Author’s response to reviews

Title: Urbanicity, hypothalamic-pituitary-adrenal axis functioning, and behavioral and emotional problems in children: A path analysis

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Reviewer reports:

Shannin Moody, M.S. (Reviewer 1): Methods:

1. It was difficult to ascertain what exactly they were excluding from the analysis when choosing to drop the neighborhood variable from the analysis. Was it the neighborhoods computed from the principle component analysis? How many neighborhoods were there in total? The following sentence makes it a bit more confusing.

"We included children in the analyses if they lived in the same neighborhood between T1 and T2 in order to minimize within-subject variance in neighborhood-level variables (27 of the 513 moved neighborhoods and were excluded)."

The highlighted material should be clarified.

Response: These sections refer to different levels of the model. The first part pertains to an examination of whether it was necessary to use multilevel modeling, as individuals in the study were nested in neighborhoods. We tested whether it was necessary to use multilevel modeling by calculating intraclass correlations. As these estimates were very low, in light of parsimony, we did not include neighborhood as a level in the analysis, and estimated single-level models for the main analysis. This is clarified in the revised manuscript in the Analysis sections, pg 7, lines 27-28 and pg 8, line 7 and pg 12, lines 4-5.
The second part refers to individuals who were excluded from the analysis when they had moved to a different neighborhood between the first data collection wave (T1) and the second (T2). We did this in order to increase the robustness of the neighborhood measures, as we could then be sure that they had lived in that neighborhood for at least one year. This is clarified in the Available data section, pg 7, lines 19-21.

Controls:

2. A supplemental chart that shows the variability in urban versus rural areas would be helpful in gauging whether there was sufficient variability in their sample size. Especially considering that there were no significant differences found in urbanicity for the population.

Response: Thank you for this suggestion. We included a histogram of the distribution of the urbanicity measure in both samples in the supplements (see Additional file 3), which is referred to in the main text on pg 12, lines 23-24.

Conclusions:

3. The author's conclusions and critiques of their work are very well pointed. I would have liked to have known whether the 10% of the lower SES participants showed any differences between the rest of the populations. The contribution of the paper seems almost as if it should read Urbanicity HPA axis functioning not associated with behavioral emotional problems in high SES families.

Response: Indeed, this is an interesting question whether the effects would be different in the participants with low SES. We tested this in the JOiN sample (there were no participants with a low family SES background in the BIBO sample) and the results were not different. However, the sample of those from a low SES background was very small (n = 32 for HPA axis reactivity and n = 30 for basal HPA) and therefore there was insufficient power to test this reliably. In the revised manuscript, we mention this additional analysis in a footnote on pg 13. In order to emphasize that the majority of children in our samples were from average and high SES families, we have noted this in the abstract (pg 2, lines 18-19).
Statistics:

4. A supplemental chart that depicts the variability in urban verses rural areas would be helpful in gauging whether there was sufficient variability in their sample size. The mean was not helpful with ascertaining the variance.

Response: Please see our response to comment 2.

Fabian Streit (Reviewer 2): The authors present a very interesting and well designed study, investigating the link between urban upbringing and children's mental well-being, and whether this is mediated by HPA axis functioning.

Authors have pre-registered the article in OSF, which is good scientific practice.

Introduction:

5. There is evidence that selective migration (partially genetically driven) and socioeconomic factors contribute to the association of urbanicity and mental health. While this is only explaining a share of the variance, I think the first sentences of the introduction are misleading in this regard. Please refine this section.

Response: Thank you for pointing out the interesting work on selective migration. The first paragraph has been revised to reflect the current work in this field (pg 3, lines 2-8).

6. The open science framework link for citation 25 is not publicly available. However it seems the work is already described in citation 24? Please clarify. I also think it would be better if all research question from the registration would be reflected as such in the article. In my view, preregistered RQ 1, 2, 3, 5, and 6 of the pre-registration are part of the current manuscript. Please elaborate why heart rate measures are not included in the present manuscript.
Response: We apologize for the confusion, which stems from a mistake in the previous reference 24 (osf.io/v7eyx should have been osf.io/dvk2z). The OSF link in reference 24 in the original manuscript refers to another study within the Urbanicity and stress project. The Urbanicity and stress project (osf.io/45j88) has three studies/components: Urbanicity, stress reactivity, behavioral and emotional problems in children (osf.io/dvk2z), Urbanicity, basal stress system functioning, and behavioral and emotional problems in children (osf.io/ug8de), and Urbanicity, stress reactivity, behavioral and emotional problems in adolescents (osf.io/wjsw2). The results from the first two studies (osf.io/45j88 and osf.io/dvk2z) are reported in the current manuscript. The third study (osf.io/wjsw2) tests the same overall hypothesis (including heart rate reactivity as a mediator) in a sample of adolescents, the report of which is currently in revision at PLoS ONE. Heart rate reactivity was not proposed as a mediator in the current manuscript because it was not included in the BIBO study. These three studies are now linked in OSF via the Urbanicity and stress project and all links are now public. Thanks for noticing this.

