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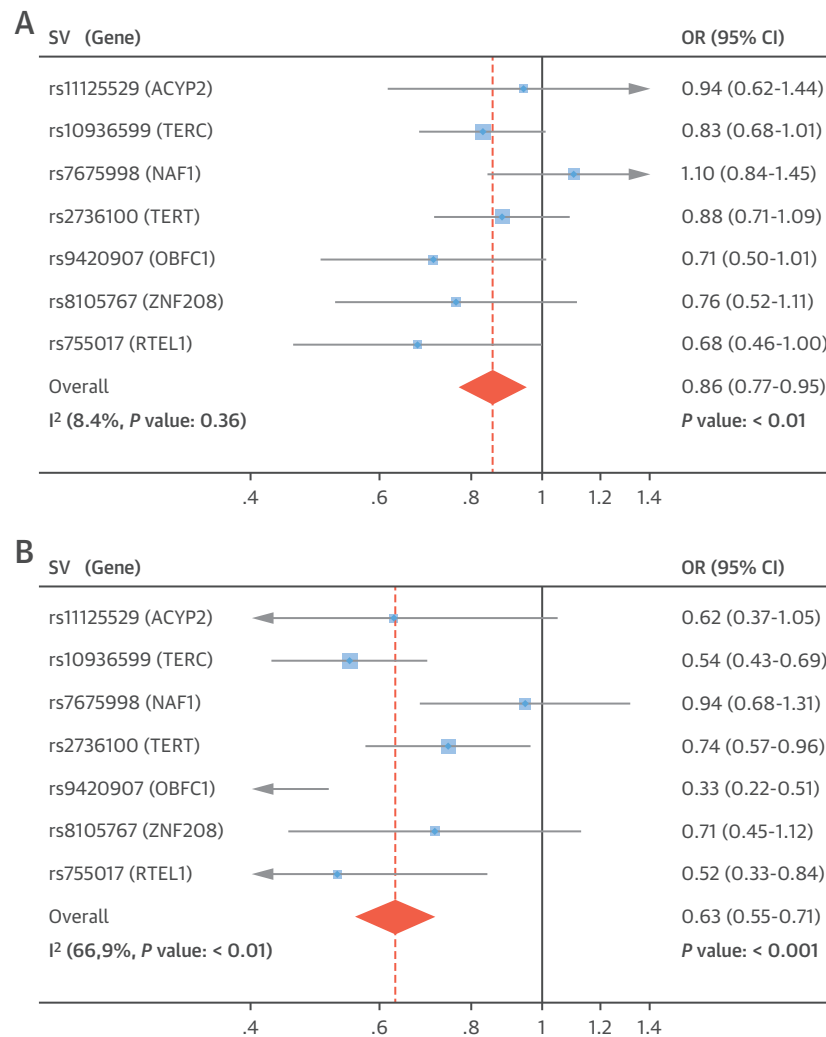
Telomere Length and Risk of Cardiovascular Disease and Cancer



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.

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