

# Autism Spectrum Disorder: Understanding the Female Phenotype

Luigi Mazzone  
Martina Siracusano  
Kevin A. Pelphrey  
*Editors*

 Springer

---

# Autism Spectrum Disorder: Understanding the Female Phenotype

---

Luigi Mazzone

Martina Siracusano • Kevin A. Pelphrey

Editors

# Autism Spectrum Disorder: Understanding the Female Phenotype

 Springer

*Editors*

Luigi Mazzone  
Department of System Medicine  
University of Rome Tor Vergata  
Rome, Italy

Martina Siracusano  
Department of Biomedicine and Prevention  
University of Rome Tor Vergata  
Rome, Italy

Kevin A. Pelphrey  
Department of Neurology  
University of Virginia  
Charlottesville, VA, USA

ISBN 978-3-031-62071-3      ISBN 978-3-031-62072-0 (eBook)  
<https://doi.org/10.1007/978-3-031-62072-0>

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2024

This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

If disposing of this product, please recycle the paper.

---

# Contents

## **Part I Autistic Female Phenotype: Gender Differences from Infancy to Adulthood**

- 1 Autism Spectrum Disorder: Prevalence and Symptoms' Onset. . . . . 3**  
Martina Siracusano and Luigi Mazzone
- 2 Female Autism Phenotype . . . . . 11**  
Martina Siracusano, Claudia Marcovecchio, Elisa Carloni, Assia Riccioni, and Luigi Mazzone
- 3 Cognition and Neuropsychological Profiles . . . . . 23**  
Martina Siracusano, Lucrezia Arturi, Assia Riccioni, and Luigi Mazzone
- 4 Adulthood: Do the Sex/Gender Differences in Autistic Phenotype Persist in Adult Life? . . . . . 39**  
Roberto Keller, Domenica Leone, Angela Aresi, Luana Salerno, Elisa Carloni, Martina Siracusano, and Luigi Mazzone

## **Part II Neurogenetics of Female Autism**

- 5 Neurogenetics of Autism Spectrum Conditions in Individuals Assigned Female at Birth . . . . . 49**  
Allison Jack, Goldie A. McQuaid, and Abha R. Gupta

## **Part III Psychiatric and Other Medical Comorbidities**

- 6 Internalizing Disorders and Female Autism. . . . . 83**  
Chiara Davico, Ilaria Secci, and Benedetto Vitiello
- 7 Female Autism and Externalizing Disorders . . . . . 99**  
Chiara Davico, Caterina Lux, and Benedetto Vitiello
- 8 Sex Differences in Epilepsy and Other Medical Comorbidities . . . . . 113**  
Laurie A. Brenner, Erika J. Axeen, and Katheryn F. Frazier

**Part IV Treatment**

- 9 The Role of Sex and Gender Differences in Psychosocial Treatment Strategies for Autism Spectrum Disorder . . . . . 129**  
Julia Zhong, Eliya Ahmad, Carla B. Kalvin,  
and Denis G. Sukhodolsky
- 10 Pharmacological Interventions and an Emerging Understanding of the Need to Consider Sex Differences in Treatment Planning . . . . . 157**  
Annie Fanta, Aniela Bordofsky, Cheyanne Sebolt, and Roger Jou

**Part V Quality of Life for Transition Age Youth**

- 11 Autism and Gender and Sexuality Diversity . . . . . 171**  
Jeroen Dewinter, Zosia Zaks, Nikki Brörmann,  
Ivan Henczyk, Elizabeth K. Graham, and John F. Strang
- 12 Evaluation of Sexual and Socio-Emotional Well-Being in Persons Affected by ASD: Are We Ready? . . . . . 187**  
Erika Limoncin, Giacomo Ciocca, Tommaso B. Jannini,  
Martina Siracusano, Luigi Mazzone, and Emmanuele A. Jannini
- 13 Independent Living and Employment Options . . . . . 197**  
Laura Maria Fatta, Martina Siracusano, and Luigi Mazzone

**Part VI Case Reports**

- 14 Clinical Case Reports . . . . . 213**  
Assia Riccioni, Martina Siracusano, and Luigi Mazzone

---

**Part I**

**Autistic Female Phenotype: Gender  
Differences from Infancy to Adulthood**



# Autism Spectrum Disorder: Prevalence and Symptoms' Onset

# 1

Martina Siracusano and Luigi Mazzone

## 1.1 Which Is the Sex/Gender Prevalence of ASD?

The Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network estimated that about 1 in 36 children has been diagnosed with autism spectrum disorder (ASD) among children aged 8 years [1], reporting a 4.3:1 male-to-female ratio, resulting in a significant sex/gender difference in prevalence. The male-to-female ratio increases as the severity of intellectual disability decreases [2]. Thereafter, 42.1% of females diagnosed in the spectrum are characterized by intellectual disability (intelligence quotient [IQ]  $\leq 70$ ), which is a higher percentage in comparison to male individuals (36.9%) [1].

