Rate of telomere shortening and cardiovascular damage: a longitudinal study in the 1946 British Birth Cohort

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Aim
Cross-sectional studies reported associations between short leucocyte telomere length (LTL) and measures of vascular and cardiac damage. However, the contribution of LTL dynamics to the age-related process of cardiovascular (CV) remodelling remains unknown. In this study, we explored whether the rate of LTL shortening can predict CV phenotypes over 10-year follow-up and the influence of established CV risk factors on this relationship.

Methods and results
All the participants from the MRC National Survey of Health and Development (NSHD) with measures of LTL and traditional CV risk factors at 53 and 60–64 years and common carotid intima-media thickness (cIMT), cardiac mass and left ventricular function at 60–64 years were included. LTL was measured by real-time polymerase chain reaction and available at both time points in 1033 individuals. While LTL at 53 years was not linked with any CV phenotype at 60–64 years, a negative association was found between LTL and cIMT at 60–64 years (β = 0.017, P = 0.015). However, the strongest association was found between rate of telomere shortening between 53 and 60–64 years and values of cIMT at 60–64 years (β = 0.020, P = 0.006). This association was not affected by adjustment for traditional CV risk factors. Cardiac measurements were not associated with cross-sectional or longitudinal measures of LTL.

Conclusion
These findings suggest that the rate of progression of cellular ageing in late midlife (reflected by the rate of LTL attrition) relates to vascular damage, independently from contribution of CV risk factor exposure.

Keywords
Ageing • Telomeres shortening • Cardiovascular diseases • Carotid artery

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Rate of telomere shortening and cardiovascular damage

Introduction

Telomeres are multiple repetitions of standard DNA sequences (TTAGGG), which cap the ends of eukaryotic chromosomes and protect them from aberration and fusion. As DNA polymerase cannot fully replicate the 3’ end of linear DNA, somatic cell replication results in a progressive loss of telomeres repeats, a process eventually resulting in cellular senescence or apoptosis. The recent availability of high throughput assays to measure telomere length on peripheral leucocytes (leucocyte telomere length, LTL) has allowed investigation into the role of telomere length biology in the evolution of cardiovascular (CV) disease. This has led to several observational studies reporting cross-sectional associations between LTL, levels of CV risk factors and clinical or subclinical measures of CV damage. Consequently, LTL has been suggested as a novel marker of CV ageing, integrating the cumulative lifetime burden of genetic factors and environmental stressors involved in the evolution of CV damage. It remains unknown, however, whether CV phenotypes in mid and later life are influenced by the dynamic change of LTL, and whether any such associations are independent of traditional CV risk factors.

The MRC National Survey of Health and Development (NSHD, also known as the 1946 British Birth Cohort) is the oldest of the British Birth Cohort studies, and is unique in providing measures of LTL and CV risk factors at the ages of 53 and 60–64 years, together with a characterization of the cardiac and vascular phenotypes at the later time point. The aim of this study was to determine whether the rate of LTL shortening over 10 years predicts cardiac and vascular phenotypes independent of established CV risk factors.

Methods

Population and cardiovascular risk factors assessment

The MRC NSHD is a social class stratified sample of all singleton births to married parents in England, Scotland, and Wales during 1 week in March 1946. LTL measures were available in 1033 participants at both 53- and 64-year follow-up visits. The 53-year visit was performed at home by a team of trained nurses while at 60–64 year participants were invited to attend one of six clinical research facilities (CRFs) across Britain or, if they were unable or unwilling to travel, to have a research nurse visit them at home. More details on the assessment of CV risk factors are reported in the Supplementary material online. Ethical approval for the study was obtained from the Greater Manchester Local Research Ethics Committee and the Scotland A Research Ethics Committee for the 60–64 years collection and from the Multicentre Research Ethics Committee for the 53 years collection. Written, informed consent was obtained from the study member for each component of each data collection.

Leucocyte telomere length assay

At both ages, DNA was extracted from frozen EDTA blood samples using Puregene DNA isolation kits (Flowgen, Leicestershire, UK). LTL at both ages was measured in the same laboratory according to a previously validated real-time polymerase chain reaction technique in a blinded fashion. More details on the method used to measure LTL are reported in the Supplementary material online.

