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Gender and Age Differences in the Core Triad of Impairments in Autism Spectrum Disorders: A Systematic Review and Meta-analysis

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Abstract Autism is an extensively studied disorder in which the gender disparity in prevalence has received much attention. In contrast, only a few studies examine gender differences in symptomatology. This systematic review and meta-analysis of 22 peer reviewed original publications examines gender differences in the core triad of impairments in autism. Gender differences were transformed and concatenated using standardized mean differences, and analyses were stratified in five age categories (toddlerhood, preschool children, childhood, adolescence, young adulthood). Boys showed more repetitive and stereotyped behavior as from the age of six, but not below the age of six. Males and females did not differ in the domain of social behavior and communication. There is an underrepresentation of females with ASD an average to high intelligence. Females could present another autistic

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phenotype than males. As ASD is now defined according to the male phenotype this could imply that there is an ascertainment bias. More research is needed into the female phenotype of ASD with development of appropriate instruments to detect and ascertain them.

Keywords Autism spectrum disorder · Gender · Age

Introduction

Autism spectrum disorder (ASD) is a collective term for a group of heterogeneous disorders characterized by impairments in social interaction and verbal and non-verbal communication, and repetitive and stereotyped behaviors. ASD is more common in males than in females, with a male to female ratio of 4.3:1 (Fombonne 2003) and a prevalence of 60-70/10,000 (Fombonne 2009). As a consequence, most research has involved male patients. However, there is some evidence that the clinical presentation is different in males and females (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983), and it is argued that phenotypic gender differences might lead to delayed diagnosis or even missed diagnosis in girls and women with autism (Rivet and Matson 2011b). For instance, girls and women with relevant symptoms may be diagnosed with other disorders, such as social phobia or borderline personality disorder, instead of ASD (Attwood 2007). As yet, there have been relatively few studies of gender differences in symptoms, and available findings are inconsistent. While some studies have reported girls to have more social problems and to be less able to perform social play and social imitative play than boys (Holtmann et al. 2007; McLennan et al. 1993; Tsai and Beisler 1983) others have not found gender differences in social behavior or have reported that social behavior is better in girls than in boys (Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007; McLennan et al. 1993). Findings about communication patterns are also discrepant. Some studies found girls to have less expressive and advanced receptive language skills (Carter et al. 2007; Holtmann et al. 2007), while others did not find any differences (McLennan et al. 1993). One study found repetitive and stereotyped behaviors to be less common in females than in males (Bölte et al. 2011), whereas three other studies did not find any gender differences in this domain (Banach et al. 2009; Carter et al. 2007; Holtmann et al. 2007). Thus, findings regarding gender differences in the core triad of impairments seen in ASD remain ambiguous. In addition, age may influence potential gender-related differences in the symptoms of ASD, as there is some evidence that age has a gender-specific role in symptom severity. For example, two studies found that ASD was detected earlier in infant girls than in infant boys (Ozonoff et al. 2010; Rivet and Matson 2011b) however, other studies found that mild autism was diagnosed far later in high functioning females than in males (Begeer et al. 2013; Lugnegård et al. 2011).

Because ASD is far more prevalent in males than in females, relatively little attention has been paid to how the disorder manifests in females, despite there being some evidence that core symptoms of ASD differ by gender and that age influences these gender differences in symptomatology. For this reason, we performed a systematic review and meta-analysis to investigate possible gender differences in the core symptoms of ASD from infancy to adulthood, because a better understanding of gender differences may lead to an earlier diagnosis and better treatment of ASD in girls and women.

Methods

Literature Search

Multiple electronic databases (PubMed, Scopus, Medline, Web of Science Direct) were searched for relevant articles, published between 1943 and June 2013, on gender differences in the core triad of impairments seen in ASD (impaired social interaction, impaired (non)verbal communication, and restricted patterns of behavior and interest), using the following keywords: 'autism spectrum disorder', 'ASD', 'pervasive development disorder', 'PDD', or 'autism' in combination with 'gender, 'gender differences', 'sex', or 'sex differences'. Inclusion criteria were comparison of core symptoms of ASD in males and females and availability of test scores for males and females.

Procedure

The initial database search identified 504 articles. The title and abstract of these articles were screened for inclusion criteria by two researchers (a third researcher was consulted in case of doubt), which resulted in 70 potentially relevant articles. The full-text documents were retrieved and screened for inclusion. The reference lists of these articles were checked to identify additional relevant articles. Decisions made at this stage were discussed in a research team including psychiatrists, a psychologist, and an epidemiologist.

Articles were excluded if no distinction was made between the core symptoms in the triad of impairments in ASD (n = 16), if the article was a review and did not include new data (n = 8), if the information provided was unclear (n = 1), if gender differences in ASD were not explicitly investigated (n = 6), or if the study merely included gross epidemiological data (n = 2). Of the remaining 37 articles, 15 were excluded after a thorough examination of the data provided (11 articles did not provide scores for core symptoms of ASD and 4 did not distinguish between the three core impairments). Of the 22 remaining articles, 20 reported on social impairments, 18 reported on communication deficits, and 15 reported on repetitive and stereotyped behavior. Figure 1 provides an overview of this selection procedure.

