Conflict of interest: None declared.

Reference

do:10.1093/ije/dyq221
Advance Access publication 12 November 2010
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Spurious association between telomere length reduction over time and baseline telomere length

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Ehrlenbach *et al*.1 found a linear relationship between baseline relative telomere length (RTL) and the decrease of RTL over 10 years ($r=0.674; P<0.001$). 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 70–91 years, we found a largely identical association ($r=0.733; P<0.001$; EJ Giltay *et al*., unpublished results).

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-year 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 with 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 $2.3 \times 10^{-90}$ 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 think, therefore, that the reported association is explained neither 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 consequence of mathematical coupling. It seems more likely that the attrition rate of RTL is biologically independent of baseline RTL.

<table>
<thead>
<tr>
<th></th>
<th>When Portugal played</th>
<th>When Portugal did not play</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events (number of days)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Euro 1996</td>
<td>70 (4)</td>
<td>0.87 (0.56–1.35)</td>
</tr>
<tr>
<td>Euro 2000</td>
<td>107 (5)</td>
<td>1.09 (0.78–1.53)</td>
</tr>
<tr>
<td>World Cup 2002</td>
<td>110 (3)</td>
<td>1.27 (1.00–1.61)</td>
</tr>
<tr>
<td>Euro 2004</td>
<td>219 (6)</td>
<td>1.11 (0.91–1.34)</td>
</tr>
<tr>
<td>Overall</td>
<td>506 (18)</td>
<td>1.02 (0.92–1.13)</td>
</tr>
</tbody>
</table>

The RR of AMI on match days involving the Portuguese team is compared with the other days of the competition.

*Adjusted for day of the week.
References

doi:10.1093/ije/dyq235
Advance Access publication 12 December 2010
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Authors’ Response
Correlation between baseline telomere length and shortening over time—spurious or true?
From ANITA KLOSS-BRANDSTÄTTER,1* PETER WILLEIT,2,3 CLAUDIA LAMINA,1 STEFAN KIECHL2 and FLORIAN KRONENBERG1

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Although we do not concur with their conclusions, we very much appreciate the stimulating comments by Erik Giltay et al.1 regarding our previous report2 on the association between baseline telomere length and subsequent telomere shortening. They argue that the correlation observed in our and in other studies3–4 is mainly due to mathematical coupling and suggest using the correlation due to mathematical coupling as the comparator rather than a correlation coefficient of zero. To enforce their view, Giltay and co-workers have also performed simulation studies with two random variables, X and Y, and then tested the correlation between X and Δ = X−Y.

However, this simulation is not appropriate because it ignores that X and Y are repeated measurements in the same individuals and highly correlated (rSpearman = 0.652, P = 4.7 × 10−63).2 Only for two series of independent random numbers X and Y with the same standard deviation, the correlation between X−Y and X expected based on mathematical coupling is indeed 1/2 ≈ 0.71 as formulated by Giltay et al. (please see Tu and Gilthorpe3 for a comprehensive review). However, as Giltay et al. correctly state, the null hypothesis β = 0 is not a correct null hypothesis any more. Tu and Gilthorpe5 proposed a method for testing the correlation between X and X−Y (corr[X, X−Y]). Since this test is based on Pearson’s correlation coefficient, it cannot be seen as a correction for the Spearman’s correlation coefficient, which we presented in the paper, but it is comparable with the P value presented for the linear regression model.

The correct null hypothesis can be derived by setting s = s. In this case, the Pearson’s correlation coefficient that is only due to mathematical coupling is rPearson = corr[X, X−Y] = √1−corr[X, Y]/2. If X and Y are not correlated (corr[X, Y] ≈ 0), then corr[X, X−Y] = 1/2. Therefore, corr[X, X−Y] has to be compared with the expected correlation coefficient under the hypothesis of no effect, which is 1−corr[X, Y]/2. To make them comparable, Fisher’s z transformation has to be performed. In our data, rPearson = corr[RTLbaseline, RTLchange] = 0.743 is clearly higher than the expected correlation coefficient of 1−corr[RTLbaseline, RTLfollow−up]/2 = 1−0.616/2 ≈ 0.438. The test on Fisher’s z-transformed values yields a value of P = 2.52 × 10−25. In comparison, the crude P value of corr[RTLbaseline, RTLchange] is P = 1.01 × 10−90. This P value is not adjusted for age, gender, and smoking, but since adjustment did not alter the P value of baseline RTL on the change of RTL (adjusted to baseline age and years of smoking).