Vascular phenotype

The right and left common carotid arteries (cIMT) were imaged longitudinally, 1 cm proximal to the carotid bifurcation following a standardized protocol. All measures were undertaken using an ultrasound scanner (Vivid I or Vivid 7, GE Healthcare) with a high-resolution probe (12 MHz). More details on the methods used for image acquisition and analysis are reported in the Supplementary material online.

Cardiac phenotype

Echocardiography was performed by a trained, experienced sonographer using GE Vivid I machines. Echocardiographic images were obtained from parasternal long-axis and short-axis, apical five-chamber, four-chamber, three-chamber, two-chamber and aortic views along with conventional and tissue Doppler in the four-chamber view. Image analysis, including wall and chamber measurements for the evaluation of left ventricular mass, ejection fraction, and diastolic function, was undertaken in a single core laboratory according to ASE/EAE guidelines by three experienced readers blinded to patient identity using the GE EchoPac software (GE CT, USA). The left ventricular mass (LVM) was indexed to the body surface area (LVM/BSA).

Quality assurance of echocardiography was performed throughout the study and blind duplicate reading reproducibility studies were carried out to establish inter- and intra-reader reliability. These showed excellent reproducibility (intra-class correlation coefficients were >0.9).

Statistical analysis

Linear regression models were used to investigate the unadjusted association between LTL at 53 years, LTL at 60–64 years and their difference with each measure of vascular (cIMT) and cardiac phenotype at 60–64 years. A series of multiple regression models were then fitted to examine whether the traditional CV risk factors and other potential confounders influenced any associations observed between LTL and the vascular and cardiac phenotypes. More details on the statistical methods are reported in the Supplementary material online.

Results

Descriptive statistics

Characteristics of the study population at both time points are shown in Table 1. Not all individuals with LTL at 53 years had a measure of LTL at 60–64 years. However, the characteristics at age 53 years of...
the groups with and without an LTL measure at 60–64 years were similar. Overall, the population was overweight with relatively high levels of systolic blood pressure and tendency to high levels of cholesterol and HbA1c. However, values of cIMT and cardiac measures were consistent with a relatively healthy population with largely normal left ventricular systolic and diastolic function, normal cIMT, and normal cardiac structure. Table 1S (Supplementary material online) shows the characteristics of the population based on tertiles of LTL changes. Only HDL-cholesterol varied significantly across the categories of rate of change in LTL.

### Associations between leucocyte telomere length at 53 and 60–64 years and cardiovascular phenotypes

LTL at 53 years was not associated with vascular (cIMT) measures at 60–64 years (Figure 1A). Similarly, there was no evidence of associations between LTL at 53 years and any of the cardiac phenotypes at 60–64 years old (Supplementary material online, Table S1).

At the age of 60–64 years, LTL was inversely associated with cIMT [regression coefficient (β) = −0.017 mm per 1 standard deviation (SD) LTL; 95% confidence interval (CI): −0.031, −0.003; P = 0.015; R² = 0.005] (Figure 1B and Supplementary material online, Table S2). The association was greatly attenuated in the adjusted model (Model 2) (total cholesterol, systolic blood pressure at age 60–64, socio-economic status, medications use, clinic centre, and past history of myocardial infarction) (β = −0.008; 95% CI: −0.023, 0.006; P = 0.257; R² = 0.07). Addition of LTL measure at 60–64 years in the fully adjusted model (model 2) did not substantially increase the overall model fit (R² change = 0.005, P = 0.134). No associations were observed between LTL at 60–64 years and cardiac measurements (Supplementary material online, Table S2).

### Associations between longitudinal change of leucocyte telomere length and cardiovascular phenotypes

In 74% of participants, there was telomere shortening over the follow-up (Figure 2). A greater decrease in LTL change between the ages of 53 and 60–64 years was associated with thicker cIMT at 60–64 years old (unadjusted model: β = −0.020 mm per 1 SD decrease in LTL; 95% CI: −0.027, −0.005; P = 0.006; R² = 0.008) (Table 2 and Figure 2). The strength of this association was not affected by multiple adjustment (model 3: β = −0.016, 95% CI: −0.029, −0.002; P = 0.022; R² = 0.12) (Table 2). Addition of LTL change in the fully adjusted model (model 3) only slightly increased the overall model fit (R² change = 0.007, P = 0.108). This association was linear so that the association with cIMT was observed in individuals with telomere elongation and those with telomere shortening. The right cIMT showed very similar findings, with the left showing a somewhat weaker association (Table 2). No associations were found between changes in LTL and cardiac phenotype measures of left ventricular mass, ejection fraction, and diastolic function (data not shown).

