

Psychiatry Research

CAUTION NEEDED IN ASCRIBING SUBTHRESHOLD SYMPTOMS AS AUTISM SPECTRUM DISORDER: COMMENTARY ON “AUTISTIC TRAITS DISTRIBUTION IN DIFFERENT PSYCHIATRIC CONDITIONS: A CLUSTER ANALYSIS ON THE BASIS OF THE ADULT AUTISM SUBTHRESHOLD SPECTRUM (AdAS SPECTRUM) QUESTIONNAIRE”

--Manuscript Draft--

Manuscript Number:	PSY-D-23-02660R1
Article Type:	Correspondence
Corresponding Author:	Marco O. Bertelli CREA (Research and Clinical Centre), Fondazione San Sebastiano, Misericordia di Firenze Florence, ITALY
First Author:	Marco O. Bertelli
Order of Authors:	Marco O. Bertelli Veronica Boniotti Annamaria Bianco Giulia Vannucchi Elisabetta Filomena Buonaguro Martina Micai Laura Fatta Michele Rossi Edoardo Pecchini Valeria Bizzari Michele Conte Gianpaolo Lombardi Serafino Corti Katrina Scior Muhammad Waqar Azeem Angela Hassiotis Amaria Baghdadli Maria Luisa Scattoni Luis Salvador-Carulla Afzal Javed Kerim Munir
Abstract:	No abstract required.
Suggested Reviewers:	Luciana Forte luciana.forte@unifi.it Rory Sheehan rory.sheehan@kcl.ac.uk Martina Billeci martina.billeci@aslnapoli2nord.it

	<p>Gregorio Katz katz.guss@gmail.com Expert in the field</p>
	<p>Giovanni Stanghellini giostan@libero.it</p>
<p>Response to Reviewers:</p>	<p>The title has been changed, including an explicit reference to the manuscript addressed in the letter. The letter was fully revised by a native English speaking colleague, who helped me with the language--making it more concise. I began the correspondence with "Dear Editor". In the first paragraph I referenced the paper I'm commenting on. Adjunctively, I inform you that I included a new author and inverted the position of the last two authors.</p>

Response to Reviewers

The title has been changed, including an explicit reference to the manuscript addressed in the letter.

The letter was fully revised by a native English-speaking colleague, who helped me with the language--making it more concise.

I began the correspondence with "Dear Editor". In the first paragraph I referenced the paper I'm commenting on.

Adjunctively, I inform you that I included a new author and inverted the position of the last two authors.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CAUTION NEEDED IN ASCRIBING SUBTHRESHOLD SYMPTOMS AS AUTISM SPECTRUM DISORDER:
COMMENTARY ON “AUTISTIC TRAITS DISTRIBUTION IN DIFFERENT PSYCHIATRIC CONDITIONS: A CLUSTER
ANALYSIS ON THE BASIS OF THE ADULT AUTISM SUBTHRESHOLD SPECTRUM (AdAS SPECTRUM)
QUESTIONNAIRE”

