PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Telomere length: Population epidemiology and concordance in 11-12 year old Australians and their parents
AUTHORS	Nguyen, Minh Thien; Lycett, kate; Vryer, Regan; Burgner, David; Ranganathan, Sarath; Grobler, Anneke; Wake, Melissa; Saffery, Richard

VERSION 1 - REVIEW

REVIEWER	Kyle W. Murdock The Pennsylvania State University; USA
REVIEW RETURNED	09-Nov-2017

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript entitled "Telomere length: Population epidemiology and concordance in 11-12 year old Australians and their parents." Below, major and minor concerns with the manuscript are outlined. Major 1. When describing comparisons between telomeres among father-child and mother-child pairs, no statistical comparisons are made. Differences are inferred only from the strength of associations. Accordingly, the authors should statistically compare the strength of the associations in order to be able to state that there are indeed differences. Given the overlap in confidence intervals, it is unlikely that there is a statistical difference. It would be inappropriate to suggest there are differences if this is the case. Comment #2 below reflects this as well. Minor 1. In the sample characteristics section, it would be useful to describe why telomere data was missing for many of the participants. 2. It doesn't appear appropriate to suggest that the parent sample was from relatively less disadvantaged areas compared to the national average. The standard deviations easily overlap, so it is unlikely that this is a significant difference. 3. Were mothers and fathers of children within families allowed to participate? It not completely clear if two parents within one family are included in the analyses. 4. The authors indicate that survey weights were utilized and that more detail on the calculation of weights is provided elsewhere. I googled the title of the citation provided and could not identify the information. If the information is not readily available, it should be described in greater detail.

REVIEWER	Pam Factor-Litvak Mailman School of Public Health Columbia University New York, New York USA
REVIEW RETURNED	14-Nov-2017

GENERAL COMMENTS	This is an interesting paper which describes associations between telomere length in children age 12 and characteristics of their parents. The paper brings new information regarding associations in middle childhood, but would be improved by addressing the comments below. 1. Do the investigators have any data comparing their T/S ratios with other laboratories? i ask because the use of T/S ratios can be somewhat controversial without across laboratory quality control results. 2. T/S ratios were higher in girls, compared to boys but not higher in women compared to men. Would the authors please comment on this, as telomere length is usually found to be longer in women than men; could it be that there were too few men in this analysis? 3. In reference 41, the authors incorrectly state that telomere length was not different by sex (page 15, lines 5-6 and page 16, lines 11-12); in that study telomere length was longer in girl newborns, compared to boy newborns, and in mothers compared to fathers and both were statistically significant. 4. Also in reference 41, the correlations beween telomere length in newborns and mothers was stronger than with fathers. 5. The authors appear to be confused about the correlation between telomere length in fathers and telomere length in newborns compared to paternal age being a strong predictor of telomere length in newborns (page 16, beginning at line 17). They argue that their findings of a lower correlation at higher parental ages may be due to telomere attrition during adult life due to environmental exposures. However, it is likely that the point of life in which telomere attrition is the greatest is during gestation when the cells are dividing rapidly. Hence, their argument needs to be reformulated. 6. It would be perhaps a better analytic strategy if the authors predicted child telomere length based on parental telomere length and parental ages at birth, which are easily calculated. 7. Finally, the number of fathers in the study is extremely small, making inferences regarding paternal characteristics tenuous at best.

REVIEWER	Pamela Kurjanowicz University of Toronto, Canada
REVIEW RETURNED	23-Nov-2017

GENERAL COMMENTS	A very nicely designed study, with children of a similar age, and parents across a wide age range. The diligence taken to ensure reliability of telomere data is appropriate and acknowledged. The authors found that both parents contribute to offspring leukocyte telomere length (TL), particularly younger parents. Overall the paternal effect was stronger than maternal. A novel, sex-specific inheritance pattern was observed.</p> A few suggestions for improvement:</p>