Funnel plots (Appendix 3 in ESM) of the standardized mean differences were made for each core symptom using Review Manager 5.1 (Nordic Cochrane Centre, 2011) to check for outliers. If there were outliers (n = 2), two independent authors (RG and PW) checked the research method, sample size, reproducibility, and possible bias of these studies. None of the articles were excluded.

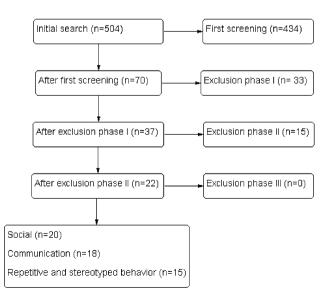


Fig. 1 Flow chart study selection

| Study or Subarous | | male sn | Total | | emale SD | Tetal | Waiaht | Std. Mean Difference | Std. Mean Difference |
|--|-----------------|------------|--------------------|-----------------------|-------------|-----------------------|----------------------|---|--------------------------|
| Study or Subgroup 1.1.1 Toddlers and pr | Mean B-schoo | | Total | Mean | 50 | rotal | Weight | IV, Random, 95% CI | IV, Random, 95% Cl |
| | | | | 70.0 | | | 0.400 | 0.001440.047 | |
| Andersson 2012 | 73.4 | 10.7 | 20 | 78.3 | 8.2 | 20 | 2.4% | -0.50 [-1.13, 0.13] | |
| Carter 2007 (1) | 10.4 | 2.8 | 68 | 10.8 | 2.6 | 22 | 2.8% | -0.14 [-0.63, 0.34] | - T |
| Carter 2007 (2) | -12 | 2.9 | 21 | -12.8 | 3 | 67 | 2.8% | 0.27 [-0.23, 0.76] | |
| Carter 2007 (3) | 16.3 | 4.1 | 68 | 17.5 | 3.9 | 22 | 2.8% | -0.29 [-0.78, 0.19] | |
| Hartley 2009 (4) | 11.33 | 0.19 | 157 | 11.79 | 0.36 | 42 | 3.1% | -1.94 [-2.34, -1.55] | |
| Lord 1982 | 48.1 | 20.78 | 384 | 41.79 | 21.22 | 91 | 3.5% | 0.30 [0.07, 0.53] | |
| McLennan 1993 | 8.87 | 0.7 | 21 | 7.69 | 0.74 | 21 | 2.2% | 1.61 [0.90, 2.31] | |
| Tsai 1983 Subtotal (95% CI) | 41.47 | 24.03 | 52 791 | 30.53 | 22.47 | 23 308 | 2.8% 22.4% | 0.46 [-0.04, 0.96] -0.05 [-0.72, 0.62] | • |
| Heterogeneity: Tau ² = Test for overall effect: . | | | | = 7 (P < | 0.0000′ | 1); l² = l | 95% | | |
| 1.1.3 Children | | | | | | | | | |
| Auyeung 2007 | 21.7 | 4.8 | 156 | 21.8 | 6.2 | 36 | 3.2% | -0.02 [-0.38, 0.34] | + |
| Auyeung 2007 Auyeung 2007 | 21.9 | 5.1 | 312 | 23.4 | 4.4 | 36 | 3.2% | -0.30 [-0.64, 0.05] | |
| Banach 2009 | -60.82 | | 103 | -58.98 | | 47 | 3.2% | -0.10 [-0.44, 0.25] | - |
| Banach 2009 Banach 2009 | -54.18 | | 103 | | 15.67 | 47 | 3.2% | | _ |
| | | | | | | | | | 1 |
| Banach 2009 Banach 2009 | 23.32 | 5.3 | 144 | 24 | 4.1 | 50 | 3.3% | -0.13 [-0.46, 0.19] | 1 |
| Banach 2009 | 23.39 | 5.08 | 106 | 23.06 | 4.61 | 48 | 3.2% | 0.07 [-0.27, 0.41] | T |
| Dworzynski 2012 | 6.83 | 2.73 | 129 | 6.68 | 2.63 | 22 | 2.9% | 0.05 [-0.40, 0.51] | <u> </u> |
| Holtmann 2007 | 9.5 | 2 | 23 | 9.6 | 2.9 | 23 | 2.6% | -0.04 [-0.62, 0.54] | |