Methods

7. In the JOiN sample, the stress test was carried out either on midday or the afternoon. This should be tested as a covariate in the respective models.

Response: We examined whether it was necessary to control for time of the stress test in the JOiN sample by calculating a bivariate correlation with the AUCi measure (as described on pg 7, lines 9-17 and pg 8, lines 8-11). Since the correlation was not statistically significant, we did not control for it in the models. The covariates that were included in the models is clarified in the revised manuscript (please see our response to comment 12).

8. I think the AUCg measures is problematic in regard to this point.

The calculation of the AUCs need to be explained in more detail, especially as missings were allowed in their calculation. This might result in different time frames. In general, using AUC with varying distances between measures creates a confounding with test duration/sample timing that should be addressed.

Response: The AUC measures were adjusted for time between each sample, as described by (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). In the case of a missing sample, the calculation was adjusted accordingly. We note this in the revised manuscript on pg 6, lines 14-15.
9. The distribution of the cortisol measures should be depicted in histograms, so that the reader can judge their distribution, as skewed distributions are common.

Response: We have included histograms of all the cortisol measures used in the analysis in the supplements of the revised manuscript (see Additional files 5 and 6, which are referred to in the main text in the results section on pg 12, lines 25-26).

10. Please specify "normal day" for basal cortisol collection. Were week Vs. weekend days controlled for?

Response: Participants were instructed to collect the basal cortisol samples on a 'normal school day'. We did not have information on which day of the week the samples were actually taken to examine adherence to the instructions, unfortunately. In the revised manuscript, we now specify 'normal school day' (see pg 6, line 17 and 19).

11. Please explain why for the decline BC1 and not BC2 was used for Join.

Response: We used BC1 for the calculation of decline in the JOiN sample so that it would be calculated in the same manner as in the BIBO sample, to facilitate comparison of the results. BC1 was taken at awakening in both the JOiN sample (pg 6, line 18) and in the BIBO sample (pg 10, line 28).

12. The variables correlating with HPA measures should be clearly depicted in the main manuscript

Response: In the revised manuscript, we moved the correlation table to the main text (now Table 2, see pg 15). Furthermore, we included a description of the covariates included in the models in the results section (pg 13, lines 8-10 and 17-19). We also added a correlation table of all potential covariates that might be related to the cortisol measures (described on pg 7, lines 9-17 and pg 8, lines 8-11), see Additional file 7, referred to in the main text on pg 13, lines 10 and 19).

Results

13. The number of missing values, and the number of subjects with complete measures for stress test and basal assessment should be clearly described.
Response: Missing data and final sample sizes are described in the Available data sections (JOiN: pg 7, lines 18-25; BIBO: pg 11, lines 22-27). We have made some revisions to this section in the JOiN sample in order to clarify it further (please see our response to comment 1).

14.  It seems that the design of the authors was not the most powerful to test the more basic hypothesis, e.g. urbanicity/HPA axis measures are associated with emotional or behavioural problems (RQ1-4 in OSF). I suggest the run a meta analytic approach over both samples. This would strengthen the interpretation of the null finding, if still non significant.

Response: Thank you for this suggestion. We ran meta-analyses on the direct and indirect effects hypothesized in our study. The null findings were confirmed, with the exception of a significant effect of urbanicity on the AUCg measure of basal HPA axis functioning. We describe this addition at the end of the method section on pg 12, lines 13-18, in the results section (pg 13, lines 20-26) and in Table 3, Additional files 9 and 10, and in the discussion section (pg 17 lines 26-27, pg 18, lines 1 and 15-17).

Discussion

15.  The interpretation that the exposure might have bit been sufficiently long to affect HPA axis functioning should be discussed in regard to the literature describing dose response effects of urban upbringing on mental health (e.g. Pedersen 2001).

Response: Thank you for this suggestion. We now discuss this study in the discussion (pg 18, lines 9-10).

16.  Interpretation of power. Please consider more powerful analysis approaches.

Response: We have included a description of the meta-analysis that was added to the manuscript in the discussion. Please see our response to comment 13.

17.  Please describe the power analysis in the manuscript/supplements.

Response: We added a description of the power analysis to the supplementary information (see Additional file 11) which is referred to in the main manuscript on pg 18, lines 13-14.