ESC European Society of Cardiology

European Journal of Preventive Cardiology (2022) **29**, e22–e24
doi:10.1093/eurjpc/zwaa123

RESEARCH LETTER
CVD Risk Factors

Telomere length and cardiovascular disease precursors: a 7-year follow-up from childhood to early adolescence

Nathalie Michels *†, Carola J.C. van Aart†, Dries S. Martens, Stefaan De Henauw, and Tim S. Nawrot

Department of Public Health and Primary Care, Faculty of Medicine and Health Sciences, Ghent University, Corneel Heymanslaan 10 4K3, 9000 Ghent, Belgium

Received 13 August 2020; revised 18 October 2020; editorial decision 3 November 2020; accepted 5 November 2020; online publish-ahead-of-print 23 November 2020

Keywords Telomere • Longitudinal studies • Child • Metabolic syndrome • Blood pressure • Microcirculation

Leucocyte telomere attrition is considered a marker for cellular ageing caused by cumulative exposure to oxidative stress, inflammation, and endocrine dysfunction. Apart from a reflection of biological ageing (and thus telomeres being an outcome), telomere attrition is potentially involved in the onset of cardiovascular disease as cellular senescence reduces proliferative potential of cardiovascular systems limiting the regenerative capacity of aged and injured myocardium and vasculature.[1] In a meta-analysis of prospective studies, short telomere length or attrition was a predictor for future coronary heart disease.[2] A recent critical mechanistic interpretation tried to distinguish telomeres as atherosclerosis cause vs. atherosclerosis consequence.[3] Even though cardiovascular diseases are more common in older age, the origins can be tracked back to childhood. Indeed, a recent study showed that telomere dynamics during early life might be important in cardiovascular disease development as short telomere length in atherosclerosis is largely determined before the clinical manifestations.[4] On the contrary, telomere length was cross-sectionally associated with blood pressure and vascular elasticity in midlife adults but not in 11–12 years old children.[5] As the identification of cardiovascular disease predictors from childhood onwards is important, we used a childhood/adolescence cohort. The first objective was to investigate the cross-sectional association of children's telomere length with cardiovascular disease precursors, i.e. body mass index (BMI), blood pressure, blood lipid levels, insulin/glucose and retinal microvasculature. Secondly, the longitudinal relation between telomere length and these cardiovascular disease precursors was tested over three measurement waves. Herein, (bi)directionality could be tested via cross-lagged modelling.

Belgian children were followed-up for 7 years in spring 2008, 2010, and 2015. From 242 participants at follow-up, 181 had complete data for biological measures (9–15 years, 4.4% overweight), as part of different study projects approved by the Ethics Committee following the Declaration of Helsinki guidelines.[6] The average relative telomere length was measured by a quantitative real-time polymerase chain reaction protocol[7] and calculated using qBase software expressed as the ratio of telomere copy number to single-copy gene number (T/S) and normalized to the average T/S ratio of the entire sample set. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an electronic sphygmomanometer (Welch Allyn 4200B-E2) in triplicate. Retinal photographs were taken from both eyes in 2015 only (Canon 45° 6.3-megapixel nonmydriatic retinal camera; retinal vessel measurement system IVAN). Arterioles and venules in an area 0.5–1 disc diameter from the optic disc margin were summarized in the central retinal arteriolar and venular equivalent (CRAE and CRVE) and arteriolar-to-venular ratio. Fasting blood samples were assessed on glucose, insulin, leptin, high density lipoprotein (HDL), total cholesterol, and triglyceride. The homeostasis model assessment estimating insulin resistance (HOMA-IR) was calculated.

Cross-lagged models were performed in Mplus (version 5.1) using maximum-likelihood estimation with robust standard errors. The cross-lagged models allow to consider interdependencies within repeatedly measured data, while testing bidirectionality. Each cross-lagged model included correlations within waves (e.g. cross-sectional: telomere Time 1 to cardiovascular precursor Time 2), cross-lagged paths (e.g. longitudinal: from telomere Time 1 to cardiovascular precursor Time 2) while also adjusting for autoregressive paths (e.g. telomere Time 1 to telomere Time 2) and the confounders age, sex and parental socio-economic status (see Figure 1). Additional adjustment for BMI did not change the *P*-value level. For descriptive purposes, telomere attrition d-score was calculated to avoid regression to the mean.[8]

* Corresponding author. Tel: +32 9 332 83 74, Email: nathalie.michels@ugent.be
† These authors are shared first authors.

