Telomere Length and Risk of Cardiovascular Disease and Cancer

Said, M Abdullah; Eppinga, Ruben N; Hagemeijer, Yanick; Verweij, Niek; van der Harst, Pim

Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2017.05.044

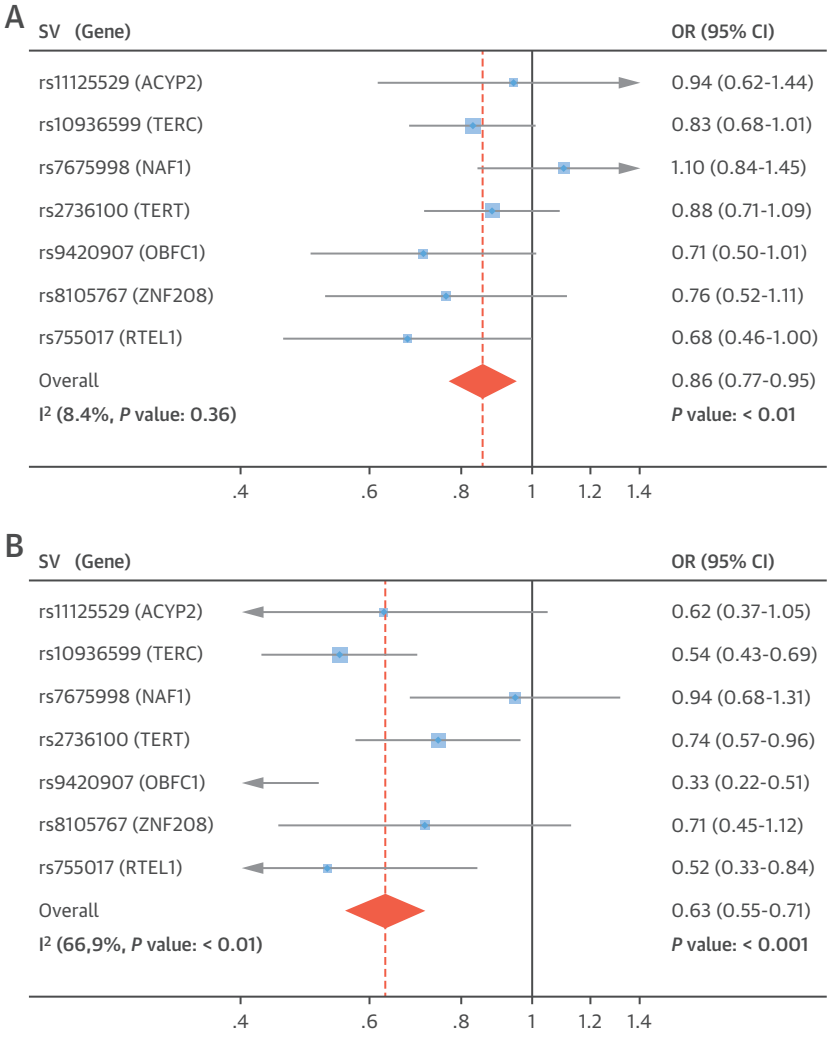
Publication date:
2017

JACC VOL. 70, NO. 4, 2017
JULY 25, 2017:504–11

Telomere Length and Risk of Cardiovascular Disease and Cancer

Telomeres are DNA repeat structures with protein complexes capping the ends of chromosomes important for chromosomal stability and cellular integrity (1). Telomeres shorten with each cell division and under environmental conditions such as oxidative stress. Therefore, telomere length (TL) has been proposed to reflect biological age (1). Many associations between shorter TL and various age-associated cardiovascular conditions have been reported, including hypertension, coronary heart disease, and heart failure (1). Shorter and longer TL have also been linked to specific malignancies (2). These cross-sectional data do not provide evidence for causality. We report a Mendelian randomization using 7 sequence variants (SVs) previously associated with TL (3) and created a genetic risk score. We studied the association of

FIGURE 1 Genetically Determined Telomere Length Variants and Risk of Cardiovascular Disease and Cancer



Genetically determined telomere length (gTL) variants and risk of **(A)** cardiovascular disease (CVD) and **(B)** cancer. Forest plots display the effect of longer gTL on CVD and cancer risk for each gTL sequence variant (SV). The overall effect is from fixed-effects meta-analysis of all SVs. Odds ratio (OR) shown with 95% confidence interval (CI) relates to a change in risk per-SD lengthening in gTL.

genetically determined TL (gTL) with cardiovascular conditions, and mortality in 134,773 individuals of the UK Biobank population (4).