Dear Editor,

The article by Dell’Osso and colleagues (Dell’Osso et al., 2023) examines the co-occurrence of psychiatric disorders among adults with autistic traits (ATs) or those with subthreshold autism spectrum disorder without intellectual and communication impairments using the Adult Autism Subthreshold Spectrum (AdAS) questionnaire. We would like to highlight several important limitations of this line of research on psychiatric comorbidity in autism spectrum disorders (ASD). First, as the authors themselves acknowledge, cross-sectional research does not allow temporal and causal inferences to be established in postulating a true relationship between AdAS Spectrum and psychiatric disorders of interest. Second, the study’s developmental approach to ASD is insufficient; as a neurodevelopmental disorder, ASD has by definition an early onset in childhood, and the AdAS Spectrum does not include a reference neither to this point nor to the extent it impacts on early adaptive functioning. Third, there are considerable gender and age variations among the study’s five groups that bias outcomes. Fourth, the AdAS Spectrum at best emerge as a vulnerability framework masking and unmasking of symptoms with psychiatric comorbidity as well as non-pathological characteristics. In fact, all study participants enrolled as controls have resulted to be classified through cluster analysis into ASD, “low or medium autism cluster”, and none to any degree of ASD at all. The AdAS Spectrum questionnaire is a self-administered instrument leading to subjective reporting that is not validated by clinical assessment with limited specificity and sensitivity of a diagnostic threshold. Further AdAS questionnaire broadens the content of other ASD questionnaires used in screening, e.g., the Autism Spectrum Quotient, by inclusion of questions on empathy and other phenomenological dimensions not included in DSM-5-TR. The correspondence of AdAS items to established ASD, at best, remains presumptive. Although the AdAS Spectrum questionnaire includes the DSM’s term ‘spectrum,’ the DSM-5 and DSM-5-TR ASD is based on a categorical definition with inclusion, exclusion, onset, and impairment criteria. Fifth, with respect to the domain of restricted interests, the use of the term ‘rumination’ is phenomenologically additive. Further, the repetitive behaviour trait tends to be uniquely inherited (Ronald et al., 2006), with most ATs focusing on the social communication skills, and not repetitive behaviours. Indeed, it is as yet questionable whether any single trait can have the same pathognomonic value associated with ASD diagnosis, meaning when fewer specific traits are taken out of context or outside the full constellation of features that define ASD, they may represent a variety of conditions other than ASD. Although there is continuity in the distribution of ATs (Robinson et al., 2011), there is also evidence of separate domain heritability (Williams et al., 2019). Sixth, the concept of subthreshold ASD is a fundamental taxonomic question; it is not only relevant in assessment of co-occurring psychiatric disorders. Seventh, nevertheless, the increased broadening of ASD and the AdAS Spectrum bring psychiatric over attention to an uncharted territory that otherwise requires much greater precision. Moving away from categorical diagnosis towards dimensional approaches without substantive information about contextual background risks prematurely pathologizing normal human psychological frailty, diminishes diagnostic meaning, and compromises appropriateness of therapeutic considerations, as well as diverting health system resources. The AdAS Spectrum approach de-emphasizes the study of psychiatric co-occurrence patterns with emphasis of those adults with ASD without cognitive and adaptive impairments. It diverts the focus of care away from adults with established ASD, a state of affairs that is already severely constrained in many countries worldwide. Finally, the AdAS Spectrum approach, understandably, is a consequence of the insufficiency of unitary approaches in DSM-5-TR classification, that include the ASD and intellectual developmental disorders (Salvador-Carulla, Bertelli, 2008) that require a more enhanced approach to

capture the highly complex and diverse neurodevelopmental conditions, neurodevelopmental differences and functioning, and associated co-occurring psychiatric disorders.

Marco O. Bertelli¹, Veronica Boniotti¹, Annamaria Bianco¹, Giulia Vannucchi², Elisabetta F. Buonaguro³, Martina Micai⁴, Laura Fatta⁴, Michele Rossi¹, Edoardo Pecchini¹, Valeria Bizzari⁵⁻⁶, Michele Conte⁷, Gianpaolo Lombardi⁸, Serafino Corti⁹, Katrina Scior¹⁰, Muhammad Waqar Azeem¹¹⁻¹², Angela Hassiotis¹³, Amaria Baghdadli¹⁴⁻¹⁵, Maria Luisa Scattoni⁴, Luis Salvador-Carulla¹⁶, Afzal Javed¹⁷⁻¹⁸, and Kerim Munir¹⁹⁻²⁰.

1. CREA (Research and Clinical Centre), Fondazione San Sebastiano della Misericordia di Firenze, Florence, Italy
2. Psychiatry Unit, Versilia Hospital, Lido di Camaiore, Lucca, Italy
3. School of Medicine, University of Naples Federico II, Naples, Italy
4. National Observatory on Autism, National Institute of Health, Rome, Italy
5. Department of General Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany
6. Husserl Archives, KU Leuven, Belgium
7. IPSICO (Institute of Behavioural and Cognitive Psychology and Psychotherapy), Florence, Italy
8. IAF.F (Institute of Family Psychotherapy and Higher Education), Florence, Italy
9. Fondazione Istituto Ospedaliero di Sospiro Onlus, Cremona, Italy
10. Research Department of Clinical, Educational and Health Psychology, University College London, London, UK
11. Department of Psychiatry, Sidra Medicine, Doha, Qatar
12. Weill Cornell Medicine Qatar
13. Division of Psychiatry, University College of London, London, UK
14. Department of Paediatric Psychiatry, Centre Hospitalier Universitaire de Montpellier, Montpellier, Languedoc-Roussillon, France
15. Centre de Ressources Autisme Languedoc-Roussillon, Montpellier, Languedoc-Roussillon, France
16. School of Public Health, Australian National University (ANU), Canberra, Australia
17. Institute of Applied Health Research, University of Birmingham, UK
18. Pakistan Psychiatric Research Centre, Fountain House, Lahore, Pakistan
19. Division of Developmental Medicine, Boston Children's Hospital, Boston, Massachusetts, United States
20. Harvard Medical School, Boston, Massachusetts, United States