	1) Disadvantage Index/socioeconomic status (SES) and TL are pooled and averaged in Table 1. Although the SD is fairly narrow for SES, more information may be contained within this dataset. Emerging evidence suggests that SES, suboptimal health, and TL are linked in adults, due to changes in environmental health risk factors (e.g. smoking, obesity, inactivity), that become particularly prominent with age. The dataset here could determine whether TLs between children are equal, despite differences in the SES/health risks and TL of their parents. Alternatively, an intergenerational effect may still be observed. Parent age cohorts should be maintained in the analysis.</p> 2) A novel sex-specific inheritance pattern was observed. This should be reported in the Abstract and Discussion, expanding on the potential cause(s).</p> 3) In qPCR methods, state whether T and S reactions were performed in the same or separate plates.</p> 4) Statements were made in the Abstract and Discussion that were not supported with complete statistics in the Results: (1) TL was longer in children than adults, and (2) no difference in TL was observed between the sexes for children and adults. A power analysis should be conducted for (2), given the small number of male participants. </p> 5) The Discussion states that the population under investigation was advantaged, while the Results section reports that they were disadvantaged. Racial background should also be mentioned in the Methods prior to Discussion. Weighted analysis to account for SES and race is mentioned in the Discussion but not shown in the Results.</p> Overall, a well-executed study with proper experimental design, methodology and statistics. An expanded analysis using SES/health risk factors would be highly beneficial, if sample size permits. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Editor/Reviewer Comments	Author's Response	Reference page
Reviewer 1 : Kyle W. Murdock , the Pennsylvania State University, USA		
Major R.1.1. When describing comparisons between telomeres among father-child and mother-child pairs, no statistical comparisons are made. Differences are inferred only from the strength of	There is a large emerging body of literature critiquing the use of p-values as the main tool for interpretation of findings between groups (i.e. 'an effect' vs 'no effect', or 'a difference' vs 'no difference'). The debate regarding whether to limit or even eliminate the p-value has gained serious traction, as outlined in Leek's 2017 Nature paper, 'Five Ways to Fix Statstics'.[1] Given that these findings are largely descriptive, and in accordance with the American Statistical Association,[2] we believe that the reporting of correlations and confidence intervals in	Page 15, line 29

associations. Accordingly, the authors should statistically compare the strength of the associations in order to be able to state that there are indeed differences. Given the overlap in confidence intervals, it is unlikely that there is a statistical difference. It would be inappropriate to suggest there are differences if this is the case. Comment #2 below reflects this as well.	the absence of p-values is appropriate and enables readers to draw their own conclusions. We have further emphasized the need for cautious interpretation with the following text: “Our findings regarding paternal characteristics should be interpreted with caution due to the limited number of fathers.” - (page 15, line 29)	
Minor R.1.2. In the sample characteristics section, it would be useful to describe why telomere data was missing for many of the participants.	Thank you, we have added the following text: “Telomere length was not obtained from 1197 individuals (1 removed due to a lack of consent for the use of venous blood, 728 attended a home visit where blood was not collected, 451 attended an assessment centre but did not produce a venous blood sample, 1 did not have sufficient DNA, and 16 failed qPCR).” - (page 10, line 15)	Page 10, line 15
R.1.3. It doesn’t appear appropriate to suggest that the parent sample was from relatively less disadvantaged areas compared to the national average. The standard deviations easily overlap, so it is unlikely that this is a significant difference.	Our sample size is large and we simply aimed to describe how representative the subsample used for telomere length analysis was relative to the larger population. We have revised the text to now read, ‘The parent sample predominantly comprised women (n=1168, 89%) with a slightly higher (mean (1011) and narrower spread (SD 62) than the national average (mean 1000, SD 100), meaning that families living in disadvantaged areas were under-represented.’ - (page 12, line 3). Note also our comments above (R.1.1).	Page 12, line 3
R.1.4. Were mothers and fathers of children within families allowed to participate? It not completely clear if two parents within one family are	We have clarified this by adding the following text: “Only one parent/guardian was invited to participate in assessments; families were free to choose whether this was the mother or father, and in some cases another relative/guardian attended.” - (page 6, line 37)	Page 6, line 37