Genotypes based on UK Biobank arrays (BiLEVE and Axiom) imputed to the merged UK10K and 1000 Genomes Phase 3 panel were used. Participant follow-up started at inclusion and ended at death or on February 17, 2014 (participants enrolled in Scotland on December 31, 2012). We examined the association of both the individual SVs and the genetic risk score based on a summation of all 7 SVs (weighted to their effect sizes, as reported in Codd et al.) (3) with hypertension, diabetes, cardiovascular disease (CVD), cancer, and mortality, as previously described (5). We adjusted our analyses for age, sex, genotyping arrays, and the first 10 principal components (generated by flashPCA based on covariance) that were provided by UK Biobank. Two-sided p values < 0.05 were considered statistically significant.

During the 1.2-year follow-up period, 2,395 (1.8%) participants died, 756 (0.6%) due to CVD and 1,499 (1.1%) due to cancer. The prevalence of overall CVD was 34.9% (n = 46,979). Although the effect size of individual SVs was small for CVD, the combined effect of all 7 SVs was substantial. Shorter gTL was associated with 14% (95% confidence interval [CI]: 5% to 23%; p = 0.004) higher risk of CVD per SD change in gTL (**Figure 1A**). The prevalence of hypertension was 31% (n = 41,847). Two SVs, rs10936599 (*TERC*) and rs9420907 (*OBFC1*), were individually associated (p values <0.05) with hypertension. The weighted linear combination of all 7 SVs was associated with 16% (95% CI: 7% to 25%; p = 0.002) increased hypertension risk per SD shorter gTL. The prevalence of overall cancer was 16.7% (n = 22,448). Four SVs were associated with overall cancer. The strongest association was observed for rs9420907 (*OBFC1*) (**Figure 1B**). The weighted linear combination of the SVs showed 37% (95% CI: 29% to 45%; p < 0.001) increased overall cancer risk and a 45% (95% CI: 12% to 65%; p = 0.01) increased cancer mortality risk per SD shorter gTL. We did not observe an association between gTL and diabetes (n = 7,969 [5.9%]; 9%; 95% CI: −12% to 26%; p = 0.38) or all-cause mortality (19%; 95% CI: −17% to 44%; p = 0.26).

Previous studies suggested associations between shorter TL with various CVD conditions (1). Although the exact origin of these associations remains to be elucidated, a first indication for causality was derived from a subanalysis of the CARDIoGRAM (Coronary ARtery DIsease Genome-Wide Replication and Meta-Analysis) study. In this previous work, a 21% (95% CI: 5% to 35%) increased risk of coronary heart disease was observed per SD shorter gTL (3). We now provide independent data further supporting this causal association between shorter gTL and both overall CVD and hypertension. Similar to the CARDIoGRAM study, rs7675998 (*NAF1*) had a contrasting effect for both CVD and hypertension risk. Our results on cancer also suggest causality for previously reported associations between shorter TL and increased cancer risk, although contrasting findings have also been reported and the reason for this discrepancy remains to be resolved (2).

In conclusion, we applied a Mendelian randomization approach and report evidence for a causal link among shorter gTL and CVD, hypertension, and cancer in 134,773 participants of the UK Biobank.

M. Abdullah Said, BSc
Ruben N. Eppinga, MD
Yanick Hagemeijer, MSc
Niek Verweij, PhD
***Pim van der Harst, MD, PhD**

*Department of Cardiology
Department of Genetics
University of Groningen
Unversity Medical Center Groningen
Hanzeplein 1
9700 RB Groningen
the Netherlands
E-mail: p.van.der.harst@umcg.nl

http://dx.doi.org/10.1016/j.jacc.2017.05.044

Please note: Mr. Said was supported by the Royal Netherlands Academy of Arts and Sciences Van Walree grant. The Royal Netherlands Academy of Arts and Sciences did not have any role in any stage of the study design, data analysis, or preparation of the manuscript. Dr. Verweij was supported by ICIN-NHI and Marie Sklodowska-Curie GF (call: H2020-MSCA-IF-2014, Project ID: 661395), neither of which had any role in any stage of the study design, data analyses, or preparation of the manuscript. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Mr. Said and Eppinga contributed equally to this work and are joint first authors.

REFERENCES

1. Samani NJ, van der Harst P. Biological ageing and cardiovascular disease. Heart 2008;94:537–9.

2. Rode L, Nordestgaard BG, Bojesen SE. Peripheral blood leukocyte telomere length and mortality among 64,637 individuals from the general population. J Natl Cancer Inst 2015;107:djv074.

3. Codd V, Nelson CP, Albrecht E, et al. Identification of seven loci affecting mean telomere length and their association with disease. Nat Genet 2013;45:422–7. 427e1–2.

4. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.

5. Nelson CP, Hamby SE, Saleheen D, et al. Genetically determined height and coronary artery disease. N Engl J Med 2015;372:1608–18.