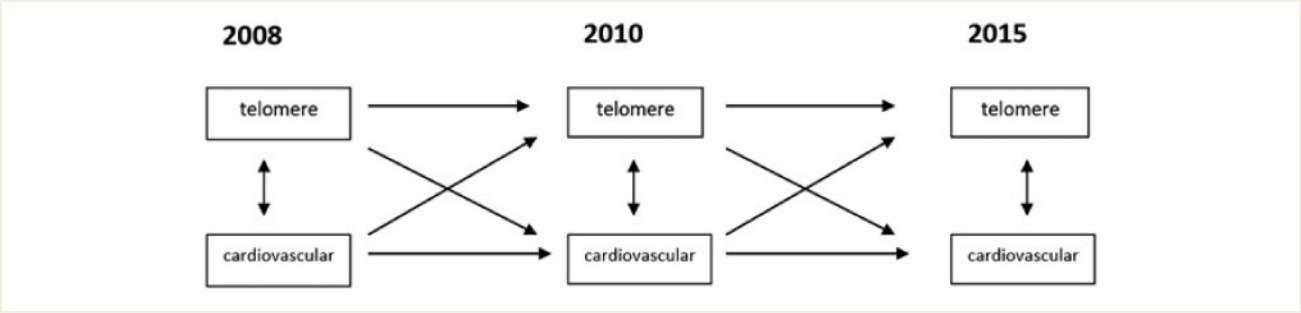

Figure 1 Theoretical cross-lagged model.Data availability

Data is available upon request to the corresponding author.

Table 1 Standardized coefficients from cross-lagged associations between telomere length and cardiovascular disease precursors measured in 2008 (T1), 2010 (T2), and 2015 (T3)

Cross-sectional				Telomere length as predictor		Telomere length as outcome	
	2008 (T1)	2010 (T2)	2015 (T3)	Telomere T1→ cardiovascular T2	Telomere T2→ cardiovascular T3	Cardiovascular T1→ telomere T2	Cardiovascular T2→ telomere T3
Cardiovascular disease precursors							
BMI (z-score)	0.071	0.095	**−0.151***	-0.014	0.076	0.002	-0.053
Blood pressure							
SBP (mmHg)	0.105	0.057	**−0.134***	**0.265****	−0.051	0.016	0.047
DBP (mmHg)	0.081	−0.024	0.009	0.175	−0.080	0.039	**0.120***
Retinal microvasculature							
CRAE (μm)			0.012		−0.117		
CRVE (μm)			−0.078		0.048		
AVR			−0.008		−0.084		
Metabolic markers							
Total cholesterol (mg/dL)	0.012	0.082	−0.025	0.040	−0.002	0.031	−0.094
HDL (mg/dL)	0.071	0.049	0.083	0.007	−0.007	0.105	−0.004
Triglyceride (mg/dL)	**−0.155***	**0.235***	0.094	**−0.339****	0.079	−0.006	**−0.194***
Insulin (mU/L)	**−0.156***	0.005	−0.063	0.198	0.033	−0.024	−0.110
Glucose (mmol/L)	−0.075	0.148	−0.008	0.101	0.017	−0.067	−0.098
HOMA-IR	−0.158	−0.017	−0.069	**0.281***	0.045	−0.031	−0.107
Leptin (ng/mL)		−0.016	−0.013		0.104		0.075

Each row represents one cross-lagged model including cross-lagged paths (e.g. longitudinal: from telomere Time 1 to cardiovascular precursor Time 2), autoregressive paths (e.g. telomere Time 1 to telomere Time 2), and correlations within waves (e.g. cross-sectional: telomere Time 1 to cardiovascular precursor Time 2). Models were adjusted for age, gender, and socioeconomic status. Bold, p<0.05.

AVR, arteriolar to venular ratio; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment estimating insulin resistance score; SBP, systolic blood pressure.

Relative telomere length tracked across the different follow-up surveys ($r = 0.68$–0.73, $P < 0.0001$). Baseline telomere length was correlated with telomere attrition rate D-score over 7 years ($r = 0.20$, $P = 0.008$). Descriptive data over the three waves can be found in the Supplementary material online, *Table*.

Cross-sectional and longitudinal associations between telomere length and cardiovascular disease precursors are shown in *Table 1*. Cross-sectionally, a negative association was observed for telomere length with SBP, insulin and BMI but only at one of the three measurement waves. For triglycerides both an unexpected positive as well as a negative cross-sectional association were observed. Longitudinally, shorter telomeres predicted higher triglyceride values which further predicted shorter telomeres. Also some unexpected positive longitudinal associations were found: shorter telomeres as predictor of lower SBP and HOMA, while lower DBP as predictor of shorter telomeres.

