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Ascertainment and Gender in Autism Spectrum Disorders

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To the editor

We read with great interest the article from the March issue of the Journal titled "Behavioral and Cognitive Characteristics of Females and Males with Autism in the Simons Simplex Collection" by Frazier et al.[1] The investigators analyzed gender differences in standardized measurements in patients with autism spectrum disorder (ASD) from the large Simons Simplex Collection (SSC) dataset, using an approach to take into account potential sampling and measurement biases. They examined all patients with ASD and used regression analyses to examine effects of IQ, age, and other characteristics. The main findings of the article were that female patients with ASD had greater impairments in social communication and adaptive functioning, heightened irritability and externalizing problems, but had lower levels of restricted interests. These differences were small but statistically significant and were largely mediated by lower cognitive ability seen in female patients, with the exception of restricted interests and irritability.

We also conducted an analysis of gender differences in standardized measurements in patients from the Autism Consortium (AC), Autism Genetics Resource Exchange (AGRE), and Autism Speaks Autism Treatment Network (ATN) datasets, in addition to the SSC. We selected patients older than 5 years with an Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule (ADOS) diagnosis of autism or ASD. We found differences in results pertaining to gender-specific presentations in autism depending on ascertainment protocols. Our conclusions, therefore, are that gender differences in autism presentation are highly dependent on ascertainment or the context in which patients present. The SSC is designed for simplex pedigrees specifically[2] and therefore may not be generalizable to the ASD population as a whole. Our approach differed from that of Frazier et al. in that we further separated patients into groups based on verbal ability and the ADOS module administered. This created subgroups of comparable age and IQ across datasets.

Overall, we found it difficult to draw generalizable conclusions because results were often inconsistent between datasets and differed based on subgroup. Results in the SSC in particular were often different from those in the other datasets. For example, the SSC had a higher male-to-female ratio than the other datasets. This was most striking in those who were fluently verbal, among whom the male-to-female ratio in SSC was 7.6 versus 4.4, 5.9, and 6.2 seen in the AGRE, AC, and ATN, respectively. Furthermore, results differed depending on which subgroup was analyzed. In nonverbal patients (administered module 1 of the ADOS), we found no statistically significant gender differences in any dataset. In those with phrase speech (ADOS module 2), our results in the SSC and the ATN datasets were consistent with those of Frazier et al., with female patients having lower IQ and lower Vineland Adaptive Behavioral Scale scores. We also found more impairing externalizing symptoms in female patients on the Child Behavior Checklist in this subgroup, but only in SSC participants.

The overall profile for those who had fluent speech (ADOS module 3 or 4) was slightly different in the SSC than in the other datasets. Consistent with Frazier et al., in the SSC we noted slightly lower IQ scores and Vineland Adaptive Behavioral Scale daily living scores in female patients but no differences between genders in Social Responsiveness Scale, Child Behavior Checklist, or ADOS severity scores. However, in the AC, AGRE, and ATN datasets, there were no significant differences between genders or slightly better scores on Vineland Adaptive Behavioral Scale standard scores, Social Responsiveness Scale raw total scores, and ADOS severity scores, in contrast to the SSC. This is similar to other studies and suggests that female patients with ASD who have higher IQs might in fact have similar or better social communication abilities than male patients with ASD.[3,4]

In summary, we applaud Frazier et al. for their careful study and agree that this is a step forward in understanding the nature of gender differences in ASD. In addition, we believe the results of the study raise important questions for the field. In analyzing multiple datasets, we found it difficult to make broad generalizations about the female phenotype in ASD, possibly owing to different ascertainment approaches used in creating the datasets. The SSC dataset was designed for simplex pedigrees specifically, the AGRE dataset emphasized recruitment of multiplex families, the AC dataset is geographically limited to Boston-area families, and the ATN dataset recruited individuals from multiple clinical sites across the country. Future work with large existing datasets should take into account ascertainment protocols when conclusions are drawn and before generalizing results to the full population and spectrum of people with ASD.

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References

1. Frazier TW, Georgiades S, Bishop SL, Hardan AY. Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. J Am Acad Child Adolesc Psychiatry. 2014; 53:329–340. [PubMed: 24565360]
2. Fischbach GD, Lord C. The Simons Simplex Collection: a resource for identification of autism genetic risk factors. Neuron. 2010; 68:192–195. [PubMed: 20955926]
3. Lai MC, Lombardo MV, Pasco G, et al. A behavioral comparison of male and female adults with high functioning autism spectrum conditions. PLoS One. 2011; 6:e20835. [PubMed: 21695147]
4. Mandy W, Chilvers R, Chowdhury U, Salter G, Seigal A, Skuse D. Sex differences in autism spectrum disorder: evidence from a large sample of children and adolescents. J Autism Dev Disord. 2012; 42:1304–1313. [PubMed: 21947663]