included in the analyses.		
R.1.5. The authors indicate that survey weights were utilized and that more detail on the calculation of weights is provided elsewhere. I googled the title of the citation provided and could not identify the information. If the information is not readily available, it should be described in greater detail.	We apologise that this technical information isn't yet available online. We submitted the paper in the knowledge that a summary of this information is provided in a partner submitted cohort profile manuscript, which will appear in the same BMJ Open Special Issue as the current manuscript. We are also in the process of obtained a DOI to reference our technical document on survey weights, which will be live before publication. In the meantime, we have also attached the document for the reviewer's reference.	NA
Reviewer 2: Pam Factor-Litvak, Mailman School of Public Health, Columbia University, New York, USA		
R.2.1. Do the investigators have any data comparing their T/S ratios with other laboratories? I ask because the use of T/S ratios can be somewhat controversial without across laboratory quality control results.	We acknowledge that there is some debate over the consistency of telomere measurements across laboratories. We now note this in the 'Strengths and weaknesses' section of the manuscript: "Unfortunately, we were unable to compare our T/S ratios with other laboratories, but we have compared our T/S ratios with those generated from another cohort within the same laboratory (data not included). The T/S ratios show similar distributions and age-specific effects." - (page 15, line 12) In addition to R.1.5 above, our Standard Operating Procedure (outlining our extensive steps to minimise the effects of potential sources of sample/batch effects) for telomere length measurement will be released ahead of publication of the paper with its own DOI, which we will reference in the manuscript when available (reference 37). We have appended the draft SOP for the reviewer's information.	Page 15, line 12
R.2.2. T/S ratios were higher in girls, compared to boys but not higher in women compared to men. Would the authors please comment on this, as telomere length is usually found to be longer in women than men; could it be that there were too few men in this analysis?	It is true that the effect estimate is the same for women and men. While the smaller father sample size means that their estimate was less precise than for mothers, it is in keeping with the meta-analysis of over 36,000 individuals that similarly found no difference according to sex using this type of qPCR analysis. Differences between males and females were only reliably detected by Southern hybridisation, with the authors concluding that the difference between methodologies 'was not associated with random measurement error'.[3] We have noted this point in the 'Discusssion' section, as follows: "While the smaller father sample size means that their estimate was less precise, it is keeping with a previous meta-analysis that similarly found no difference according to sex using this type of qPCR analysis.[50]	Page 16, line 14

	Differences between males and females were only reliably detected by Southern hybridisation." - (page 16, line 14)	
R.2.3. In reference 41, the authors incorrectly state that telomere length was not different by sex (page 15, lines 5-6 and page 16, lines 11-12); in that study telomere length was longer in girl newborns, compared to boy newborns, and in mothers compared to fathers and both were statistically significant.	Our apologies. We have corrected the following text from: "Interestingly, a another study showed no sex difference in telomere length at birth, (35)" - (page 16, line 19) To the correct sentence (it is now reference 20): "Several population studies have reported longer telomeres in females at different ages. (20 22 50)" - (page 16, line 3)	Page 16, line 19 Page 16, line 3
R.2.4. Also in reference 41, the correlations between telomere length in newborns and mothers was stronger than with fathers.	We have amended the following text to include this reference for the correct sentence (it is now reference 20): "Initial studies were interpreted as telomere length being maternally inherited. (17 19 20)" - (page 5, line 25)	Page 5, line 25
R.2.5. The authors appear to be confused about the correlation between telomere length in fathers and telomere length in newborns compared to paternal age being a strong predictor of telomere length in newborns (page 16, beginning at line 17). They argue that their findings of a lower correlation at higher parental ages may be due to telomere attrition during adult life due to environmental exposures. However, it is likely that the point of life in which telomere	We agree that telomere length attrition is likely greatest during gestation and early development, but note that this developmental stage was not in the scope of the current manuscript. We have reformulated this paragraph to highlight the interesting possibilities arising from the observations made (also see response R.3.2 below) while also the caution implicit in the small father sample size: "We showed that parent-child telomere length concordance was greatest for younger fathers, and diminished with parent age. Our oldest father group had a mean age of 58.6 years (SD 5.65), which is comparable to the ages of other studies but showed smaller father-child concordance. (18 22 24) Njajou et al found a father-child correlation coefficient of 0.46 (CI not reported) in 164 pairs with mean father age of 49.0 years (SD 17.0). (22) It is possible that genetics plays a larger role in parent-child concordance for younger parents because, the older an individual, the more likely their telomere length is influenced by environmental factors. Alternatively, some element of vertical transmission prior to birth may be different for older parents. All of these possibilities must be considered in light of the small father-child sample size but nonetheless warrant further investigation." - (page 16, line 26)	Page 16, line 26