The sex/gender prevalence rate estimated has been considered as the objective of a "male bias" [3, 4]. Among the factors contemplated as responsible for this male prevalence, there are methodological issues (the use of sex/gender-biased diagnostic tools and the population samples included in the studies) and questions related to developmental sex/gender differences [3, 5]. The whole book attempts to clarify (at different levels: clinical, genetic) the reason why ASD prevalence is actually reported to be higher in males; within this chapter, we introduce the topic.

---

M. Siracusano (✉)

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

Child Neurology and Psychiatry Unit, Department of Wellbeing of Mental and Neurological, Dental and Sensory Organ Health, Policlinico Tor Vergata Hospital, Rome, Italy

e-mail: [martina.siracusano@uniroma2.it](mailto:martina.siracusano@uniroma2.it)

L. Mazzone

Child Neurology and Psychiatry Unit, Department of Wellbeing of Mental and Neurological, Dental and Sensory Organ Health, Policlinico Tor Vergata Hospital, Rome, Italy

Systems Medicine Department, University of Rome Tor Vergata, Rome, Italy

e-mail: [luigi.mazzone@uniroma2.it](mailto:luigi.mazzone@uniroma2.it)



## 1.2 Why ASD Is More Frequently Reported in Males?

Are there less females with an autism condition or girls less easily and later diagnosed in comparison to their male peers? Whether ASD is less represented in females or it is underestimated in this sex/gender remains an open question, being an objective of a growing body of research.

Misdiagnosis or later diagnosis? Nosological or diagnostic challenge [3, 5]?

Several can be the reasons why girls are exposed to these phenomena (Fig 1.1), and two are the main diagnostic conditions which frequently occur: females receiving later diagnosis (condition of “**later age of diagnosis**”) and females diagnosed in early infancy (condition of “**more severe profile leading to earlier diagnosis**”) [3].

Autistic females with higher cognitive skills (low level of support needs) may be under-recognized [6, 7] due to the better communicative skills (verbal and nonverbal) and good social motivation [8, 9]; the difficulties in friendships’ maintenance [3] and the restricted and repetitive interests—due to the less atypical content (i.e., singers, celebrities) in comparison to their male peers [10]—may be hardly identified until late childhood, adolescence, and even adulthood (condition of “**later age of diagnosis**”).

However, the presence of comorbid cognitive delay (high level of support needs) defines a “classical male-typical presentation,” which implies a minor diagnostic challenge (condition of “**more severe profile leading to earlier diagnosis**”) [3] (see Chap. 3).

Recent research discussed whether “[...] *our understanding of autism may have been substantially biased towards males* [...]” identifying the so-called diagnostic challenge in females [3, 4].

First of all, a problem of diagnostic tools has been hypothesized: instruments employed for capturing symptoms of ASD (ADOS-2; ADI-R) may be male biased and therefore less sensitive in detecting autism features among females [6, 11–17]. Moreover, culture-related gender developmental differences may contribute masking social difficulties (females are culturally expected as being shy) and atypical behaviors in females. Thus, these symptoms are later identified as related to the condition of ASD [3, 18].

### What may influence age of diagnosis within sex/genders:

Research issues: SOURCE OF THE SAMPLE	DEVELOPMENTAL SEX/GENDER DIFFERENCES	LEVEL OF IMPAIRMENT	TYPE OF SYMPTOMS EVALUATED
-Clinical samples -High/low risk infants	may influence gender comparisons regardless the presence of a neurodevelopmental disorder	-low cognitive skills leads to earlier diagnosis; -high cognitive skills implies later diagnosis	-SOCIAL BEHAVIOR: better social skills or greater impairment within females? -RESTRICTED AND REPETITIVE BEHAVIORS: less atypical or equal level in comparison to males?

**Fig. 1.1** Main factors with a possible influence on sex/gender difference in ASD onset

“*Setting the scene for future research*” is a critical issue as suggested by Lai et al. [3] trying to understand the implications from the actual research on sex/gender and ASD, in order to contribute to the design of future studies. In particular, the authors identified the need of using representative sample size of both sexes/genders as one of the main methodological concerns in gender research. Most of the studies, in fact, include a number of female participants according to the wide male–female ratio 4:1, leading to male-biased study [3]. In these terms, research may be in some ways responsible for the prevalence rate.

### 1.3 Is There Any Sex/Gender Difference in Autism Symptoms' Onset?

How ASD symptoms appear/arise/come out in early infancy is variable, and different clinical patterns have been identified as a possible way of ASD onset [19] (see Table 1.1). Even if ASD prevalence is significantly higher in males in comparison to females, this aspect may not reflect a sex/gender difference in the emergence of autism symptoms in early childhood [3]. However, despite the growing interest in defining an autism female phenotype, few researches have specifically investigated if there are evident sex/gender differences in early autism manifestations [20–24].

