Review of: "The Relationship Between Fibromyalgia and Neurodivergent Traits Is Partially Mediated by Hypermobility: A Self-Selected Population Based Survey"

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Potential competing interests: No potential competing interests to declare.

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Disclosure: I'm a psychiatrist, epidemiologist, and population genomics researcher, by training. I have a BA degree in psychology and some experience in human subjects and survey-based research. I feel most qualified to evaluate the study design and statistical analyses. I have some prior experience in studies of autism from these limited perspectives. My medical and psychiatric training provides some background in understanding hypermobility/EDS, dysautonomia, and fibromyalgia.

General comments:

The paper is succinct and clearly written. I think the topic is important, interesting, and timely. The treatment of certain variables (e.g., dichotomizing continuous variables, then analyzing them again later as continuous variables) is sub-optimal and makes parts of the results somewhat redundant. Overall, it makes a valuable contribution to a growing body of literature.

Introduction:

Informative and mostly appropriate. I was not aware of the substantial comorbidity among the targeted traits / conditions. The authors state that they consider the terms “hypermobility” and “hypermobile EDS” to be interchangeable, but I don't think this is appropriate. As they state later in their introduction, hypermobility is trait (which occurs along some distribution of joint flexibility within the population), and is not necessarily associated with an underlying syndrome or disease in all persons. Hypermobile EDS refers to a subtype of EDS (which are thought to be connective tissue disorders, some with causal genetic explanations). Hypermobile EDS and other hypermobility-spectrum disorders are associated with other signs and symptoms, beyond hypermobility, which is why they meet criteria as distinct medical syndromes. The diagnostic criteria for hypermobile EDS also include skin, dental, cardiac, and muskuloskeletal findings (https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjtwdymr6z8AhVgF1kFHfHPD-IQFnoECCgQAQ&url=https%3A%2F%2Fwww.ehlers-danlos.com%2Fwp-content%2Fuploads%2F2019%2F09%2FhEDS-Dx-Criteria-checklist-1-Fillable-form.pdf&usg=AOvVaw30st1EbwXLcf3DWb9iOsZI). The authors also have no way of

ruling out the conditions that would exclude a diagnosis of hEDS. So, the authors should not equate hypermobility with hypermobile EDS, as this is misleading. They should make sure to be specific about whether a particular reference is ascertaining hypermobility or hypermobile EDS. They should revise the methods, results, and discussion of their findings to properly refer to the thing they measured as “hypermobility” and not “hEDS.”

Methods:

-The authors correctly describe how the WPI and SSS are applied to the diagnosis of fibromyalgia, but they omit the other criteria: (2) Symptomatology has been present at a similar level for at least 3 months. (3) The patient does not demonstrate any other disorder that would otherwise explain the pain. So the authors should mention these additional criteria and indicate whether they were assessed in the research participants.

-I'm confused about the decision to use the SSS as continuous data, but to use the WPI as categorical dichotomized data. I thought both items were used together and the cumulative score would be thresholded to support the presence of “FM” like clinical symptoms.

-Decision to dichotomize BS scale seems appropriate, given it's clinical cut-point.

-This paragraph is problematic: “The percentage of participants who fulfilled criteria for the diagnosis of each of ASD, FM and hypermobility was calculated for the overall group and for age and gender bands, with Chi-square analyses to assess the relationships between each condition and both variables. Directional Pearson correlations were conducted to assess the strength of the relationships between each disorder.” Specifically, the participants did not fulfill criteria for ASD or for FM. But they measured above a cutpoint on a clinical or research scale. The text should be revised to avoid the word “diagnosis”.

-If the goal of the study was to characterize a younger sample, I'm confused by they allowed the age range as high as 60 years old.

-Given the self-reported and self-selected nature of this observational study, the authors should publish an example of the advertisement used for the study. Similarly, the authors should provide a text transcript of the “purpose of the study” and the description of “real world implications” provided to study participants. It seems like some obfuscation of the true purpose of the study could have been helpful to mask true aims of the study and avoid “demand characteristics” or “desirability bias” for participants

- It wasn't until I arrived at the results section, that I realized the SSS is being used as an index of “dysautonomia”. This should be stated more clearly in the methods section. I don't have expertise to comment on whether this is appropriate. Now I understand why you examined it as continuous variable.

-The authors use many statistical tests, but they provide no correction for multiple testing.

- The authors alternate inconsistently between full spellings and abbreviations for FM

Results:

- Authors should report what proportion of patients were university students vs. community recruitment.

- The authors should report the s.d. in addition to mean and range for ages.

-Table 1. The abbreviation JH appears for the first time, but is not introduced anywhere in the main text or table footnote. Again, diagnostic labels of ASD and FM are not appropriate. Instead, indicate the cutpoints of your scales.