| Holtmann 2007 | 23.3 | 5.6 | 23 | 23.4 | 6.8 | 23 | 2.6% | -0.02 [-0.59, 0.56] | |
| Mandy 2011 | 35.18 | 19.52 | 154 | 31.45 | 24.02 | 35 | 3.1% | 0.18 [-0.19, 0.55] | <u>+</u> |
| Mandy 2011 | 15.53 | 3.51 | 273 | 14.8 | 3.44 | 52 | 3.3% | 0.21 [-0.09, 0.51] | |
| Park 2012 | 10.25 | 3.83 | 91 | 8.55 | 4.43 | 20 | 2.8% | 0.43 [-0.06, 0.92] | |
| Spiker 2001 | 34.5 | 6.8 | 222 | 34.8 | 7.2 | 66 | 3.4% | -0.04 [-0.32, 0.23] | + |
| Volkmar 1993 | 63.1 | 16.2 | 58 | 56.8 | 19.9 | 16 | 2.6% | 0.37 [-0.19, 0.92] | + |
| Volkmar 1993 Subtotal (95% CI) | 36.5 | 17.4 | 156 2053 | 34.3 | 16.1 | 43 564 | 3.2% 45.8% | 0.13 [-0.21, 0.47] 0.02 [-0.08, 0.11] | + |
| Heterogeneity: Tau ² = Test for overall effect 1.1.4 Adolescents | | | | 14 (P = | 0.53); P | ²= 0% | | | |
| Baron-Cohen 2006 | 8.2 | 1.8 | 63 | 7.3 | 2 | 16 | 2.6% | 0.48 [-0.07, 1.04] | <u> </u> |
| Baron-Cohen 2006 | 7.4 | 1.0 | 38 | 8.8 | 1.4 | 14 | 2.0% | -0.85 [-1.48, -0.21] | |
| Bolte 2011 | 23.3 | 5.9 | 35 | 23.1 | 7.1 | 21 | 2.4% | 0.03 [-0.51, 0.57] | |
| Bolte 2011 | 4.8 | 1.8 | 35 | 5.1 | 1.5 | 21 | 2.7% | | _ |
| McLennan 1993 | 4.0 8.66 | 0.63 | 21 | 9.65 | 0.69 | 21 | 2.7% | -0.17 [-0.72, 0.37] -1.47 [-2.16, -0.78] |] |
| Solomon 2011 | 7.3 | 2.49 | 20 | 9.00 7.8 | 2.35 | 20 | 2.3% | | |
| Solomon 2011 | 7.3 104.6 | | | 103.85 | | 20 20 | 2.4% 2.4% | -0.20 [-0.82, 0.42] 0.02 [-0.60, 0.64] | |
| Subtotal (95% CI) | 104.0 | 02.04 | 232 | 100.00 | 21.04 | 133 | 17.4% | -0.29 [-0.74, 0.16] | • |
| Heterogeneity: Tau ² = 1 | 0.28° Ch | F= 24 (| | 6(P = 0) | 0005). | | | | • |
| Test for overall effect: 2 | | | | - ₁ , - 0. | | | | | |
| 1.1.5 Adults | | | | | | | | | |
| Baron-Cohen 2001 | 7.4 | 2 | 45 | 7.9 | 1.4 | 13 | 2.4% | -0.26 [-0.88, 0.36] | -+ |
| Lai 2011 | 18 | 5 | 33 | 16.9 | 4.8 | 29 | 2.8% | 0.22 [-0.28, 0.72] | + |
| Lai 2011 | 5 | 7.97 | 33 | 3 | 7.73 | 29 | 2.8% | 0.25 [-0.25, 0.75] | † - - |
| Sipes 2011 | 12.45 | 7.97 | 73 | 12.37 | 7.73 | 26 | 2.9% | 0.01 [-0.44, 0.46] | + |
| Sipes 2011 | 19.74 | 7.97 | 221 | 18.19 | 7.73 | 70 | 3.4% | 0.20 [-0.07, 0.46] | t- |
| Subtotal (95% Cl) Heterogeneity: Tau² = I | | | | l (P = 0.6 | 6); I²= | 167 0% | 14.3% | 0.13 [-0.05, 0.32] | Ť |
| Test for overall effect: 2 | ∠ = 1.43 | (P = 0.1 | | | | | | | |
| T-1-1 (0C0/ ON | | | 3481 | | | 1172 | 100.0% | -0.04 [-0.20, 0.13] | · · · • · · |
| Total (95% CI) | | | | | | | | | |
| Heterogeneity: Tau ² = 1 | 0.19; Ch | r = 175 | .50, df = | = 34 (P < | 0.0000 | 01); I ^z = | 81% | | -4 -2 0 2 |
| | Z = 0.44 | (P = 0.6 | 66) | | | | | | -4 -2 0 2 Female Male |