Some studies including infants and toddlers with ASD did not reveal significant sex/gender differences at these early stages of life [23, 25, 26]. In contrast, other researches identified better social communication skills and reduced RRBs as characteristics of young females with ASD in comparison to their male counterpart [24, 9]. Others found equal level of RRBs within sex/gender in early infancy but greater impairment of social skills [27].

These varied findings lead to a huge confusion, which has been attributed to clinical and research issues such as broad age ranges of the samples (6 months–5 years of age) with a possible influence of developmental issues on the autism manifestations rather than reflecting a specific gender phenotype [27]. For example, studies conducted on early infancy samples may hardly capture sex/gender differences in RRBs: Are children too young to show significant differences in the symptoms' manifestation [26]?

As a matter of fact, an important point is whether **developmental sex differences** may influence gender comparisons regardless of the presence of a neurodevelopmental disorder. In regard to this, a Baby Siblings Research Consortium study conducted on a sample of 1824 infants (including 1241 high-risk siblings, 583

**Table 1.1** Based on Rogers [20], Pearson et al. [21] and Boterberg et al. [22]

	Congenital	Plateau	Regression	Mixed
ASD SYMTPOMS'ONSET	Emergence of atypical behaviors in the first year of life	Early milestone achievement followed by a developmental plateau	Attainment of developmental milestones followed by a regression/loss of skills	Pattern of early delays followed by later loss

low-risk)—evaluated at different age time (18, 24, 36 months)—examined sex differences in the development of ASD symptoms and in cognitive skills.

Interestingly, the authors found that, regardless of the condition of risk (high or low) and outcome (ASD/non-ASD), lower levels of cognitive functioning and higher levels of restrictive and repetitive behaviors emerged within males in comparison to females. Thus, this study suggests that “early sex differences are not autism specific” but mirror a sex-related variability not linked to the neurodevelopmental disorder [28].

Moreover, not only age—and subsequent developmental issues—but also **source of the sample** (clinical, high/low-risk individuals) may be responsible for the varied and inconsistent results actually characterizing sex/gender research. In fact, it is necessary to specify that most of the studies were conducted on clinical samples (infants and toddlers already diagnosed with ASD) [23, 24, 27] and few on cohorts including high-risk infant samples (i.e., siblings of ASD individuals) [29, 30]. In regard to studies conducted on clinical samples, Lawson et al. [27] examined (across time) sex/gender differences in early autism clinical manifestations and cognitive development in a very young community-ascertained sample of toddlers with ASD aged from 24 to 48 months. More social communication impairment emerged within females in comparison to the male counterpart.

When sex/gender differences were examined within high-risk infant cohorts, higher social skills better characterized females (i.e., increased attention to social stimuli) in comparison to male peers.

However, also results obtained from high-risk cohort studies—due to the fact that they include siblings—cannot reflect ASD as a whole but withstand underlying genetic mechanisms linked to ASD multiplex families.

Therefore, actual research on the topic does not clarify whether ASD symptoms differently emerge within sex/gender, but it has focused its attention on a possible female phenotype in early infancy characterized by less RRBs and better social skills (see Chap. 2). However, further studies are necessary in order to better investigate and understand this puzzling issue.

Specifically concerning **social behavior**, atypical attention to social stimuli is considered an important attentional and behavioral issue of ASD risk in early childhood [29, 31]. In this context, eye-tracking technology represents the main objective way to measure these abilities, in particular the attentional patterns [32].

What we have learned from eye-tracking studies is that toddlers with ASD or at risk for this condition present less attention to social targets and stimuli (faces of interactive people, objects attended by others, activities performed by interactive partners) [32].

Preliminary eye-tracking research shows that sex/gender differences may exist in ASD children specifically concerning social attention [33–35]. Of particular interest, an eye-tracker prospective research (experimental study of social attention) suggests that, in early infancy (6 and 12 months of age, period during which social cognitive skills are expected to develop), **females** at high risk for ASD (siblings of ASD children) are characterized by a “social advantage” consisting of increased attention to socially relevant targets such as faces, in comparison to males with the

same risk of ASD and peers of both genders with lower risk [29]. Interestingly, high-risk females were characterized by a greater attention to social stimuli also in comparison to females at low risk of ASD. This neurobehavioral finding, even if preliminary, is in line with clinical researches reporting better clinical social skills in females later diagnosed with ASD (social camouflage theory).

Noteworthy, differences in social attention at early stages of life may be responsible for developmental trajectories, predicting later behavioral outcome [29, 36]. For example, less attention to social scenes in toddlers with ASD was related to poor cognitive and language outcome at 3 years [36].

In fact, given the relevant role of social attention in learning derived from experience—with subsequent effect on shaping the cognitive system—the existence of sex/gender differences in social attention in early infancy may influence developmental trajectories [37]. In this context, further research specifically investigating sex/gender differences in the development of social attention within population at risk for ASD is necessary in order to better understand if such female social advantage in early infancy corresponds to a different developmental trajectory in terms of ASD symptom severity and comorbid conditions.