Similarly, a greater shortening of LTL was associated with higher odds of increased cIMT [OR (95% CI) per one SD of LTL = 1.83 (1.03–3.25); P = 0.038]. Individuals diagnosed with carotid plaques had higher shortening of LTL during the follow-up compared with...
Discussion

This is the first study, to our knowledge, to explore the association between changes in LTL over 10 years and CV phenotypes. We found, using data from a nationally representative cohort of 60–64-year-old men and women, that a faster rate of decrease in LTL over 10 years was associated with increased cIMT. This association was seen in participants with both elongation and shortening of LTL and persisted after adjustment for potential confounders and mediators. Furthermore, single measures and longitudinal variations of LTL were not related with cardiac phenotypes. These results suggest that, over and above the contribution of classic CV risk factor exposure, a small proportion of the variation in vascular phenotype in late midlife relates to mechanisms regulating the rate of cellular ageing.

Several studies have reported cross-sectional associations between shorter LTL with subclinical and clinical markers of atherosclerosis. We have shown that the negative relationship between LTL and cIMT described in previous studies is likely to be consequent to a faster rate of LTL change during the lifespan. This suggests that, either regulation of LTL dynamics has a role in the evolution of vascular disease, or that the processes of cellular ageing and atherosclerosis are influenced by similar factors and proceed in parallel. A
recent subanalysis of the Cardiovascular Health Study supports the first hypothesis, suggesting a causal relationship between ageing pathways and risk of CV disease. The ability of LTL to directly influence the evolution of vascular damage could lie on the unique feature of LTL to mirror telomere dynamics in haematopoietic stem cells (HSCs). As these cells also represent the haematological precursors of endothelial progenitor cells, a faster rate of LTL shortening may reflect a faster rate of telomere attrition in HSC reserves, ultimately resulting in a limited ability of the bone marrow to supply an adequate number of endothelial progenitor cells for effective repairation of vascular damage. On the other hand, several studies have supported the second hypothesis, suggesting oxidative stress as a potential mediator of the association between shorter LTL and higher levels of vascular damage. Oxidative stress exposure is currently considered the main driver of atherosclerosis. Similarly, an elevated burden of oxidative stress may result in a faster rate of LTL attrition by increasing the oxidative stress-mediated damage to the telomere sequence. Therefore, exposure to increased levels of oxidative stress may lead to telomere shortening and, consequently, to an increased risk of CV disease.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>cIMT (mm)</th>
<th></th>
<th>R_cIMT (mm)</th>
<th></th>
<th>L_cIMT (mm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (95% CI)</td>
<td>$P$-value</td>
<td>$\beta$ (95% CI)</td>
<td>$P$-value</td>
<td>$\beta$ (95% CI)</td>
<td>$P$-value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>$-0.020$ ($-0.027; -0.005$)</td>
<td>0.006</td>
<td>$-0.019$ ($-0.032; -0.006$)</td>
<td>0.004</td>
<td>$-0.014$ ($-0.027; -0.001$)</td>
<td>0.033</td>
</tr>
<tr>
<td>Model 1</td>
<td>$-0.015$ ($-0.026; -0.003$)</td>
<td>0.011</td>
<td>$-0.019$ ($-0.032; -0.006$)</td>
<td>0.005</td>
<td>$-0.012$ ($-0.025; -0.001$)</td>
<td>0.068</td>
</tr>
<tr>
<td>Model 2</td>
<td>$-0.017$ ($-0.030; -0.003$)</td>
<td>0.007</td>
<td>$-0.018$ ($-0.035; -0.005$)</td>
<td>0.009</td>
<td>$-0.014$ ($-0.029; -0.001$)</td>
<td>0.074</td>
</tr>
<tr>
<td>Model 3</td>
<td>$-0.016$ ($-0.029; -0.002$)</td>
<td>0.022</td>
<td>$-0.017$ ($-0.033; -0.003$)</td>
<td>0.012</td>
<td>$-0.015$ ($-0.030; -0.001$)</td>
<td>0.052</td>
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LTL measures and all other confounders available in 672 participants at 53 and 64 years follow-up.