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Fig. 2 Forest plot social behavior

Data Selection and Extraction

The following information was extracted from the articles: (1) sample size, (2) gender distribution, (3) age, (4) autism diagnostic criteria used, (5) test instrument used, (6) scorer (for example, self-report, parental report, observer report),

and (7) test scores for the impairments investigated. The latter data were entered into Review Manager 5.1. The main characteristics and results of the included studies are presented in Appendix 1 in ESM. In total, the analysis included 4,195 patients with an ASD, 3,207 males and 988 females. Some participants were included in more than one

| | | Male | | F | emale | | | Std. Mean Difference | Std. Mean Difference |
|--|----------------------|--------------------|--------------------------------|------------|------------|-----------|---------------|----------------------|----------------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 2.1.1 Toddlers and p | re-schoo | lers | | | | | | | |
| Carter 2007 (1) | -13.6 | 4.8 | 21 | -15.3 | 4.7 | 67 | 3.1% | 0.36 [-0.14, 0.85] | |
| Carter 2007 (2) | 10.8 | 2.4 | 61 | 11 | 2.6 | 21 | 3.1% | -0.08 [-0.58, 0.42] | |
| Carter 2007 (3) | 4.3 | 1.5 | 68 | 4.8 | 1.6 | 22 | 3.1% | -0.33 [-0.81, 0.16] | |
| Hartley 2009 (4) | 6.35 | 0.14 | 157 | 7.02 | 0.26 | 42 | 3.1% | -3.88 [-4.39, -3.37] | |
| Andersson 2012 | 73.9 | 10.7 | 20 | 80.7 | 16.4 | 20 | 2.9% | -0.48 [-1.11, 0.15] | + |
| McLennan 1993 (5) | 6.66 | 0.55 | 21 | 5.97 | 0.6 | 21 | 2.8% | 1.18 [0.52, 1.84] | |
| Subtotal (95% CI) | | | 348 | E (10) | | 193 | 18.1% | -0.54 [-1.94, 0.86] | |
| Heterogeneity: Tau² = Test for overall effect: | | | | = 5 (P < | 0.0000 | 1); | 98% | | |
| 2.1.3 Children | | | | | | | | | |
| Spiker 2001 | 0 | 0 | 0 | 0 | 0 | 0 | | Not estimable | |
| Auyeung 2007 | 24.4 | 4 | 312 | 24.9 | 4.2 | 36 | 3.4% | -0.12 [-0.47, 0.22] | |
| Auyeung 2007 | 24 | 3.9 | 156 | 23.5 | 5 | 36 | 3.3% | 0.12 [-0.24, 0.48] | + |
| Dworzynski 2012 | 7.96 | 2.34 | 129 | 7.5 | 2.77 | 22 | 3.2% | 0.19 [-0.26, 0.64] | +- |
| Park 2012 | 22.31 | 6.16 | 91 | 17.75 | 8.2 | 20 | 3.1% | 0.69 [0.20, 1.18] | |
| Banach 2009 | -61.63 | 28.18 | 103 | -51.49 | 21.92 | 47 | 3.4% | -0.38 [-0.73, -0.03] | |
| Banach 2009 | 17.18 | 4.52 | 144 | 15.58 | 4.04 | 50 | 3.4% | 0.36 [0.04, 0.69] | |
| Banach 2009 | 14.74 | 4.01 | 106 | 15.19 | 4.99 | 48 | 3.4% | -0.10 [-0.44, 0.24] | + |
| Banach 2009 | -63.46 | | 103 | | 22.18 | 47 | 3.4% | 0.04 [-0.31, 0.38] | + |
| Mandy 2011 | 24.46 | | 154 | 21.27 | 20.26 | 35 | 3.3% | 0.18 [-0.19, 0.55] | + |
| Mandy 2011 | 13.87 | 3.58 | 273 | 13.6 | 3.75 | 52 | 3.4% | 0.07 [-0.22, 0.37] | + |
| Volkmar 1993 | 68.3 | 24.7 | 58 | 61.1 | 26.1 | 16 | 3.0% | 0.29 [-0.27, 0.84] | + |
| Volkmar 1993 | 37.5 | 19.8 | 156 | 34.2 | 15.6 | 43 | 3.4% | 0.17 [-0.16, 0.51] | <u>+</u> |
| Holtmann 2007 | 18.3 | 4.1 | 23 | 16.7 | 4.9 | 23 | 3.0% | 0.35 [-0.23, 0.93] | |
| Holtmann 2007 | 5.2 | 1.4 | 23 | 5.4 | 1.8 | 23 | 3.0% | -0.12 [-0.70, 0.46] | - T |
| Subtotal (95% CI) | 0.00.06 | 7 20 | 1831 | 40.00 | 0.000.1 | 498 | 45.5% | 0.10 [-0.03, 0.23] | t t |
| Heterogeneity: Tau² = | | | | 13(P= | 0.08), 1 | -= 319 | D | | |
| Test for overall effect: | Z = 1.48 | (P = 0. | 14) | | | | | | |
| 2.1.4 Adolescents | | | | | | | | | |
| Solomon 2011 | 3.75 | 2.07 | 20 | 2.95 | 0.94 | 20 | 2.9% | 0.49 [-0.14, 1.12] | + |
| Baron-Cohen 2006 | 8.1 | 1.5 | 63 | 7.6 | 1.6 | 16 | 3.0% | 0.33 [-0.23, 0.88] | |
| Baron-Cohen 2006 | 7.9 | 1.6 | 38 | 9 | 1.4 | 14 | 2.9% | -0.70 [-1.33, -0.07] | |
| Bolte 2011 | 8.9 | 3.4 | 35 | 9.3 | 3.6 | 21 | 3.0% | -0.11 [-0.65, 0.43] | -+ |
| Bolte 2011 | 16.9 | 5.8 | 35 | 17.3 | 4.8 | 21 | 3.0% | -0.07 [-0.61, 0.47] | - |
| McLennan 1993 | 7.65 | 0.81 | 21 | 7.78 | 0.73 | 21 | 2.9% | -0.17 [-0.77, 0.44] | -+ |
| McLennan 1993 Subtetel (95% CI) | 3 | 0.7 | 21 233 | 2.88 | 0.68 | 21 134 | 2.9% | 0.17 [-0.44, 0.78] | T |
| Subtotal (95% Cl) | 0.05 05 | z _ 0 0 | | s/D = 0 | 1 (2) - 12 | | 20.6% | -0.01 [-0.28, 0.27] | Ţ |
| Heterogeneity: Tau² = Test for overall effect: | | | | 5 (P = 0.1 | 10), h= | 30% | | | |
| | ∠ - 0.04 | (r = 0. | 57) | | | | | | |
| 2.1.5 Adults | | | | | yan a- | 1210-024 | _ | | |
| Baron-Cohen 2001 | 7.2 | 2 | 45 | 7.3 | 2.1 | 13 | 2.9% | -0.05 [-0.67, 0.57] | - |
| Lai 2011 | 15.2 | 3.5 | 33 | 13.6 | 4.4 | 29 | 3.1% | 0.40 [-0.10, 0.90] | <u>†</u> – |
| Lai 2011 | 3 | 6.59 | 33 | 1 | 6.62 | 29 | 3.1% | 0.30 [-0.20, 0.80] | 1- |
| Pinoo 2011 | 11.67 | 6.59 | 221 | 11.26 | 6.62 | 70 | 3.5% | 0.06 [-0.21, 0.33] | Ť |
| Sipes 2011 | 9.92 | 6.59 | 73 | 9.81 | 6.62 | 26 | 3.2% | 0.02 [-0.43, 0.46] | $\overline{\mathbf{T}}$ |
| Sipes 2011 | | | 405 | | | 167 | 15.7% | 0.12 [-0.06, 0.31] | Ţ |
| Sipes 2011 Subtotal (95% CI) | | | | | K 711 분 - | 11% | | | |
| Sipes 2011 | | | | ŧ (Ρ = υ. | 07), 1 - | | | | |
| Sipes 2011 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: | | | 20) | + (P = U. | 07), 1 - | | 100.0% | -0.03 [-0.26. 0.21] | |
| Sipes 2011 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) | Z = 1.29 | (P = 0. | 20) 2817 | | | 992 | 100.0% | -0.03 [-0.26, 0.21] | • |
| Sipes 2011 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: | Z = 1.29 0.39; Ch | (P = 0. F = 274 | 20) 2817 I.10, df | | | 992 | | -0.03 [-0.26, 0.21] | -4 -2 0 2 4 Female Male |