Finally, as reported in previous paragraphs, different patterns of ASD onset may occur (Table 1.1), including “**regression**” (meant as a loss of acquired skills—not specifically defined in terms of onset time and type of ability) occurring in 32% of cases, which represent one of the main parental concerns. However, no sex/gender differences have been reported specifically concerning this way of onset, or this issue has not been deeply investigated yet [20].

Noteworthy, a study investigating if the **initial impression** (5-min observation of toddlers presenting for an ASD evaluation) of expert clinicians matched the final ASD diagnosis did not find sex/gender differences in its results (ASD diagnosis matched in 92% of cases) [19]. These findings highlight the fact that being female or male did not significantly influence the match between first impression and diagnosis of clinicians who are expert in the field. Thus, sex did not make more difficult “diagnosis at a glance in 5 min” within their very young sample. However, age and developmental aspects should be taken into account before going to conclusions. In fact, the study included toddlers referring for an ASD evaluation at very early age (part of a multicenter screening project), more likely affected by evident atypical features in comparison to children who later refer for mild socio-communicative difficulties, which could necessitate an evaluation longer than 5 min for a correct diagnosis.

---

## 1.4 Conclusion

We are still far away from understanding with certainty why the male prevalence of ASD is significantly higher in comparison to female and if a sex/gender pattern of ASD symptom onset—independently or not from developmental sex differences—exists indeed.

However, even if most of the questions addressed in this chapter remain unanswered, we can affirm that the greater awareness of a “female diagnostic challenge” is leading to a greater consciousness of families, teachers, researchers, and clinicians.

### Key Points

- ASD prevalence is significantly higher in males in comparison to females.
- Main question is if females are later diagnosed or misdiagnosed.
- A more severe clinical profile with associated intellectual disability leads to earlier diagnosis.
- A sex difference in the emergence of autism symptoms in early childhood has not been concordantly reported.
- Developmental sex differences may influence gender comparisons regardless of the presence of a neurodevelopmental disorder.

### References

1. Maenner MJ, Warren Z, Williams AR, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2020. *MMWR Surveill Summ.* 2023;72(2):1–14. <https://doi.org/10.15585/mmwr.ss7202a1>.
2. Zeidan J, Fombonne E, Scora J, et al. Global prevalence of autism: a systematic review update. *Autism Res.* 2022;15(5):778–90. <https://doi.org/10.1002/aur.2696>.
3. Lai MC, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/gender differences and autism: setting the scene for future research. *J Am Acad Child Adolesc Psychiatry.* 2015;54(1):11–24. <https://doi.org/10.1016/j.jaac.2014.10.003>.
4. Ochoa-Lubinoff C, Makol BA, Dillon EF. Autism in women. *Neurol Clin.* 2023;41(2):381–97. <https://doi.org/10.1016/j.ncl.2022.10.006>.
5. Di Vara S, Guerrero S, Menghini D, et al. Characterizing individual differences in children and adolescents with autism spectrum disorder: a descriptive study. *Front Psychol.* 2024;15:1323787. Published 2024 Feb 27. <https://doi.org/10.3389/fpsyg.2024.1323787>.
6. 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(6):e20835. <https://doi.org/10.1371/journal.pone.0020835>.
7. Lai M-C, Lombardo MV, Ruigrok AN, Chakrabarti B, Auyeung B, Szatmari P, et al. Quantifying and exploring camouflaging in men and women with autism. *Autism.* 2017a;21:690–702. <https://doi.org/10.1177/1362361316671012>.
8. Napolitano A, Schiavi S, La Rosa P, Rossi-Espagnet MC, Petrillo S, Bottino F, et al. Sex differences in autism Spectrum disorder: diagnostic, neurobiological, and behavioral features. *Front. Psych.* 2022;13:889636. <https://doi.org/10.3389/fpsyg.2022.889636>.
9. Knutsen J, Crossman M, Perrin J, Shui A, Kuhlthau K. Sex differences in restricted repetitive behaviors and interests in children with autism spectrum disorder: an autism treatment network study. *Autism.* 2019;23:858–68. <https://doi.org/10.1177/1362361318786490>.
10. Saure E, Castrén M, Mikkola K, Salmi J. Intellectual disabilities moderate sex/gender differences in autism spectrum disorder: a systematic review and meta-analysis. *J. Intellect. Disabil. Res.* 2023;67:1–34. <https://doi.org/10.1111/jir.12989>.
11. Rutter M, Caspi A, Moffitt TE. Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. *J Child Psychol Psychiatry.* 2003;44(8):1092–115. <https://doi.org/10.1111/1469-7610.00194>.