<table>
<tr><td>attrition is the greatest is during gestation when the cells are dividing rapidly. Hence, their argument needs to be reformulated.</td><td></td><td></td></tr>
<tr><td>R.2.6. It would be perhaps a better analytic strategy if the authors predicted child telomere length based on parental telomere length and parental ages at birth, which are easily calculated.</td><td>We did not run this analysis initially because the ages of our children have a very small range (11-12 years), which would essentially be subtracting a constant from the parent ages. Hence, we expected the fitted statistical model to not change. We have now confirmed this by re-running the analysis using parent age at child birth instead of at child age 11-12 years, and saw no substantive difference in findings. We have added the following text in the ‘Statistical Analysis’ section: “Alternatively, we conducted a sensitivity analysis adjusting for parent age at birth instead of at child age 11-12 years, and there were no substantive differences (data not shown).” - (page 9, line 31). For reference, please see below results of the sensitivity analysis (differences highlighted):
<table>
<tr><th></th><th></th><th>Parent age at birth</th><th>Parent age at study</th></tr>
<tr><td>Parent-child</td><td>1143</td><td>0.36 (0.28 to 0.45)</td><td>0.36 (0.28 to 0.45)</td></tr>
<tr><td>Father-child</td><td>143</td><td>0.46 (0.24 to 0.67)</td><td>0.45 (0.24 to 0.67)</td></tr>
<tr><td>Father-son</td><td>78</td><td>0.48 (0.21 to 0.76)</td><td>0.48 (0.21 to 0.76)</td></tr>
<tr><td>Father-daughter</td><td>65</td><td>0.39 (0.01 to 0.77)</td><td>0.38 (0.01 to 0.76)</td></tr>
<tr><td>Mother-child</td><td>1000</td><td>0.34 (0.25 to 0.43)</td><td>0.34 (0.25 to 0.43)</td></tr>
<tr><td>Mother-son</td><td>473</td><td>0.27 (0.14 to 0.39)</td><td>0.27 (0.14 to 0.39)</td></tr>
<tr><td>Mother-daughter</td><td>527</td><td>0.40 (0.27 to 0.53)</td><td>0.40 (0.27 to 0.53)</td></tr>
</table></td><td>Page 9, line 31</td></tr>
<tr><td>R.2.7. Finally, the number of fathers in the study is extremely small, making inferences regarding paternal characteristics tenuous at best.</td><td>We agree and had already noted this in the Limitations section. We hope the amended text in the ‘Strengths and weaknesses’ section in response to R.2.5 above also addresses this: “Our findings regarding paternal characteristics should be interpreted with caution due to the limited number of fathers.” - (page 15, line 29)</td><td>Page 15, line 29</td></tr>
<tr><td colspan="3">Reviewer 3: Pamela Kurjanowicz, University of Toronto, Canada</td></tr>
<tr><td>R.3.1. Disadvantage Index/socioeconomic status (SES) and TL are pooled and averaged in Table 1.</td><td>We agree that SES and suboptimal health have emerging and important links to telomere length, and that (once CheckPoint is linked to the full multiwave LSAC dataset) we will have a dataset that will allow us to look at such links. We plan to examine these</td><td>NA</td></tr>
</table>

	Although the SD is fairly narrow for SES, more information may be contained within this dataset. Emerging evidence suggests that SES, suboptimal health, and TL are linked in adults, due to changes in environmental health risk factors (e.g. smoking, obesity, inactivity), that become particularly prominent with age. The dataset here could determine whether TLs between children are equal, despite differences in the SES/health risks and TL of their parents. Alternatively, an intergenerational effect may still be observed. Parent age cohorts should be maintained in the analysis.	associations in subsequent papers, but they were not within our a priori hypotheses for this paper.	
R.3.2.	A novel sex-specific inheritance pattern was observed. This should be reported in the Abstract and Discussion, expanding on the potential cause(s).	This is certainly novel and interesting, but must be balanced against Reviewer 2's concerns that we might already be over-stating these associations – mainly because of the small (around 200) sample of fathers. Please see our response R.2.5 above, highlighting the interesting possibilities arising from this observation while also the caution implicit in the small father sample size.	NA
R.3.3.	In qPCR methods, state whether T and S reactions were performed in the same or separate plates.	We have added the following text in the Measures section: "Corresponding 'T' and 'S' reactions were performed on the same plate." - (page 7, line 51)	Page 7, line 51
R.3.4.	Statements were made in the Abstract and Discussion that were not supported with complete statistics in the	(1) We have provided further statistics and added the following text in 'Statistical Analysis' section: "Comparisons between group means were conducted using the student's t-test." - (page 9, line 23)	Page 9, line 23 Page 12, line 15 Page 15, line 29