Fig. 3 Forest plot communication

analysis of core symptoms because symptom severity was assessed with different test instruments. Thus for social behavior, 4,783 test scores for males and 1,277 test scores for females were analyzed; for communication, 2,781 and 992 test scores, respectively; and for repetitive and stereotyped behaviors, 2,093 and 781 test scores, respectively. Post-hoc analyses showed that the multiple inclusions of some participants did not affect the results.

Data Analysis

Data were standardized using the standardized mean difference (SMD), to account for the use of different instruments, such as the Vineland Adaptive Behavior Scales (Sparrow et al. 1984), Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al. 2000), Autismspectrum quotient (Baron-Cohen et al. 2001) and Autism diagnostic interview-revised (ADI-R) (Le Couteur et al. 1989) The SMD and 95 % CI were calculated using Review Manager 5.1. If no standard deviation (SD) was provided (Sipes et al. 2011), the mean SD of all studies was used as an approximation. A SMD above zero indicates that males are more affected and a SMD below zero indicates that females are more affected.

Heterogeneity was calculated using Chi squared (χ^2) and I-squared (I^2) tests. If the mean scores of different samples differ, then the samples may originate from different populations (heterogeneity). Heterogeneity was found for social impairments ($I^2 = 81 \%$), communication impairments $(I^2 = 89 \%)$, and repetitive and stereotyped behaviors $(I^2 = 91 \%)$. This necessitated the use of random effects models, which correct for heterogeneity, to test for gender differences. To determine whether age was a cause of heterogeneity, a stratified sensitivity analysis based on age was performed, using the following age strata: toddlers (0-3 years), preschoolers (0-6 years), children (6-12 years), adolescents (12-18 years), and adults (18 years and older). 'Toddlers' was selected as age category because of evidence that there are gender differences in symptoms in toddlerhood (Rivet and Matson 2011a). Further, sensitivity analyses were performed post hoc to evaluate whether the choice of test instrument and the intelligence quotient (IO) and the development quotient (DQ) of the participants affected the results.

Instruments Used to Measure Core Symptoms

Fifteen different instruments were used to score symptoms of ASD; two instruments had two versions (i.e., the ADI and ADI-R, the ADOS and ADOS-G). The ADOS and ADI-R were used most frequently (23.9 and 15.9 %, respectively). All instruments were based on parent report, except for ADOS and ADOS-G (observer report) and autism quotient (patient report) (Appendix 2 in ESM). In total, 14 instruments assessed current symptoms and 4 articles assessed (partial) retrospective symptoms (Appendix 2 in ESM).

Results

Meta-analysis

To examine whether there are gender differences in the core symptoms of ASD, differences in symptom severity between males and females were determined overall and then in the specific age groups. Overall, females with ASD exhibited less severe symptoms of repetitive and stereo-typed behaviors than did males with ASD (SMD 0.51, 95 % CI 0.22–0.80) (Fig. 4), but there were no gender differences in social behavior (SMD 0.4, 95 % CI

0.20–0.13) or communication (SMD 0.03, 95 % CI 0.26–0.21). The gender difference in the severity of repetitive and stereotyped impairments was seen from 6 years onwards but not in the younger children (Table 1). Thus, female children, adolescents, and young adults had less severe symptoms of repetitive and stereotyped behaviors than males of the same age.