12. Gould J, Ashton-Smith J. Missed diagnosis or misdiagnosis: girls and women on the autism spectrum. *Good Autism Pract.* 2011;12:34–41.
13. Constantino JN, Charman T. Gender bias, female resilience, and the sex ratio in autism. *J Am Acad Child Adolesc Psychiatry.* 2012;51(8):756–8. <https://doi.org/10.1016/j.jaac.2012.05.017>.
14. Lai MC, Lombardo MV, Chakrabarti B, Baron-Cohen S. Subgrouping the autism “spectrum”: reflections on DSM-5. *PLoS Biol.* 2013;11(4):e1001544. <https://doi.org/10.1371/journal.pbio.1001544>.
15. Kreiser NL, White SW. ASD in females: are we overstating the gender difference in diagnosis? *Clin Child Fam Psychol Rev.* 2014;17(1):67–84. <https://doi.org/10.1007/s10567-013-0148-9>.
16. Tillmann J, Ashwood K, Absoud M, Bölte S, Bonnet-Brilhault F, Buitelaar JK, et al. Evaluating sex and age differences in ADI-R and ADOS scores in a large European multi-site sample of individuals with autism spectrum disorder. *J Autism Dev Disord.* 2018;48:2490–505. <https://doi.org/10.1007/s10803-018-3510-4>.
17. Navarro-Pardo E, López-Ramón F, Alonso-Esteban Y, Alcantud-Marín F. Diagnostic tools for autism Spectrum disorders by gender: analysis of current status and future lines. *Children (Basel).* 2021;8:262. <https://doi.org/10.3390/children80402>.
18. Lai M-C, Szatmari P. Sex and gender impacts on the behavioural presentation and recognition of autism. *Curr Opin Psychiatry.* 2020;33:117–23. <https://doi.org/10.1097/YCO.0000000000000575>.
19. Wieckowski AT, de Marchena A, Algur Y, et al. The first five minutes: initial impressions during autism spectrum disorder diagnostic evaluations in young children. *Autism Res.* 2021;14(9):1923–34. <https://doi.org/10.1002/aur.2536>.
20. Rogers SJ. Developmental regression in autism spectrum disorders. *Ment Retard Dev Disabil Res Rev.* 2004;10(2):139–43. <https://doi.org/10.1002/mrdd.20027>.
21. Pearson N, Charman T, Happé F, Bolton PF, McEwen FS. Regression in autism spectrum disorder: reconciling findings from retrospective and prospective research. *Autism Res.* 2018;11(12):1602–20. <https://doi.org/10.1002/aur.2035>.
22. Boterberg S, Charman T, Marschik PB, Bölte S, Roeyers H. Regression in autism spectrum disorder: a critical overview of retrospective findings and recommendations for future research. *Neurosci Biobehav Rev.* 2019;102:24–55. <https://doi.org/10.1016/j.neubiorev.2019.03.013>.
23. Postorino V, Fatta LM, De Peppo L, et al. Longitudinal comparison between male and female preschool children with autism spectrum disorder. *J Autism Dev Disord.* 2015;45(7):2046–55. <https://doi.org/10.1007/s10803-015-2366-0>.
24. Hartley SL, Sikora DM. Sex differences in autism spectrum disorder: an examination of developmental functioning, autistic symptoms, and coexisting behavior problems in toddlers. *J Autism Dev Disord.* 2009;39(12):1715–22. <https://doi.org/10.1007/s10803-009-0810-8>. Epub 2009 Jul 7. PMID: 19582563; PMCID: PMC3590797
25. Andersson GW, Gillberg C, Miniscalco C. Pre-school children with suspected autism spectrum disorders: do girls and boys have the same profiles? *Res Dev Disabil.* 2013;34(1):413–22. <https://doi.org/10.1016/j.ridd.2012.08.025>.
26. Van Wijngaarden-Cremers PJ, van Eeten E, Groen WB, Van Deurzen PA, Oosterling IJ, Van der Gaag RJ. Gender and age differences in the core triad of impairments in autism spectrum disorders: a systematic review and meta-analysis. *J Autism Dev Disord.* 2014;44(3):627–35. <https://doi.org/10.1007/s10803-013-1913-9>.
27. Lawson LP, Joshi R, Barbaro J, Dissanayake C. Gender differences during toddlerhood in autism spectrum disorder: a prospective community-based longitudinal follow-up study. *J Autism Dev Disord.* 2018;48(8):2619–28. <https://doi.org/10.1007/s10803-018-3516-y>.
28. Messinger DS, Young GS, Webb SJ, Ozonoff S, Bryson SE, Carter A, Carver L, Charman T, Chawarska K, Curtin S, Dobkins K, Hertz-Picciotto I, Hutman T, Iverson JM, Landa R, Nelson CA, Stone WL, Tager-Flusberg H, Zwaigenbaum L. Early sex differences are not autism-specific: A Baby Siblings Research Consortium (BSRC) study. *Mol Autism.* 2015;6:32. <https://doi.org/10.1186/s13229-015-0027-y>. PMID: 26045943; PMCID: PMC4455973.