Generalized linear model; Model 1 = age difference in years, gender, smoking status 99, difference in BMI (99–09); Model 2 = Model 1 + cholesterol 2009, systolic BP 2009, socio-economic status, anti-inflammatory use, OAC, lipid lowering, clinic centre and history of MI; Model 3 = CVD risk SCOREs (including age, gender, smoking, total- and HDL-cholesterol, systolic blood pressure) based on the SCORE charts, difference in BMI (99–09), socio-economic status, anti-inflammatory use, OAC, lipid lowering and clinic centre.

cIMT, average carotid artery; R_cIMT, right carotid artery; L_cIMT, left carotid artery.

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**Figure 2** Scatter plot of relative change in leucocyte telomere length (%) during the follow-up and values of carotid intima-media thickness at 60–64 years. Relative change in LTL = [(LTL (bp) at 60–64 years) – (LTL (bp) at 53 years)]/[LTL (bp) at 53 years] * 100. Values of carotid intima-media thickness are unadjusted and the reference dashed line separates individuals with telomere elongation from those with telomere shortening during the follow-up. Individuals with leucocyte telomere length shortening during the follow-up have increased values of carotid intima-media thickness at 60–64 years ($R = -0.10; P = 0.01$).
stress may explain the parallel evolution of vascular damage and telomere attrition, potentially accounting for our findings.

Several studies have reported cross-sectional associations between LTL and smoking, obesity, and levels of insulin resistance. We did not find associations that the association between LTL dynamics and markers of CV risk factors to effectively influence LTL dynamics and to mediate its association with CV phenotypes. Our study demonstrates that the association between LTL dynamics and markers of CV disease is unlikely to be dependent on traditional CV risk factor exposure, suggesting that other factors (such as oxidative stress or genetic mechanisms regulating the progression of cellular ageing) could drive this association.

Inconsistent associations have been reported between LTL and LVM or left ventricular function. We did not find associations between single measures and longitudinal measures of LTL and cardiac phenotypes. Our results are in line with current understanding of the LTL biology and the processes regulating the mechanisms of myocardi remodeling. Given that the haematopoietic system is the most proliferative among human tissues, age-dependent telomere shortening in HSCs, as expressed in LTL dynamics, is unlikely to reflect the evolution of the ageing process of cells with slow turnover rate, such as cardiomyocytes. Our findings support this hypothesis and provide the first epidemiological evidence of a possible different role of LTL biology in the evolution of cardiac and vascular remodeling. In keeping with our results, previously reported data from a meta-analysis including NSHD did not documented associations between LTL and clinical measures of muscular ageing, such as peripheral muscle strength.

The MRC NSHD has a number of strengths for the investigation of LTL biology and its relationship with CV risk factors and phenotypes. Firstly, the 10-year follow-up between LTL measures and the relatively large number of participants included in the analysis represents the most important strengths. Indeed, the yearly rate of change of LTL is extremely low when compared to the ability of current LTL assays to detect small differences in telomere length. Consequently, changes in LTL over a long follow-up period and a large sample size are necessary to detect inter-individual variations in telomere attrition rates with confidence. Secondly, the acquisition of cIMT images was performed according to current guidelines. Furthermore, the use of automated edge detection programme has enabled a considerable reduction in differences between readers and has minimized the risk of change in reading behaviour over time (reader drift).

The high interclass correlation between readers and the presence of an average cIMT in keeping with reference values confirm the quality of our cIMT acquisition and analysis protocols. While longitudinal studies have documented uncertain utility of repeated cIMT measures for prediction of CV outcome, a single measure of cIMT remains a useful tool to identify people at higher CV risk. The utility of this measure is strongly influenced by accuracy and standardization of the protocols for cIMT images acquisition and analysis. Finally, the availability of data on a wide range of established and novel CV risk factors and potential confounders at both ages, where LTL was measured allowed, for the first time, investigation of the independent contribution of LTL dynamics to CV phenotype.