Analysis indicated that the data heterogeneity was mainly due to the large variance in the toddler group (see Figs. 2, 3, 4), because exclusion of the toddler group drastically reduced heterogeneity in all three core domains (to $I^2 = 60 \% I^2 = 24 \%$ and $I^2 = 61 \%$, respectively). Funnel plot analysis identified three outliers (Hartley and Sikora 2009; McLennan et al. 1993; Sipes et al. 2011), and these studies involved the toddlers responsible for the data heterogeneity. However, there were no valid reasons to exclude these studies, based on research method, sample size, reproducibility, and possible bias. Thus, the variance in gender differences was largest at a very young age. Lastly, the results of the studies that used the ADI-R and the ADOS, the most frequently used instruments, were compared. Heterogeneity was low when only studies using the ADI-R and the ADOS were included (social $I^2 = 0$ %, communication $I^2 = 39$ %, repetitive and stereotyped behavior $I^2 = 0$ %), indicating that the results of these studies were homogeneous, but that the other studies that used other instruments might have contributed to heterogeneity. Furthermore, a post hoc sensitivity analysis was conducted to check whether DQ and IQ influence the results. Only one study (Sipes et al. 2011) included patients with a low DQ, excluding these results did not change the SMD of social behavior (-0.05, 95 % CI -0.22 to 0.13), communication (-0.03, 95 % CI -0.28 to 0.22) or repetitive and stereotyped behavior (0.54, 95 % CI 0.23-0.85). Two studies included patients with an IO below 70 (Tsai and Beisler 1983; Volkmar et al. 1993). When these results are excluded no change in SMD of social behavior (-0.07,95 % CI -0.25 to 0.11) or communication (-0.04, 95 % CI -0.29 to 0.21) was observed. Repetitive and stereotyped behavior was not measured in both studies.

Discussion

This meta-analysis of 20 studies investigated gender differences in ASD symptoms. Overall, there were few differences in symptom severity between males and females. Males and females with ASD showed similar symptom severity on communication and social behavior, but girls showed less restricted interests and behaviors and stereotypes than boys.

These results can be discussed from three perspectives. The first perspective hypothesizes that girls with ASD truly

| | | Male | | | emale | | | Std. Mean Difference | Std. Mean Difference |
|--|-----------|------------------|----------|------------|-------------------|-------------------|--------|----------------------|---------------------------------------|
| Study or Subgroup | Mean | | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% Cl |
| 3.1.1 Toddlers and p | | | | | | | | | |
| Carter 2007 (1) | 4.5 | 2 | 68 | 4.1 | 2.3 | 22 | 4.5% | 0.19 [-0.29, 0.67] | 1 |
| Carter 2007 (2) | 4 | 1.5 | 68 | 3.8 | 1.8 | 22 | 4.5% | 0.13 [-0.36, 0.61] | 7- |
| Hartley 2009 (3) | 3.48 | 0.13 | 157 | 2.81 | 0.25 | 42 | 4.4% | 4.11 [3.58, 4.64] | |
| Lai 2011 (4) | 5.7 | 2.5 | 33 | 4.5 | 2 | 29 | 4.5% | 0.52 [0.01, 1.03] | |
| Lai 2011 | 1 | 3.49 | 33 | 0 | 3.07 | 29 | 4.5% | 0.30 [-0.20, 0.80] | - |
| Subtotal (95% CI) | | | 359 | | | 144 | 22.4% | 1.05 [-0.39, 2.49] | |
| Heterogeneity: Tau ² = | 2.63; Ch | 1 F = 169 | 5.87, df | 7 = 4 (P · | < 0.000 | 01); I ² = | : 98% | | |
| Test for overall effect: | Z = 1.42 | (P = 0. | 15) | | | | | | |
| 3.1.3 Children | | | | | | | | | |
| Banach 2009 | 7.22 | 2.35 | 144 | 6.62 | 2.1 | 50 | 4.8% | 0.26 [-0.06, 0.58] | |
| Banach 2009 | 6.18 | 2.33 | 106 | 5.75 | 2.41 | 48 | 4.8% | 0.18 [-0.16, 0.52] | <u>+-</u> |
| Dworzynski 2012 | 4.48 | 1.7 | 129 | 4.23 | 1.66 | 22 | 4.6% | 0.15 [-0.31, 0.60] | _ |
| Holtmann 2007 | 4.40 | 3.1 | 23 | 4.23 | 3.1 | 23 | 4.0% | 0.10 [-0.48, 0.67] | <u> </u> |
| Mandy 2011 | 4.43 | 2.6 | 273 | 3.58 | 2.66 | 52 | 4.3% | 0.32 [0.03, 0.62] | L |
| Mandy 2011 Mandy 2011 | 22.69 | | 154 | 14.44 | | 35 | 4.7% | 0.38 [0.02, 0.75] | |
| Park 2012 | 5.48 | 22.14 | 91 | 4.1 | 2.51 | 20 | 4.7% | 0.50 [0.02, 0.75] | |
| Spiker 2001 | 14.4 | 4.4 | 222 | 14.6 | 5.2 | 20 66 | 4.9% | -0.04 [-0.32, 0.23] | 4 |
| Worley 2010 | 4.52 | 3.48 | 44 | 5.13 | 3.61 | 26 | 4.5% | -0.17 [-0.66, 0.31] | |
| Subtotal (95% CI) | 4.02 | J.40 | 1186 | 0.15 | 3.01 | 342 | 4.0% | 0.19 [0.06, 0.32] | • |
| Heterogeneity: Tau ² = Test for overall effect: | | | • | 8 (P = 0 | l.38); I ² | = 7% | | | |
| 3.1.4 Adolescents | | | | | | | | | |
| Bolte 2011 | 3.1 | 1.3 | 35 | 2.3 | 1.1 | 21 | 4.4% | 0.64 [0.09, 1.20] | |
| McLennan 1993 | 8.27 | 0.74 | 21 | 7.84 | 0.75 | 21 | 4.2% | 0.57 [-0.05, 1.18] | — — |
| Solomon 2011 | 5 | 3.16 | 20 | 2.47 | 1.77 | 15 | 4.0% | 0.93 [0.22, 1.64] | |
| Subtotal (95% CI) | | | 76 | | | 57 | 12.5% | 0.69 [0.33, 1.05] | ◆ |
| Heterogeneity: Tau ² = Test for overall effect: | | | • | 2 (P = 0 | l.73); I² | = 0% | | | |
| | 2 - J. (3 | ν = 0. | 5552) | | | | | | |
| 3.1.5 Adults | | | | | | | | | |
| Sipes 2011 | 12.17 | 3.49 | 221 | 12.37 | 3.12 | 70 | 4.9% | -0.06 [-0.33, 0.21] | + |
| Sipes 2011 | 9.58 | 3.49 | 73 | 5.07 | 3.12 | 26 | 4.5% | 1.32 [0.83, 1.80] | |
| Lai 2011 | 5.7 | 2.5 | 33 | 4.5 | 2 | 29 | 4.5% | 0.52 [0.01, 1.03] | <u>├</u> |
| Lai 2011 | 1 | 3.49 | 33 | 0 | 3.07 | 29 | 4.5% | 0.30 [-0.20, 0.80] | + |
| Hattier 2011 | 3.221 | 3.012 | - 77 | 2.079 | 2.623 | 63 | 4.8% | 0.40 [0.06, 0.74] | <u> </u> |
| Subtotal (95% CI) | | | 437 | | | 217 | 23.1% | 0.47 [0.03, 0.92] | ◆ |
| Heterogeneity: Tau ² = Test for overall effect: | • | | • | = 4 (P ≺ | 0.0001 |); I z = 8 | 4% | | |
| Total (95% CI) | | | 2058 | | | 760 | 100.0% | 0.51 [0.21, 0.81] | |
| . , | 0.47.04 | | | - 04 /5 | - 0.00 | | | 0.01 [0.21, 0.01] | , , , , , , , , , , , , , , , , , , , |
| Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe | Z = 3.32 | (P = 0. | (0009) | | | | | | -4 -2 0 2 4 Female Male |

