

## Telomere Length and Cardiovascular Disease: A Story with an Open End

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Re: *Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis*. *BMJ* 2014; 349: g4227 (Published 08 July 2014)

To the Editor:

We read with great interest the article by Philip C Haycock and colleagues published in *BMJ*, which report on the inverse association between leucocyte telomere length and risk of coronary heart disease (CHD) (1). The authors used a meta-analytical approach in order to systematically evaluate this relation in existing epidemiological studies. Indeed, telomere length may reflect important pre-disease mechanisms such as inflammation, oxidative stress, and immune cell aging and, therefore, may provide a link between age-related increases in chronic disease risk. However, there are several concerns about the reported analyses and their interpretation.

First, the associations seemed to be stronger in the low quality studies, such as in retrospective studies, studies with minimal set of adjustment and with a small sample size, which indeed comprised majority of included studies in the meta-analysis. This fact sheds doubt whether the main conclusion of the study is not influenced by the low quality of studies included in the analysis.

Second, it does not become clear whether the associations are independent from biologically relevant pathways such as oxidative stress and inflammation. As acknowledged by the authors these processes are associated with telomere length and are known causal factors for CHD, therefore may confound the observed relations. Among the studies included in the meta-analysis, only four studies accounted for C-reactive protein (CRP) - a biomarker of chronic inflammation. Among these, the study with the most statistical power, did not observe statistically significant higher risk of CHD (1). In studying etiology, we build multivariable models on clinical significance and not on statistical significance. Therefore, the statement of the authors for an observed “independent effect after comprehensive adjustment of potential confounders” may not fully reflect main hypothesized mechanisms which may explain the potential association between telomere length and CHD.

Third, the authors report on a linear relation between telomere length and risk of CHD, however they failed to provide an estimate for non-linearity check. Previous evidence for the relation between TL and chronic disease risk such as cancer (2) and diabetes (3) – suggested that both short and long telomeres are associated with a higher disease risk. Whether this may be true for CVD remains unanswered. Indeed, one study reported similar data based on prospective cohort study in Denmark among 929 cases of myocardial infarction diagnosed over 19 years among 19,284 study participants (4). In that study, the multivariable adjusted risks of myocardial infarction were 50% higher for both short and long telomere length in an analysis by deciles of TL distribution. The authors could have addressed this issue and discuss in a more detail on the potential study implications.

Fourth, it may be arguable whether a variable such as telomere length that is closely related with age can merely reflect multi-morbidity (5). In the large prospective study cited above a tendency for an association between telomere length and risk of myocardial infarction was seen in hypertensives, diabetics, and people with elevated CRP levels, but not in healthy participants (4). Stratification by prevalent chronic diseases, including cancer, would be informative for drawing conclusions about the independent effect of telomere length in CHD.

Finally, the potential implication of telomere length measurements for cardio-vascular risk prediction has been discussed. By doing so, the authors somehow mixed the concepts of etiology and risk prediction. However, the results arising from a prediction research methodology do not imply causation. In this respect, predictive factors may or may not be causally related to the outcome. With regards to the current analysis, the relevant question to be asked is not whether telomere length may predict CHD risk, but rather how much this biomarker may improve disease prediction beyond established cardio-vascular risk factors.

Taken together, at the present moment the evidence validating the associations between telomere length and cardiovascular diseases is far from conclusive. Large prospective studies are warranted - with a high level of adjustment for biologically plausible factors on the causal pathway and a sufficient sample size for risk stratification - in order to shed more light on the potential associations.

## References

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