-The prevalence estimates for these conditions are much higher than one would expect. Strongly suspect there is self-selection bias here, which could contribute to inflated correlations, especially given that the subjects

-This method seems inappropriate: "Two-tailed Chi-square analysis showed a significant positive relationship between age and fibromyalgia (16.642, p = 0.002). However, no significant relationship between age and autistic traits was evident (13.390, p = 0.063)." Chi-squares are for testing associations between categorical variables. I did not see any mention of converting age into a categorical variable, and I don't recommend this. Age is a continuous variable. The appropriate test for gender (multiple groups) on age is a one-way ANOVA. The same is true for testing your ASD-score groups (two groups) age.

- This method is sub-optimal: "Chi-square analysis also showed a significant relationship between female gender and fibromyalgia (20.462, p = 0.005). Relationships between female gender and hypermobility (17.752, p = 0.013) and female gender and autistic traits (19.797, p = 0.006) also proved to be significant. Although females had higher rates than males for each scale, non-binary people had higher rates of both fibromyalgia and autistic traits. However, the highest rates for all three variables were seen among trans-males and trans-females, with the details of each group shown in Table 1." It would have been more appropriate to use one-way ANOVA, to test for between gender-group differences in the FM-related score and the ASD-related score. It would also be more interpretable, because you can use post-hoc t-tests to see which group differences are driving the main effect of the ANOVA.

-The findings described under the following headings would benefit from being put into a Table 2. "Subgroup differences for fibromyalgia scores by gender." "Subgroup differences for those with fibromyalgia and autistic traits by gender and age." "Subgroup differences for Beighton scores by gender."

-"Individuals that met the Beighton criteria (>5) for hypermobility scored on average higher above the threshold (>65) on the RAADS-R for autistic traits (mean 91.6, SD: 36.3), compared to those that did not meet the Beighton criteria for hypermobility (mean 77.6, SD: 30.8) P=0.02 as shown in Figure 1." - Authors should clarify whether this is a 2-tailed t-test and should report the t-value before the p-value.

-The following section (and Figure 2) are missing any statistical test values, so it's no clear how authors are support statments of group differences: “Individuals that met the Beighton criteria for hypermobility scored on average higher on the combined fibromyalgia score (mean 13.4, SD: 7.3) when compared to those that did not meet the Beighton criteria for hypermobility (mean 10.0, SD: 6.0). For the WPI assessing pain, higher average scores were found in those that met the Beighton criteria (mean 6.6, SD: 5.1) than those that did not (mean 4.6, SD: 4.1). For the SSS assessing dysautonomia, higher average scores were seen in individuals that met the Beighton criteria (mean 6.8, SD: 2.8) compared to those that did not (mean 5.5, SD: 2.5). These comparisons are presented in Figure 2.”

-"Equivalent correlations between the Beighton score and the combined FM score, WPI and SSS were 0.224, 0.250 and 0.237 respectively, all again significant with a p value of >0.01. “ and ” Equivalent correlations between the Beighton score and the combined FM score, WPI and SSS were 0.201, 0.184 and 0.177 respectively, all again significant with p values of >0.01. " Unclear if this is a typo, but perhaps should be corrected to read $p < 0.01$.

-Figure 3 appears to depict a mediation analysis based on Sobel test, but the results of the multiple regression were not clearly described in the main text. They need to report how the coefficient/p-value of the ASD ~ FM-score regression changes when the mediator (Beighton score) is entered into the regression. This could be incorporated into Figure 3 or into a table. The in-text reference to figure 3 appears in the paragraph above, but none of the coeifficients in that paragraph match those shown in Figure 3. The variable names in Figure 3 don't match the names of variables used in main-text description of regression. The authors should stick to the same nomenclature throughout the whole paper to avoid confusion (RAADS-R, BS, SSS, WPI, total FM score). The same considerations apply to Figure 4. I am unable to verify the Sobel test results using the website they reference, because the authors do not provide all betas, associated standard error, and p-values

Discussion:

- The authors make an excellent point, that this is a study that has focused on a high risk and underdiagnosed populations. They make several very nice acknowledgments of clinical considerations relevant to caring for these populations.

- They appropriately acknowledge the probability of self-selection bias. They should also acknowledge this bias in sampling (and plausibly participant motivation or expectation) can inflate the observed positive correlations, as compared to a random sampling, or a study described as “studying general relationships between psychological and medical traits.”

-The authors should acknowledge the limitation that hypermobility was self-reported, as opposed to clinically assessed with a physical examination.

-Authors should temper their language around “meeting criteria for” conditions or diagnoses, as they did not apply / verify all relevant inclusion and exclusion criteria for diagnoses of autism or FM.