Our report also has several limitations. The associations reported in this study are observational, and therefore no definitive conclusions can be made regarding causality. The proportion of cIMT variability explained by LTL dynamics is small and unlikely to be of clinical relevance. However, the aim of this paper was not to improve CV disease risk prediction by addition of a longitudinal measure of cellular ageing (such as LTL) to common CV risk factors, but to explore its relationship with a measure of vascular remodeling (surrogate outcome), to unravel possible new mechanisms of progression of atherosclerosis (i.e. biological pathways regulating cellular ageing). Furthermore, it should be highlighted that also the fully adjusted model including the continuous variable of future CVD risk (calculated with the SCORE charts) explains only a small proportion of the variability of cIMT in our population. This could be explained by the fact that our cohort comprises mainly CVD-free participants (as suggested by the normal average values of cIMT). Consequently, if LTL marks the residual ability to repair the vascular damage, a relatively low CV risk factor burden is likely to have underestimated the possible contribution of LTL dynamics to the cIMT variability in our analyses. Attrition is unavoidable in long-running studies such as NSHD, but our previous analyses have shown that the samples at 53 and 60–64 years remained broadly representative of the British born population of that age. Furthermore, we showed that the characteristics at age 53 years of the groups with and without an LTL measure at 60–64 years were similar and thus any drop out between the two ages is likely to have had a minimal effect on our findings. We did not measure telomere length in vascular cells but only in leucocytes. This is likely to have weakened the association between LTL dynamics and cIMT. However, Wilson et al. previously reported that LTL predicts vascular telomere length in humans with and without vascular disease and a strong synchronization between LTL and telomere length of other tissues was reported also by other authors. We used measures of cardiac remodeling that are strongly influenced by values of blood pressure. This might have reduced our ability to detect associations between LTL and cardiac phenotypes. However, our results raise further doubts on the associations between LTL and LVM, previously reported in cross-sectional studies. Finally, it is now well established that the delicate balance between injurious and repairing factors determines the level of genomic instability in each individual as well as his/her risk of developing age-related diseases, such as CV disease. In our paper, we measured a marker of cellular ageing which represents only one of the multiple pathways contributing to genomic instability. Larger longitudinal studies will need to confirm our results and address whether the combination of multiple ageing markers can better define the role of cellular ageing in the evolution of CV disease.

Conclusions

Our results suggest that previously reported cross-sectional associations between short LTL and measures of subclinical atherosclerosis...
are likely dependent upon a faster rate of LTL attrition. Importantly, the association was only partially confounded by exposure to CV risk factors. This suggests that, over and above chronological age and CV risk factors, a small proportion of vascular but not cardiac remodelling could be explained by mechanisms regulating the rate of progression of cellular aging during lifespan.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Acknowledgements**

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A 17-year old female presented with atypical chest pain. Clinical examination and ECG was unremarkable but an echocardiogram demonstrated ‘unusual ventricular foreshortening’.

Subsequent cardiac magnetic resonance imaging demonstrated all four characteristics of a rare primary cardiomyopathy. A truncated left ventricle (Panels A and B), spherical remodelling, and bulging of the inter-ventricular septum towards the right ventricle (Panels B, D, and E). RV apex formation with wrapping around of the RV apex around the deficient left ventricular apex (Panels A and B) and fatty replacement of the LV apex (Panels D, E and H). In this case, apical fat pad and additional apical fatty infiltration of the LV apex were clearly delineated by T1 mapping (Panel F) which to our knowledge has not been applied in this pathology before. Late gadolinium enhancement revealed mid-wall hyper-enhancement in the mid-ventricular septum (Panels D and E). Taken together these findings were diagnostic of left ventricular apical hypoplasia (LVAH) (Supplementary material online, Video 1).

Left ventricular apical hypoplasia was first identified in 2004 and is postulated to be a congenital abnormality due to inadequate dilatation of chambers during partitioning. This is the third case to identify mid-wall fibrosis in a case of LVAH. This finding has not consistently been described, as a characteristic of LVAH suggesting the possible role of CMR in risk stratifying patients with this poorly understood condition. Furthermore, this may provide evidence for an overlap with other inherited idiopathic cardiomyopathies of the DCM spectrum.

Patients usually present with mild, non-specific symptoms although arrhythmic presentations have been reported. Most respond well to standard cardiac failure therapy.

Supplementary material is available at European Heart Journal online.