29. Chawarska K, Macari S, Powell K, DiNicola L, Shic F. Enhanced social attention in female infant siblings at risk for autism. *J Am Acad Child Adolesc Psychiatry*. 2016;55(3):188–95.e1. <https://doi.org/10.1016/j.jaac.2015.11.016>.
30. Zwaigenbaum L, Bryson SE, Szatmari P, et al. Sex differences in children with autism spectrum disorder identified within a high-risk infant cohort. *J Autism Dev Disord*. 2012;42(12):2585–96. <https://doi.org/10.1007/s10803-012-1515-y>.
31. Di Giorgio E, Rosa-Salva O, Frasnelli E, et al. Abnormal visual attention to simple social stimuli in 4-month-old infants at high risk for Autism. *Sci Rep*. 2021;11(1):15785. Published 2021 Aug 4. <https://doi.org/10.1038/s41598-021-95418-4>.
32. Hammer T, Vivanti G. Eye-tracking research in autism spectrum disorder: what are we measuring and for what purposes? *Curr Dev Disord Rep*. 2019;6:37–44. <https://doi.org/10.1007/s40474-019-00158-w>.
33. Harrop C, Jones D, Zheng S, Nowell SW, Boyd BA, Sasson N. Sex differences in social attention in autism spectrum disorder. *Autism Res*. 2018;11(9):1264–75. <https://doi.org/10.1002/aur.1997>.
34. Kleberg JL, Nyström P, Bölte S, Falck-Ytter T. Sex differences in social attention in infants at risk for autism. *J Autism Dev Disord*. 2019;49(4):1342–51. <https://doi.org/10.1007/s10803-018-3799-z>.
35. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, et al. A meta-analysis of gaze differences to social and nonsocial information between individuals with and without autism. *J Am Acad Child Adolesc Psychiatry*. 2017;56(7):546–55.
36. Campbell DJ, Shic F, Macari S, Chawarska K. Gaze response to dyadic bids at 2 years related to outcomes at 3 years in autism spectrum disorders: a subtyping analysis. *J Autism Dev Disord*. 2014;44(2):431–42. <https://doi.org/10.1007/s10803-013-1885-9>.
37. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. *Biol Psychiatry*. 2013;74(3):195–203. <https://doi.org/10.1016/j.biopsych.2012.11.022>.



# Female Autism Phenotype

# 2

Martina Siracusano, Claudia Marcovecchio, Elisa Carloni, Assia Riccioni, and Luigi Mazzone

## 2.1 Introduction

The existence of a specific “female phenotype of autism” has been proposed during the last few years, suggesting that the female diagnostic challenge may be mediated by two distinct factors contrasting but not mutually exclusive.

On the one hand, a *female protective effect* (FPE theory) has been hypothesized, which implies an innate protective factor in females, according to which they require a greater environmental and/or genetic load than males to express the same degree of autistic characteristics [1].

On the other hand, it has been proposed that diagnostic biases (employment of male-biased instruments; male-focused diagnostic criteria) contribute to delayed diagnosis or even missed diagnosis in females [2, 3].

---

M. Siracusano (✉)

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

Child Neurology and Psychiatry Unit, Department of Wellbeing of Mental and Neurological, Dental and Sensory Organ Health, Policlinico Tor Vergata Hospital, Rome, Italy

e-mail: [martina.siracusano@uniroma2.it](mailto:martina.siracusano@uniroma2.it)

C. Marcovecchio · E. Carloni · A. Riccioni

Child Neurology and Psychiatry Unit, Department of Wellbeing of Mental and Neurological, Dental and Sensory Organ Health, Policlinico Tor Vergata Hospital, Rome, Italy

L. Mazzone

Child Neurology and Psychiatry Unit, Department of Wellbeing of Mental and Neurological, Dental and Sensory Organ Health, Policlinico Tor Vergata Hospital, Rome, Italy

Systems Medicine Department, University of Rome Tor Vergata, Rome, Italy

e-mail: [luigi.mazzone@uniroma2.it](mailto:luigi.mazzone@uniroma2.it)



Understanding and recognizing female autism phenotype are necessary to allow early identification and diagnosis of autistic females and to develop sex/gender-appropriate intervention for ASD.

In this chapter, we explore sex/gender differences in phenotypic presentation of ASD, focusing on the two core symptoms according to the DSM 5 TR [4, 5]: *social communication, social interaction abilities, and restricted and repetitive behaviors* (RRBs).

## 2.2 Social Communication and Social Interaction Skills

One of the main questions the research is attempting to answer within ASD is whether there are—and how are they influenced by—sex/gender differences in socio-communicative skills (Table 2.1).