Fig. 4 Forest plot repetitive and stereotyped behavior

| Age | Social SMD (95 % CI) | Communication SMD (95 % CI) | Repetitive and stereotyped behaviour SMD (95 % CI) |
|-------|----------------------------------|----------------------------------|--|
| 0–6 | -0.05 (-0.72 to 0.62) p = 0.89 | -0.54 (-1.94 to 0.86) $p = 0.45$ | 1.05 (-0.39 to 2.49) $p = 0.15$ |
| 6-12 | 0.02 (-0.08 to 0.11) $p = 0.74$ | 0.10 (-0.03 to 0.23) $p = 0.14$ | 0.19 (0.06 - 0.32) * p = 0.004 |
| 12-18 | -0.29 (-0.74 to 0.16) p = 0.21 | -0.01 (-0.28 to 0.27) p = 0.97 | 0.64 (0.34-0.94) * p < 0.0001 |
| >18 | 0.13 (-0.05 to 0.32) $p = 0.15$ | 0.12 (-0.06 to 0.31) p = 0.20 | 0.47 (0.03–0.92) $*p = 0.04$ |

Table 1 Gender differences in age categories, * p < 0.05

show less restricted interests and behaviors and stereotypes than boys. In other words, females present another autistic phenotype than males. This dimorphic phenotype may be the result of sexually dimorphic underlying causal mechanisms. ASD risk is likely to be multifactorial, with many different genetic variants and environmental factors contributing to liability. Sex chromosomal gene dosage and sex hormone levels may be involved. Biological theories for the sex difference in ASD prevalence propose that females have a higher threshold for reaching affectation status than males and genetic studies hypothesize that females with ASD are likely to be carrying a higher heritable load than affected males (Werling and Geschwind 2013). But so far, the male-skewed bias towards restricted interests and behaviors and stereotypes has not been precisely elucidated by biological theories. The underlying mechanisms are yet to be identified.

If this perspective of a sexually dimorphic phenotype would be true, the formal diagnostic criteria of ASD could be unjustly biased towards males. It should be borne in mind that the diagnostic criteria were formulated on basis of behaviors and features found in boys. As early as 1,943, Kanner described ASD as being predominantly found in severely impaired boys with comorbid mild intellectual disability. It has recently indeed been recognized that the behavioral phenotype of ASD is different in girls and women than in boys and men, whereas diagnostic criteria are based on the symptoms seen in boys (Kirkovski et al. 2013). Dworzynski and her colleagues (2012) recognized this difference and hypothesized that an unknown mechanism helps girls with ASD to cope in such a way that their symptoms do not reach the diagnostic threshold. Thus it appears that there is a male bias in the clinical diagnosis of ASD. The specific features that accompany girls with ASD and that differ from boys are increasingly recognized. Girls with ASD have better imaginative play than affected boys (Knickmeyer et al. 2008), show more interest in social relations (Attwood 2007) and may have more socially accepted special interests (horses, dolls, pop stars), characteristics which might mask their ASD (Kopp and Gillberg 1992). Further, parents report that their daughters with ASD have problems establishing and maintaining adequate peer relationships (Holtmann et al. 2007). In an effort to facilitate the screening and detection of ASD in girls, a new screening tool 'The autism spectrum screening questionnaire-revised extended version (ASSQ-REV)' is in development (Kopp and Gillberg 2011). The ASSQ-REV is sensitive to female features of ASD.