As mentioned in the introduction, bidirectional associations are possible. An interesting finding in our relatively small child cohort was a vicious circle between low telomeres and high triglycerides, but not for the other lipids HDL and total cholesterol. A potential mechanistic explanation might be the cumulative inflammation and oxidative stress burden on telomeres as a result of dyslipidaemia, while shorter

telomeres might further aggravate inflammation. Similarly, a large 6-year follow-up in adults found baseline telomere being associated with triglycerides and HDL at follow-up and same trends for HDL in the other cause-effect direction (although not analysed in one same model).[9] The latter cohort found the same negative bidirectionality for glucose, while our study could not find significances for glucose, only a cross-sectional negative insulin correlation and an unexpected positive association between telomeres at baseline with HOMA at follow-up. For blood pressure, we found a logic cross-sectional association while a positive longitudinal association with telomere length as predictor (in the case of SBP) or as outcome (in the case of DBP). A meta-analysis of epidemiological studies showed that telomere length might be shorter in hypertensive adults as compared to normotensive adults despite substantial heterogeneity,[10] while no longitudinal telomere associations with SBP were found in a large longitudinal adult cohort.[9] The relatively healthy population in our study (only 4% overweight) and potential residual confounding might have influenced results towards unexpected associations. Different time windows between waves (2 and 5 years) might also explain varied findings over the waves.

In conclusion, our longitudinal data during childhood found some but limited evidence for a negative association between telomere length and cardiovascular precursors. Interestingly, bidirectionality (a vicious circle with triglycerides) and even some positive associations (blood pressure and HOMA) were detected. Larger and more diverse prospective studies are necessary to examine cause-effect directionality in populations with higher morbidity. As the risk factors for cardiovascular diseases and telomere shortening are fairly similar, a healthy lifestyle from childhood on should be emphasized as this might influence future health.

Funding

This study was supported by the Research Foundation-Flanders, Belgium (project number G073315N). The authors would also like to acknowledge the IDEFICS – I.Family study (supported by the EU sixth and seventh framework programme for research, under grant agreement number 16181 and 266044).

Conflict of interest: none declared.

Data availability

Data is available upon request to the corresponding author.

References

1. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2014;**349**:g4227.
2. Fyhrquist F, Saijonmaa O, Strandberg T. The roles of senescence and telomere shortening in cardiovascular disease. *Nat Rev Cardiol* 2013;**10**:274–283.
3. De Meyer T, Nawrot T, Bekaert S, De Buyzere ML, Rietzschel ER, Andrés V. Telomere length as cardiovascular aging biomarker JACC review topic of the week. *J Am Coll Cardiol* 2018;**72**:805–813.
4. Benetos A, Toupance S, Gautier S, Labat C, Kimura M, Rossi PM, Settembre N, Hubert J, Frimat L, Bertrand B, Boufi M, Flecher X, Sadoul N, Eschwege P, Kessler M, Tzanetakou IP, Doulamis IP, Konstantopoulos P, Tzani A, Korou M, Gkogkos A, Perreas K, Menenakos E, Samanidis G, Vasiloglou-Gkanis M, Kark JD, Malikov S, Verhulst S, Aviv A. Short leukocyte telomere length precedes clinical expression of atherosclerosis the blood-and-muscle model. *Circ Res* 2018;**122**:616–623.
5. Nguyen MT, Vryer R, Ranganathan S. Telomere length and vascular phenotypes in a population-based cohort of children and midlife adults. *J Am Heart Assoc* 2019;**8**:e012707.
6. Michels N, Vanaelst B, Vyncke K, Sioen I, Huybrechts I, De Vriendt T, De Henauw S. Children's Body composition and Stress—the ChiBS study: aims, design, methods, population and participation characteristics. *Arch Public Health* 2012;**70**:17.
7. Martens DS, Plusquin M, Gyselaers W, De Vivo I, Nawrot TS. Maternal pre-pregnancy body mass index and newborn telomere length. *BMC Med* 2016;**14**:148.
8. Verhulst S, Aviv A, Benetos A, Berenson GS, Kark JD. Do leukocyte telomere length dynamics depend on baseline telomere length? An analysis that corrects for 'regression to the mean'. *Eur J Epidemiol* 2013;**28**:859–866.
9. Revesz D, Milaneschi Y, Verhoeven JE, Lin J, Penninx BWJH. Longitudinal associations between metabolic syndrome components and telomere shortening. *J Clin Endocr Metab* 2015;**100**:3050–3059.
10. Tellechea ML, Pirola CJ. The impact of hypertension on leukocyte telomere length: a systematic review and meta-analysis of human studies. *J Hum Hypertens* 2017;**31**:99–105.