hamby, S. E., Braund, P. S., Bountziouka, V., Budgeon, ...
C. A., Denniff, M., Swinfield, C., Papakonstantinou, M., Sheth, S., Nanus, D. E., Warner, S. C., Wang, M., Khera, A. V., ... Samani, N. J. (2021). Polygenic basis and biomedical consequences of telomere length variation. Nature Genetics, 53(10), 1425-1433. https://doi.org/10.1038/s41588-021-00944-6

Coviello-McLaughlin, G. M., & Prowse, K. R. (1997). Telomere length regulation during postnatal development and ageing in Mus musculus. Nucleic Acids Research, 25(15), 3051-3058. https://doi.org/10.1093/nar/25.15.3051

Danial, L., Benetos, A., Susser, E., Kark, J. D., Labat, C., Kimura, M., Desai, K. K., Granick, M., & Aviv, A. (2013). Telomers shorten at equivalent rates in somatic tissues of adults. Nature Communications, 4, 1597. https://doi.org/10.1038/ncomms2602

de Zegher, F., Devlieger, H., & Eeckels, R. (1999). Fetal growth: Boys before girls. Hormone Research, 51(5), 258-259. https://doi.org/10.1159/000023382

Ding, H., Schertzer, M., Wu, G., Gertsenstein, M., Selig, S., Kammori, M., Pourvali, R., Poon, S., Vulto, I., Chavez, E., Tam, P. P. L., Nagy, A., & Lansdorp, P. M. (2004). Regulation of murine telomere length by Rtel: An essential gene encoding a helicase-like protein. Cell, 117(7), 873-886. https://doi.org/10.1016/j.cell.2004.05.026

Factor-Litvak, P., Susser, E., Kezios, K., McKeague, I., Kark, J. D., Hoffman, M., Kimura, M., Wapner, R., & Aviv, A. (2016). Leukocyte telomere length in Newborns: Implications for the role of telomeres in human disease. Pediatrics, 137(4). https://doi.org/10.1542/peds.2015-3927

Gardner, M., Bann, D., Wiley, L., Cooper, R., Hardy, R., Nitsch, D., Martin-Ruiz, C., Shiels, P., Sayer, A. A., Barbieri, M., Beksaert, S., Bischoff, C., Brooks-Wilson, A., Chen, W., Cooper, C., Christensen, K., De Meyer, T., Deary, I., Der, G., ... Ben-Shlomo, Y. (2014). Gender and telomere length: Systematic review and meta-analysis. Experimental Gerontology, 51, 15-27. https://doi.org/10.1016/j.exger.2013.12.004

Ghani, W. G., Fountain, A. J., van Roon, A. M., Rangan, R., Das, R., Collins, K., & Nguyen, T. H. D. (2021). Structure of human telomerase holoenzyme with bound telomeric DNA. Nature, 593(7859), 449-453. https://doi.org/10.1038/s41586-021-03415-4

Jelenkovic, A., Sund, R., Yokoyama, Y., Hur, Y.-M., Ullmer, V., Almqvist, C., Magnusson, P. K. E., Willemsen, G., Bartels, M., Beijsterveldt, C. E. M. V., Bogl, L. H., Pietiläinen, K. H., Vuoksimaa, E., Ji, F., Ning, F., Pang, Z., Nelson, T. L., Whitfield, K. E., Rebato, E., ... Silventoinen, K. (2018). Birth size and gestational age in opposite-sex twins as compared to same-sex twins: An individual-based pooled analysis of 21 cohorts. Scientific Reports, 8(1), 6300. https://doi.org/10.1038/s41598-018-24634-2

Lansdorp, P. M. (2022). Telomeres, aging, and cancer: The big picture. Blood, 139(6), 813-821. https://doi.org/10.1182/blood.2021014299

Mayer, S., Brüderlein, S., Perner, S., Waibel, I., Holdenried, A., Ciloglu, N., Hasel, C., Mattfeldt, T., Nielsen, K. V., & Möller, P. (2006). Sex-specific telomere length profiles and age-dependent erosion dynamics of individual chromosome arms in humans. Cytogenetic and Genome Research, 112(3–4), 194-201. https://doi.org/10.1159/000089870

Nawrot, T. S., Staessen, J. A., Gardner, J. P., & Aviv, A. (2004). Telomere length and possible link to X chromosome. Lancet, 363(9408), 507-510.

Petropoulos, S., Edsgård, D., Reinius, B., Deng, Q., Panula, S. P., Codeluppi, S., Reyes, A. P., Linnarsson, S., Sandberg, R., & Lanner, F. (2016). Single-cell RNA-Seq reveals lineage and X chromosome dynamics in human preimplantation embryos. Cell, 167(1), 285. https://doi.org/10.1016/j.cell.2016.08.009

Ruggero, D., Grisendi, S., Piazza, F., Rego, E., Mari, F., Rao, P. H., Cordon-Cardo, C., & Pandolfi, P. P. (2003). Dyskeratosis congenita and cancer in mice deficient in ribosomal RNA modification. Science, 299(5604), 259-262. https://doi.org/10.1126/science.1079447

Scheller Madrid, A., Rode, L., Nordestgaard, B. G., & Bojesen, S. E. (2016). Short telomere length and ischemic heart disease: Observational and genetic studies in 290 022 individuals. Clinical Chemistry, 62(8), 1140-1149. https://doi.org/10.1373/clinchem.2016.258566

Sibert, N., Ferreira, M., Wagner, W., Eipel, M., Dreschers, S., Brümmendorf, T., Orlikowsky, T., & Beier, F. (2021). Cord blood telomere shortening associates with increased gestational age and birth weight in preterm neonates. Experimental and Therapeutic Medicine, 21(4), 344. https://doi.org/10.3892/etm.2021.9775

Townley, D. M., Dumitriu, B., Liu, D., Biancotto, A., Weinstein, B., Chen, C., Hardy, N., Mihaele, A. D., Lingala, S., Kim, Y. J., Yao, J., Jones, E., Gochuico, B. R., Heller, T., Wu, C. O., Calado, R. T., Scheinberg, P., & Young, N. S. (2016). Danazol treatment for telomere diseases. New England Journal of Medicine, 374(20), 1922–1931. https://doi.org/10.1056/NEJMoa1515319

Wang, Q., Codd, V., Raisi-Estabragh, Z., Musicha, C., Bountziouka, V., Kaptoge, S., Allara, E., Di Angelantonio, E., Butterworth, A. S., Wood, A. M., Thompson, J. R., Petersen, S. E., Harvey, N. C., Danesh, J. N., Samani, N. J., & Nelson, C. P. (2021). Shorter leukocyte telomere length is associated with adverse COVID-19 outcomes: A cohort study in UK Biobank. EBioMedicine, 70, 103485. https://doi.org/10.1016/j.ebiom.2021.103485

Williams, G. C. (1957). Pleiotropy, natural selection, and the evolution of senescence. Evolution, 11(4), 398-411. https://doi.org/10.2307/2406060

Wong, J. M., & Collins, K. (2006). Telomerase RNA level limits telomere maintenance in X-linked dyskeratosis congenita. Genes & Development, 20(20), 2848-2858. https://doi.org/10.1101/gad.1476206

Xu, C., Wang, Z., Su, X., Da, M., Yang, Z., Duan, W., & Mo, X. (2020). Association between leucocyte telomere length and cardiovascular disease in a large general population in the United States. Scientific Reports, 10(1), 80. https://doi.org/10.1038/s41598-019-57050-1

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