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Letter to the Editor

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Revisiting telomere length in CHD: a critical knowledge gap

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To the editor,

Advances in diagnosis, surgical correction, and long-term care have markedly improved survival among children born with CHD, resulting in a rapidly expanding population of adolescents and adults living with repaired or palliated defects. Consequently, research priorities have shifted from short-term survival to long-term morbidity, quality of life, and premature onset of age-related complications. In this context, telomere length represents a largely unexplored yet potentially informative biomarker of biological ageing in CHD.[1,2] Unlike conventional biomarkers reflecting current physiological state, telomere length integrates cumulative biological stress across the lifespan and may therefore be uniquely suited to capture the lifelong exposure burden characteristic of CHD.

Human telomeres are conserved hexanucleotide $(TTAGGG)_n$ repeats that cap chromosomal ends and, together with the shelterin complex, preserve chromosomal integrity by preventing degradation, aberrant DNA repair, and end-to-end fusion. Telomere length varies across tissues according to proliferative demand and progressively shortens with successive cell divisions due to the end-replication problem and insufficient telomerase activity accelerates attrition. Critically short telomeres activate a DNA damage response, forming telomere-induced foci that trigger replicative senescence (the *Hayflick limit*). Accordingly, telomere length functions as a biological "mitotic clock" and an integrative marker of accelerating ageing.[2] Robust evidence links telomere shortening to acquired cardiovascular disorders. A meta-analysis demonstrated a linear inverse association between telomere length and coronary heart disease risk ($p_{\text{non-linearity}} = 0.930$), with each 1-kb increase in length conferring a 23% risk reduction.[3] In addition, Mendelian randomisation analyses have reported that genetically predicted longer telomere length is associated with a significantly lower risk of coronary heart disease (*odds ratio* range: 0.72–0.87, $p < 0.010$), supporting a causal relationship.[4] In contrast, evidence in CHD remains strikingly sparse (Table 1).

Published CHD-specific evidence remains limited, with only one small cross-sectional study that has examined leukocyte telomere length in adults with CHD, reporting significantly shorter telomere length compared with age-matched controls ($p = 0.001$). Leukocyte telomere length was inversely correlated with cumulative radiological exposure ($r = -0.34$, $p = 0.030$), and the X-ray repair cross complementing-3 Thr241Met polymorphism was a significant contributor ($p < 0.010$).[5] To our knowledge, *no studies have evaluated telomere length in paediatric CHD populations,* nor are longitudinal data available tracking telomere dynamics from infancy through adulthood. Indirect evidence suggests early-life physiological stress influences telomere biology; critically ill children exhibited ~6% shorter leukocyte telomere length than healthy peers ($p < 0.001$), supporting early adversity as a trigger for accelerated ageing.[6]

Emerging prenatal data also suggest relevance of parental telomere biology. Shorter periconceptional maternal telomere length has been associated with increased risk of non-syndromic ventricular septal defects in offspring (adjusted odds ratio = 1.25, 95% confidence interval: 1.01–1.55, $p = 0.04$), potentially mediated by hyperhomocysteinemia-related oxidative stress and reduced telomerase activity.[7] Another recent study reported significantly shorter telomere length in amniotic fluid from fetuses with cardiac malformations ($p < 0.001$), although limited sample size constrains generalisability.[8] A registered prospective study (NCT05667870) proposing telomere length assessment in newborns and adults with and without CHD, with planned longitudinal follow-up to assess temporal dynamics and clinical correlates further underscores emerging interest, although results are pending.

Importantly, CHD differs fundamentally from acquired cardiovascular diseases in both timing and exposure profile. Patients experience chronic hypoxia, inflammation, cardiopulmonary bypass, repeated interventions, and altered haemodynamics beginning early in life—critical periods for establishing lifelong telomere trajectories.[3,5] Several CHD-specific factors may confound telomere length measurements and must be accounted for in study design, including syndromic diagnoses, prematurity or fetal growth restriction, cyanosis, recurrent

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Table 1. Direct and indirect evidence on telomere biology in congenital heart disease: Methodological limitations and knowledge gaps

Study (Year)	Population (P)	Exposure/ Intervention (I)	Comparator (C)	Outcome (O)	Key Findings	Methodological Limitations	Knowledge Gaps
Vecoli et al.[5] (2016)	Adults (age = 25.2 ± 9.0 years) with repaired CHD, n = 50; n = 50 controls	CHD status and cumulative radiation	Age- and gender-matched healthy controls	Leukocyte TL shortening	Shorter TL in CHD (1.0 ± 0.3 vs 1.3 ± 0.4, $p = 0.001$); inverse correlation with radiation dose (r = -0.34, $p = 0.030$); XRCC3 variants Thr/Met ($p = 0.010$) and Met/Met ($p = 0.008$) associated	Small sample; survivorship bias; radiation confounding; cross-sectional design	No pediatric data; causal direction unclear; contribution of clinical exposures vs CHD biology unknown
Aoulad et al.[7] (2022)	Mothers (age = 31.8 ± 4.7 years) of children with COD, n = 306; n = 424 controls	Shorter periconception maternal Leukocyte TL	Mothers (age = 30.9 ± 4.6 years) of children without congenital malformations	Risk of COD and ventricular septal defect (VSD) in offspring	Shorter maternal TL associated with increased VSD risk (adjusted $OR = 1.25$, 95% CI: 1.01-1.55, $p = 0.040$); No association with overall COD	Significant age difference between cases and controls ($p = 0.009$); TL measured ~15 months after pregnancy (proxy for periconception); limited power for individual CHD subtypes; residual confounding	Whether maternal TL causally influences embryonic cardiac development remains unknown
Coudrieu et al.[8] (2025)	Pregnancies (gestational age = 15.7 to 37.3 weeks) with fetal cardiac anomalies, n = 27; n = 49 controls	Shortened maternal and fetal TL	Pregnancies without fetal anomalies	Presence of cardiac malformation in fetus	Fetal TL significantly shorter in cardiac anomalies ($p < 0.001$); Maternal TL explained 15-38 % of fetal TL variance, and predicted anomalies (area under curve = 0.86, 92 % specificity)	CHD not analyzed as an isolated outcome; modest sample size	Mechanistic pathways linking fetal TL and structural heart defects not defined

CHD = congenital heart disease, COD = congenital cardiac outflow defect; TL = telomere length; XRCC3 = X-ray repair cross-complementing-3.

infections, cumulative procedures, and socio-economic stress. Large population analyses confirm that genetic determinants, environmental exposures, and inflammatory states substantially influence telomere length variation, underscoring the need for careful adjustment.[9]

Future investigations should therefore adopt phenotype-specific, longitudinal designs incorporating pre-and post-intervention leukocyte telomere length assessment, parental telomere length correlations, and telomerase activity. Methodological rigour will be essential, including control for assay variability, leucocyte subset composition, batch effects, inter-laboratory calibration, and standardised quantification of cumulative clinical exposures known to influence telomere dynamics.[10]

If validated in adequately powered longitudinal studies, telomere length may have potential as a clinically informative biomarker to refine risk stratification in CHD. Children with markedly shortened telomeres could represent a biologically vulnerable subgroup warranting closer surveillance for organ dysfunction, earlier cardiometabolic screening, or tailored perioperative planning to mitigate oxidative and inflammatory stress. However, given the limited CHD-specific evidence base, such applications should currently be considered hypothesis-generating. Future work is required to establish clinically meaningful thresholds, reproducibility, and incremental prognostic value beyond established risk markers before translation into routine practice.

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Ethical standard. Not applicable.

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