**Table 2.1** Persistent deficits in social communication and social interaction across multiple contexts (Autism Spectrum Disorder, Domain A, DSM 5 TR [5])

<p><b>A1. Deficits in social-emotional reciprocity</b> Ranging from abnormal social approach and failure of normal back-and-forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction</p>	<ul style="list-style-type: none"> <li>• Unusual social initiations (intrusive touching, licking of others)</li> <li>• Use of others as tools</li> <li>• One-sided conversation/monologues</li> <li>• Impairment in joint attention</li> <li>• Lack of showing or pointing out objects to other people</li> <li>• Failure to share enjoyment, excitement, or achievements with others</li> <li>• Indifference/aversion to physical contact and affection</li> </ul>
<p><b>A2. Deficits in nonverbal communicative behaviors used for social interaction</b> Ranging from poorly integrated, verbal and nonverbal communication, through abnormalities in eye contact and body language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures</p>	<ul style="list-style-type: none"> <li>• Abnormal prosody, rhythm, intonation, or volume in speech</li> <li>• Inability to coordinate eye contact or body language with words</li> <li>• Impairment in the use of facial expressions (limited or exaggerated)</li> <li>• Impairment in the use and understanding of gesture (i.e., nodding/shaking head, pointing, waving) or posture (i.e., facing away from a listener)</li> </ul>
<p><b>A3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers)</b> Ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people</p>	<ul style="list-style-type: none"> <li>• Inability to take another person's perspective</li> <li>• Unaware of social convention and appropriate social behavior (ask socially inappropriate questions)</li> <li>• Inappropriate expression of emotion (i.e., laughing or smiling out of context)</li> <li>• Withdrawn, lack interest in peers</li> <li>• Has an interest in friendship but lacks understanding of the convention of social interaction (i.e., extremely directive or rigid; overly passive)</li> </ul>

### 2.2.1 Are There Sex/Gender Differences in Socio-Communicative Skills?

Females on the spectrum—even if displaying a social impairment in comparison to females with typical development—generally exhibit greater social skills when compared to autistic males such as greater desire and awareness of social interactions, tendency to imitate others, compensatory strategies masking difficulties in relationships, better language abilities, and greater imagination [6, 7]. Better social skills of females may contribute to the lower rate of ASD diagnosis in girls or at least they may be responsible for the masked behavioral difficulties [2, 8].

Currently, scientific evidence shows that among factors influencing sex/gender differences within ASD, there is mainly the level of impairment and subsequently the degree of support needed.

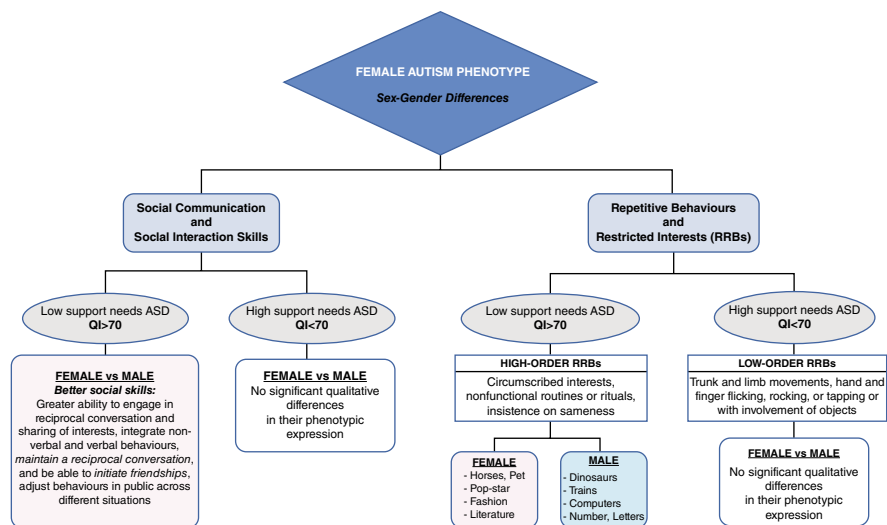
Age of first parental concern (early or late childhood and adolescence) may be linked to the level of their daughters' social impairment. As a matter of fact, girls who refer for a clinical assessment during *toddlerhood/early childhood* are characterized by a greater impairment in engaging social interaction and in reciprocal social communication [9]. On the other hand, females of same age with less social difficulties and showing higher levels of social motivation (i.e., greater desire to form friendship) may be missed during routine surveillance [9]. These girls will probably undergo psychiatric assessment during school age and/or adolescence [6, 8]. As a matter of fact, given that as age increases, the social demand rises, girls who have masked their difficulties until scholar age/adolescence might probably exhibit a social impairment—still less evident in comparison to autistic males—at this stage of life.

Specifically considering scholar age, females are more likely to show greater ability to engage in reciprocal conversation, to initiate friendship, and to share interests [6]. Furthermore, girls show greater abilities to adapt behaviors in public across different situations compared to boys including larger social setting and school environment (i.e., monitoring volume of voice, avoiding socially inappropriate comments) [2, 6, 10]. This sex/gender socio-communicative profile persists at older ages (adolescents and young adults), when female adolescents in the spectrum report a better friendship quality and empathy in comparison to autistic males [8] (Fig. 2.1).