Corresponding Author:

Marco O. Bertelli

Email: mbertelli@crea-sansebastiano.org

Disclaimer

Marco O. Bertelli is the Chair of the Italian Society for Neurodevelopmental Disorders and the Chair of the Working Group on Autism Spectrum Disorder of the World Psychiatric Association (WPA). Gianpaolo Lombardi is the Director of the Italian Institute of Family Psychotherapy and Higher Education. Serafino Corti is the Co-Chair of the Italian Society for Neurodevelopmental Disorders. Katrina Scior is the Director of the University College London Unit for Stigma Research and Co-Director of University College London Centre for Intellectual and Developmental Disabilities Research. Muhammad Waqar Azeem is Director of Sidra Medicine WPA Collaborating Center, Qatar, Chair of the WPA Working Group on Medical Students and member of the WPA Working Groups on Autism Spectrum Disorder and on Child and Adolescent Psychiatry. Angela Hassiotis is the Co-Chair of the WPA Section Psychiatry of Intellectual Developmental Disorder. Amaria Baghdadli is responsible for the Department of Paediatric Psychiatry and the Centre of Excellence on Autism and Neurodevelopmental Disorders at CHU-Montpellier, France. Maria Luisa Scattoni is the Chair of the Italian Observatory on Autism of the Italian Institute of Health. Luis Salvador-Carulla is the Co-Chair of the WPA Working Group on Autism Spectrum Disorder. Afzal Javed is the President of the WPA. Kerim Munir is the Chair of the WPA Section Psychiatry of Intellectual Developmental Disorder and Chair of the WPA Working Group on Intellectual Developmental Disorders.

All these authors contributed to this article in their personal capacity. The opinions expressed are their own and do not necessarily reflect the views of the above listed organizations.

References

- Dell'Osso, L., Carpita, B., Nardi, B., Benedetti, F., Dell'Oste, V., Massimetti, G., Cremone, I. M., Barlati, S., Castellini, G., Luciano, M., Bossini, L., Rocchetti, M., Signorelli, M. S., Ricca, V., Aguglia, E., Fagiolini, A., Vita, A., Politi, P., & Maj, M. 2023. Autistic traits distribution in different psychiatric conditions: A cluster analysis on the basis of the Adult Autism Subthreshold Spectrum (AdAS Spectrum) questionnaire. *Psychiatry Res.* 326, 115270. <https://doi.org/10.1016/j.psychres.2023.115270>
- Robinson, E.B., Munir, K., Munafò, M.R., Hughes, M., McCormick, M.C., Koenen, K.C. 2011. Stability of autistic traits in the general population: further evidence for a continuum of impairment. *J Am Acad Child Adolesc Psychiatry.* 50(4), 376-84. <https://doi.org/10.1016/j.jaac.2011.01.005>
- Ronald, A., Happé, F., Bolton, P., Butcher, L.M., Price, T.S., Wheelwright, S., Baron-Cohen, S., Plomin, R. 2006. Genetic heterogeneity between the three components of the autism spectrum: a twin study. *J Am Acad Child Adolesc Psychiatry.* 45(6),691-699. <https://doi.org/10.1097/01.chi.0000215325.13058.9d>
- Salvador-Carulla, L., Bertelli, M. 2008. 'Mental retardation' or 'intellectual disability': time for a conceptual change. *Psychopathology.* 41(1), 10-6. <https://doi.org/10.1159/000109950>
- Williams, S.M., An, J.Y., Edson, J., Watts, M., Murigneux, V., Whitehouse, A.J.O., Jackson, C.J., Bellgrove, M.A., Cristino, A.S., Cladianos, C. 2019. An integrative analysis of noncoding regulatory DNA variations associated with autism spectrum disorder. *Mol Psychiatry.* 24(11), 1707-1719. <https://doi.org/10.1038/s41380-018-0049-x>