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**Spurious association between telomere length reduction
over time and baseline telomere length**

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Spurious association between telomere length reduction over time and baseline telomere length

Ehrlenbach and co-workers found a linear relationship between baseline relative telomere length (RTL) and the decrease of RTL over 10 years ($r=0.674$; $P<0.001$).¹ Similarly, others have reported on this relationship between the telomere attrition rate and the baseline telomere length and found largely similar associations.^{2,3} Likewise, when we correlated the RTL and delta RTL during 7 years of follow-up in 75 men from the Zutphen Elderly Study⁴ with an age range of 70 to 91 years we found a largely identical association ($r=0.733$; $P<0.001$; unpublished data).

We question whether this association is trivial. We used a random number generator to produce 510 baseline RTL values, similar to the number of pairs in the study of Ehrlenbach *et al.*¹ A mean of 1.49 was aimed at for baseline values and 1.05 at 10-years follow-up, with distributions comparable to those presented in Table 1.¹ Using these random numbers, we found a beta coefficient that was nearly similar to the beta coefficient that was presented in Table 2 (0.557 as compared to 0.589, respectively). Because baseline RTL (X) was used to calculate the RTL shortening rate (X-Y), the 'dependent' and 'independent' variables were functionally related.⁵ Pearson's correlation coefficients using randomly generated factors can be estimated to be around $1/\sqrt{2}$, if baseline and outcome have equal variances.⁵ Therefore, it was to be expected that a linear regression model would best fit the data (as X was regressed on X-Y) and that an exceptional P -value of 2.3×10^{-90} was found (Table 2).¹ We think that the slope of the regression line should have been tested against the slope of a no-effect line, instead of zero (i.e., a horizontal line).

We therefore think that the reported association is not explained by older cells having lower division rates nor by telomerase that acts preferentially on short telomeres as a special protection mechanism, as was suggested as potential explanations,^{1,2} but is merely a

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3 consequence of mathematical coupling. It seems more likely that the attrition rate of RTL is
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5 biologically independent of baseline RTL.
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36 **Conflict of interest:** None declared.
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