Author's response to reviews

Title: Sex-differences in physical activity. Results from a quantitative genetic analysis.

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Author's response to reviews: see over
Sex-differences in physical activity. Results from a quantitative genetic analysis

Reviewer's report:

In this manuscript titled “Sex-differences in physical activity. Results from a quantitative genetic analysis” Diego et al. have presented a model to estimate both sex-specific genotype by sex interaction effects and sex-specific heritabilities in physical activity (PA) levels and sedentary behavior (SB) using data from three generation families. This is definitely original research and the research question posed by the authors is well defined and very timely. This is also an important area of study in the field of complex disease and behavioral genetics. The manuscript is organized logically following the standard format. All the statistical methods employed are appropriate and specific statistical genetic models used are well described.

The results of this study are interesting; particularly findings such as evidence of significant GSI effects for vigorous PA (VPA) and time spent watching television (WT) through significant heterogeneity in the additive genetic variance across the sexes. In other words, the additive genetic variance was higher in males than in females for VPA and WT, while evidence of significant heterogeneity in the residual environmental variance was found only for VPA but not WT. In addition, heterogeneity in the residual environmental variance turned out to be significant for moderate, vigorous, and total PA. These findings will contribute to a better understanding of the nature and type of sex-specific interactions between genetic and environmental factors particularly physical activity and sedentary behavior.

Minor compulsory revisions

1. Reviewer: Although the title conveys what has been done to some extent, it is very generic. The title may slightly be modified to reflect the novelty of the study something along the lines of Sex-specific genetic effects in physical activity. Abstract conveys exactly what has been found in this study.
   Answer: Corrected.

2. Reviewer: In the methods section: Given that age range varied from 7 to 85, age-specific effects are expected and particularly, 7 year olds activity patterns are usually different from 85 year olds. So how are such age effects modeled in this study?
   Answer: Age, age^2, age-by-sex, and age^2-by-sex were modeled as covariates; i.e. as fixed effects. Ideally, we should in theory incorporate a random effect for genotype-by-age interaction (GAI). Such a model would jointly model GAI and genotype-by-sex interaction (GSI) effects. However, based on our power analysis (discussed below), it
would not be prudent at this point to perform such an analysis because our study has low power to identify GSI effects by "itself" let alone jointly with GAI effects.

**3. Reviewer:** Furthermore, since the data were obtained from direct interviews for under 15 years of age individuals while most of the responses are self-reported, will there be any problem in modeling such effects?

**Answer:** To address this question, we studied the sex-specific sample variances for all traits for individuals under 15 years of age and for individuals from individuals 15 up to and including 19 years of age. If there was an impact on trait variation due to the difference in the method by which the responses were obtained (interview vs. self-reported), then the crucial question for us is if the patterns of sex-specific variation in one group relative to the other are different. For this reason, we performed the abovementioned comparisons. We found that within each group there were no significant differences (by F-tests) between the sex-specific sample variances. Regarding the latter group, we chose the stated range because we wanted to minimize the potentially confounding effect of age so that we could "maximize" the comparison in question; i.e. interview vs. self-reported responses. We believe that this demonstrates that the method by which the responses were obtained did not significantly impact the covariance patterns for the traits analyzed.

**4. Reviewer:** The sample consists of individuals varying in age from 7 years to 80 years. Does this composition affect the G x E model either positively or negatively?

**Answer:** Again, we believe that a better analysis would be to incorporate GAI effects in the model. Alternatively, we could stratify our sample into age groups (according to some grouping interval) but this would adversely affect our power (see below) to detect any effects. We feel that our results are very preliminary in this respect but that they serve as a compelling motivation to more adequately examine these phenomena after increasing our sample size.

**5. Reviewer:** The family study design was appropriate though the sample size was barely adequate. Does it have adequate power to capture the sex-specific genetic effects? It would be very helpful to show if the study has adequate power to assess the sex-specific interaction effects.

**Answer:** We performed a post-hoc power analysis with respect to rejecting both null hypotheses for the GSI model. The power analysis results reveal that we had low power overall to detect GSI effects in our sample (see attached table). We found that we had sufficient power to detect heterogeneity in the additive genetic variance across the sexes for vigorous physical activity (VPA) only. We also found that we had sufficient power to detect departures from complete positive across-sex genetic correlations for only one trait, namely watching TV (WT). We clearly need to increase
our power by recruiting more families. Also, it would seem that we may need more sensitive PA and SB measures since the sensitivity of a measure affects effect size which in turn affects power.

6. **Reviewer:** In the results section, third paragraph, first line, p-values are switched between VPA (\(=0.02\)) and WT (\(p<0.001\)). This needs to be corrected to indicate correct p-values: VPA (\(p=0.001\)), and WT (\(p=0.02\)).

   **Answer:** Corrected

7. **Reviewer:** The writing style was acceptable, but a few typos are detected. For example, in Background section, 1st paragraph, 2nd sentence from the bottom of the paragraph daily Physical activity values was misspelled as diary, needs to be corrected.

   **Answer:** Corrected

8. **Reviewer:** The sentence in the last paragraph of the introduction paragraph “Thus, with respect to the objective of elucidating sex-specific genetic effects, the sex-specific heritability indeterminate”. Need to be rephrased.

   **Answer:** Corrected.

9. **Reviewer:** The last but one sentence of the last paragraph of the discussion section the present results support the advance to association studies on DNA sequence variation is not clear. This sentence may be rephrased.

   **Answer:** Corrected.

10. **Reviewer:** The word on page 10, parameterized is misspelled.

    **Answer:** Corrected.

11. **Reviewer:** Tables and Graphs are fine except a few minor corrections as mentioned below. However small corrections are needed:

    a) **Reviewer:** in Table 3 title includes and sex-specific heritabilities? When the table only shows GSI effects. So it may be deleted from the title.

    **Answer:** Corrected.

    b) **Reviewer:** In the title of the table 5, is it different expressions or different types?

    **Answer:** Corrected.

**Discretionary revisions**
11. **Reviewer:** Results section is rather small and the presentation of results shown in tables and graphs was also brief. On the other hand, discussion and conclusion section is long and extensive. So in this case, these two sections can also be combined into one section as Results and discussion, if the authors wish to do so.

**Answer:** We think that is a good idea to follow. However, we’ve now included written material in the methods, results, and discussion sections on the power analysis that we just performed.

12. **Reviewer:** In the discussion section, results are well discussed in an unbiased manner and the interpretation of results is adequate in the context of published literature. Particularly, limitations are highlighted and discussed in the light of relevant work and references are provided appropriately. It would be helpful, if it can be slightly shortened.

**Answer:** We shortened the section slightly.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:** I declare that I have no competing interests.

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Statistical power analysis for the trait-specific parameters

<table>
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<th>Trait</th>
<th>Power or probability of rejecting a false null hypothesis for the following null hypotheses for genotype × sex interaction</th>
<th>Power or probability of rejecting a false null hypothesis for the following null hypotheses for genotype × sex interaction</th>
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</thead>
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<tr>
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<td>( \sigma_{gf}^2 = \sigma_{gm}^2 = \sigma_{g}^2 )</td>
<td>( \rho_{g(f,m)} = 1 )</td>
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<td>VPA</td>
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<tr>
<td>MPA</td>
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