Results: (1) TL was longer in children than adults, and (2) no difference in TL was observed between the sexes for children and adults. A power analysis should be conducted for (2), given the small number of male participants.	And in the 'Results' section: "The mean T/S ratio of children was longer than that of adults (1.09 vs. 0.81 units; p<0.001)" - (page 12, line 15) (2) A post-hoc power analysis will almost always indicate that there is low power (<50%) with respect to a nonsignificant difference, making any claim uninformative that a study is "underpowered" with respect to an observed nonsignificant result. Power has little role in data interpretation - this is nicely discussed by Hoenig and Heisey (2001).[4] We agree that it is useful when planning recruitment for de novo studies, but this is not possible when drawing on data from large existing cohort studies. We think the uncertainty in the adult male findings is implicit in the confidence intervals, but that the estimates are nonetheless of interest and triangulate with those of the children with their larger male sample size. As per R.2.7 above, we have further emphasised our small number of male participants by adding the following text in the 'Strengths and weaknesses' section: "Our findings regarding paternal characteristics should be interpreted with caution due to the limited number of fathers." - (page 15, line 29)	
R.3.5. The Discussion states that the population under investigation was advantaged, while the Results section reports that they were disadvantaged. Racial background should also be mentioned in the Methods prior to Discussion. Weighted analysis to account for SES and race is mentioned in the Discussion but not shown in the Results.	We have amended the following text in the 'discussion to be consistent with the wording in the results section: "…our cohort may under-represent Australian families living in disadvantaged neighbourhoods." - (page 15, line 36) We have added more information regarding indigenous background with the following text in the 'Sample Characteristics' section: "The proportion of families with Indigenous background in our sample was 2.0%, comparable to the estimated 2.8% in the national population (42)" - (page 12, line 11) All descriptive analyses (Tables 1, Figure 2 and 3) are already reported with weights applied. We have amended the statistical analysis section to be clearer as to why we do not report the weighted regression analyses: "Linear regression models were repeated by applying survey weights and taking into account clustering in the sampling frame as sensitivity analyses. As the weighted and unweighted results were virtually identical, we report only the unweighted regression analyses. More detail on the calculation of weights is provided elsewhere. (40)" - (page 9, line 47)	Page 15, line 36 Page 12, line 11 Page 9, line 47

REFERENCES

1. Leek J, McShane BB, Gelman A, et al. Five ways to fix statistics. Nature 2017;551:557-59.

2. McShane BB, Gal D. Statistical Significance and the Dichotomization of Evidence. Journal of the American Statistical Association 2017;112:885-95.

3. Gardner M, Bann D, Wiley L, et al. Gender and telomere length: systematic review and meta-analysis. Exp Gerontol 2014;51:15-27. doi: 10.1016/j.exger.2013.12.004

4. Hoenig JM, Heisey DM. The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis. The American Statistician 2001;55:1-6.

VERSION 2 – REVIEW

REVIEWER	Kyle W. Murdock The Pennsylvania State University
REVIEW RETURNED	09-Jan-2018

GENERAL COMMENTS	I agree with the authors' point about p-values being weak statistically; however, the response does not address the comment. Put simply: it is unethical to state that, for example, "overall correlations between T/S ratios in father-child pairings were stronger than mother-child pairings…" if your data do not fully support the statement. Indeed, the 95% confidence intervals for the strength of effects clearly overlap (e.g., .18 to .48 for father-child and .17 to .28 for mother-child for Pearson correlations), indicating that it is possible that there is no difference in the strength of effects. This is likely due to the lack of power that Reviewer 3 mentioned, but if your data don't support the correlations being different, you can't say that they are. In other words, there is not a statistical difference in the strength of effects, only a slightly different number associated with them (much like the argument the authors made for there not being a significant difference in R.2.2; this argument can't go both ways). You cannot interpret these effects as being different and the authors are misleading the reader when making such statements. The data provided in the present manuscript only furthers ambiguity in the literature and no "new" findings are actually observed in the data.