Overall, these aspects may make cognitive-able females less likely to be identified at all stages of life, leading to late diagnosis, prejudicing them from receiving appropriately targeted health care, early intervention, and educational resources.

#### 2.2.1.1 Sex/gender differences related to the level of support needs

Level of functioning (actually defined with the level of support needs) in autism spectrum disorder represents a crucial point on the definition of the autistic phenotype, influencing the determination of sex/gender differences between male and female [6].



**Fig. 2.1** Sex differences in symptom domains of ASD: Social Communication Skills and RRBs

Evidence of sex/gender differences in the social and communication domain may be related to different levels of support needs (Fig. 2.1). Indeed, during childhood and adolescence, both ASD males and females with high support needs did not show significant differences from each other in socio-communicative domain [11], reflecting overlapping profiles between males and females [12] (Fig. 2.1).

On the other hand, autistic females with low support needs, who possess strong social skills compared to males, require greater impairment of other core symptoms to obtain a diagnosis. Although it is currently estimated that four males are diagnosed with ASD for every one female [13], gender ratios have been seen to begin to decrease if individuals with intellectual disability are considered, making the differences between sexes/genders less apparent. These findings suggest that in individuals requiring a lower support, there may be a high portion of ASD females who go unnoticed, raising the added complexity of determining who should receive a diagnosis [2, 8].

The apparent better social functioning of autistic females compared to autistic males suggests that females may show a superficial understanding of appropriate social etiquette, and they may be able to mask their deficits through imitation and mimicry [14].

These findings could be explained by the “*camouflage hypothesis*” proposed by Wing [15] that refers to the use of conscious or unconscious strategies that allow females with ASD to develop social skills and coping mechanisms to blend in or camouflage themselves into society, obscuring a likely diagnosis of ASD, even though there may be other indications of the condition (see Box 2.1). Although camouflaging is an adaptive mechanism, it may enclose several negative implications, such as misdiagnosis, late diagnosis, or underdiagnosis that can prevent from adequate or timely intervention [16].

Therefore, the apparent advantage showed by autistic females over males may partly explain gender ratio (M:F = 4:1) within ASD. Understanding and recognizing

the social female phenotype of ASD and the camouflage hypothesis may be useful to reconsider in a sex/gender prospective the social communication diagnostic criteria. This could allow to diagnose a larger number of females leading to a prompt and adequate intervention [8].

### 2.3 Repetitive Behaviors and Restricted Interests

Restricted and repetitive behaviors (RRBs) are core symptoms of autism spectrum disorder, but they are not unique to children with autism; indeed, they can be found in children with other neurodevelopmental disorders, such as intellectual disability and language disorders, and also in other psychiatric conditions (i.e., obsessive–compulsive disorder) [17]. RRBs are also common during early typical development, but what makes the RRBs of children with typical development different from those RRBs exhibited by autistic individuals is their intensity [18]. RRBs have been found to be one of the earliest signs exhibited by infants later diagnosed with ASD and early predictors of outcome [19].

In Table 2.2, restricted, repetitive patterns of behavior, typical of ASD—regardless of sex/gender differences—are reported as stated by the DSM 5 TR [5].

**Table 2.2** Restricted, repetitive patterns of behavior, interests, or activities (Autism Spectrum Disorder, Domain B, DSM-5) with clinical examples

<p><b>B1. Stereotyped or repetitive speech, motor movements, or use of objects</b> Such as simple motor stereotypies, echolalia, repetitive use of objects, lining up toys or flipping objects, or idiosyncratic phrases</p>	<ul style="list-style-type: none"> <li>• Repetitive hand movements (i.e., flapping, clapping)</li> <li>• Toe walking</li> <li>• Unusually formal language (speaking like an adult)</li> <li>• Repetitive vocalization, words, phrases, or songs</li> <li>• Nonfunctional play with objects</li> <li>• Repetitively opens and closes doors or turns lights on–off</li> </ul>
<p><b>B2. Insistence on sameness, excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change</b> Such as motoric rituals, insistence on same route or food, rigid thinking patterns, repetitive questioning, or extreme distress at small changes</p>	<ul style="list-style-type: none"> <li>• Excessively rigid, inflexible in behavior and thought, and following specific unusual routines</li> <li>• Inability to understand nonliteral aspects of speech (i.e., irony, implied meaning)</li> <li>• Overreaction to trivial changes</li> </ul>
<p><b>B3. Highly restricted, fixated interests that are abnormal in intensity or focus</b> Such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests</p>	<ul style="list-style-type: none"> <li>• Attachment to unusual inanimate object (i.e., piece of string, wire, rubber band)</li> <li>• Excessive focus on nonrelevant or nonfunctional parts of objects (i.e., car wheels)</li> <li>• Focused on the same few objects, topics, or activities (i.e., planets, animals)</li> </ul>

(continued)