REVIEWER	Pam Factor-Litvak Mailman School of Public Health Columbia University New York, NY, USA
REVIEW RETURNED	09-Jan-2018

GENERAL COMMENTS	Response to reviewer 2, R2.4: I beg to differ with the authors. Just because the correlation is higher between child TL and maternal TL (than with paternal TL), it does NOT mean that TL is maternally inherited. Indeed, it is likely that TL in newborns and children is a complex trait, related to TL in both parents as well as prenatal and postnatal environmental factors. Response to reviewer 2, R2.5: I really take issue with the statement that genetics play a sole role in child TL. Please couch that statement to include the effects of in utero and postnatal environmental factors.

REVIEWER	Pamela Kurjanowicz Faculty of Medicine, University of Toronto, Canada
REVIEW RETURNED	08-Jan-2018

GENERAL COMMENTS	The authors' revisions have addressed the concerns described previously.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 : Kyle W. Murdock	Author's Response (for all page and line refs please refer to the clean manuscript)	Ref. page
"…Indeed, the 95% confidence intervals for the strength of effects clearly overlap (e.g., .18 to .48 for father-child and .17 to .28 for mother-child for Pearson correlations), indicating that it is possible that there is no difference in the strength of effects…"	We have discussed this and agree with the reviewer that our data are not sufficiently compelling to support the statements in the manuscript. We have now amended the text as follows: Abstract: "Father-child concordance was 0.34 (95% CI 0.18 to 0.48), while mother-child was 0.22 (95% CI 0.17 to 0.28)." – (page 3, line 38) Results: "Sex-specific pairings: Pearson correlations between T/S ratios were 0.34 (95% CI 0.18 to 0.48) for father-child pairs, and 0.22 (95% CI 0.17 to 0.28) for mother-child pairs. Relationships were similar in adjusted regression models. In both father-child and mother-child pairs, T/S ratio correlations were similar for sons and daughters." – (page 14, line 30) Discussion: "Parent-child telomere length concordance appears substantial for both father-child and mother-child pairs. The degree of concordance may be higher with younger parents." – (page 14, line 51)	Page 3, line 38 Page 14, line 30 Page 14, line 51
Reviewer 2: Pam Factor-Litvak	Author's Response	
"…Just because the correlation is higher between child TL and maternal TL (than with paternal TL), it does NOT mean that TL is maternally inherited. Indeed, it is likely that TL in newborns and children is a complex trait, related to TL in both parents as well as prenatal and postnatal environmental factors."	In addition to the issue of maternal vs paternal correlations with children (addressed above), we have also addressed the issue of heritability by amending the text as follows: Introduction: "Several studies have found stronger maternal correlations with child telomere length, (13-15) while others have reported stronger paternal influences. (16-19)" – (page 5, line 25) Discussion: "Due to our small number of fathers and overlapping confidence intervals, we cannot tell whether the larger father-child than mother-child concordance (0.34 vs 0.22) is a chance or real difference. Either way, it is clear from this and other studies (including from twins) that children's telomere length is partly heritable as a complex trait with significant contributions from genetics, prenatal and postnatal environmental factors. (12 41-43) In the case of mothers, this likely includes shared maternal factors in pregnancy that influences both maternal and offspring telomere length. Indeed, there are several maternal characteristics that have been shown to associate with fetal telomere length, including chemical	Page 5, line 25 Page 15, line 33

	exposure, stress during pregnancy and maternal diet. (43)" – (page 15, line 33)	
"I really take issue with the statement that genetics play a sole role in child TL. Please couch that statement to include the effects of in utero and postnatal environmental factors."	We completely agree with this and did not mean to overstate the likely role of genetics in the manuscript. In addition to changes above, we have also modified the text as follows: Discussion: "Complex interactions between prenatal and postnatal environment are likely to influence parent-child telomere length correlations in addition to well described genetic variants. (41) Given the general stability of the genome across the lifecourse, any parental age effect may be due to environmental influence over time, potentially manifesting in altered telomere length in the gametes (and progeny) as has previously been suggested. (45-47) Indeed, more than one study has linked elongated telomeres in progeny with advanced paternal age, (21 48) an effect not noted in our study." – (page 16, line 23)	Page 16, line 23

VERSION 3 - REVIEW

REVIEWER	Pam Factor-Litvak Mailman School of Public Health Columbia University New York, New York 10032 USA
REVIEW RETURNED	27-Mar-2018

GENERAL COMMENTS	The authors have fully responded to all previous concerns.