A second perspective on the results of the present metaanalysis incorporates the influence of intellectual disability. It is known that if ASD is accompanied by intellectual disability the female/male ratio is 1:2. Furthermore, in ASD patients without intellectual disability, males are over represented 9-10:1(Fombonne 2009; Banach et al. 2009; Lord et al. 1982; Tsai et al. 1981; Volkmar et al. 1993). This is relevant in light of the present results, because in the included studies, female ASD patients with low IQ may be overrepresented compared to male ASD patients with low IQ. Moreover restricted interests and behaviors and stereotypes are not only a core symptom of ASD, but also highly related to general intellectual disability (Matson et al. 1997, 2010; Wilkins and Matson 2009). More over, restricted interests and behaviors and stereotypes are not specific for ASD and are also seen in children with an intellectual disability (Muthugovindan and Singer 2009). A

consequence could be that a part of the females who are included in this meta-analysis show problems on these core symptoms primarily due to the intellectual disability, not to ASD. If that would be true, intellectual disability could be considered a confounding factor, leading to an overestimation of problems in the domain of communication, social behavior and restricted interests and behaviors and stereotypes, especially in females. Regretfully, we were not able to include intellectual disability as a confounder in the meta-analysis due to lack of specific data in the original articles. The only means we had to examine the potential influence of IQ or DQ on the present meta-analysis was a sensitivity analysis, in which the exclusion of studies with patients with low IQ or DQ did not change the final results. This indicates that the results of this meta-analysis were robust to the potential influence of IQ or DQ.

Another possibility is that intellectual disability is not a real but an artefactual confounding factor. That would be the case if in the true ASD population, IQ levels of males and females would be similar, but in the same time high functioning females with ASD are less likely to be referred and diagnosed than high functioning males with ASD. Indeed, recent studies support the hypothesis that ASD is only diagnosed in females presenting with classic symptoms and intellectual disability, with the diagnosis being missed in females with a higher IQ or with less extreme stereotypies (Baird et al. 2011; Begeer et al. 2013). Intellectual disability as an artefactual confounding factor may have influenced the studies that were included in the present meta-analysis. The studies that were included in the present meta-analysis may have missed the females with a higher IQ. If that were true, the present meta-analysis would in contrast overestimate problems in females in the domain of communication, social behavior and restricted interests and behaviors and stereotypes.

A third perspective on the results of the present metaanalysis considers the ascertainment bias.

Several studies have shown that girls with milder symptoms and a normal IQ tend to be diagnosed at a later age than boys (Kopp and Gillberg 1992; Goin-Kochel et al. 2006; Siklos and Kerns 2007; Begeer et al. 2013; Russell et al. 2011; Giarelli et al. 2010) or are misdiagnosed (Kopp and Gillberg 1992; Nilsson et al. 1999; Begeer et al. 2013). It has been argued that girls with ASD show different and less severe social and communicative impairments than boys do, and parents, relatives, and health professionals may consider these impairments as being due to shyness or anxiety. This misinterpretation of symptoms could lead to misreferral and misdiagnosis (Holtmann et al. 2007). Autistic girls might be diagnosed as having anxiety disorder, avoidant personality disorder, etc., which means that ASD is potentially underdiagnosed in girls and women (Mandy et al. 2011). Moreover, girls with "internalizing" problems are referred to professionals less often than boys with similar problems, probably because these behaviors are considered normal in females (Rucklidge 2010). However, once the diagnosis has been established, studies have shown that there are no differences in the type or severity of comorbid conditions accompanying ASD in girls and boys (Lugnegård et al. 2011). This indicates that the ascertainment bias is a real problem in the identification of females with ASD. ASD may show a bimodal distribution in females, with there being a group of severely impaired girls in whom the disorder is diagnosed and a group of girls with milder symptoms in whom the disorder is not or only later diagnosed.

The ascertainment bias may also have affected the present meta-analysis. The studies that were included in the present meta-analysis could have missed these high functioning girls. If that is true, the conclusion that females and males do not differ on communication a social behavior would be false, and only an artifact of the missing of a specific group of girls. As a consequence, the true conclusion would then be that females with ASD show better communication and social behavior than males with ASD.

A final thought from the perspective of the ascertainment bias is that it may not only affect referral and diagnosis of females, but also of males. The main result of the present meta-analysis is that boys with ASD show more restricted interests and behaviors and stereotypes than girls with ASD. It is important to realize that restricted interests and behaviors and stereotypes are not specific for ASD and are seen in both children with an intellectual disability and severe deprivation and in typically developing children with normal intelligence (Muthugovindan and Singer 2009). It should be considered that there might be falsepositive ASDs among the patients with restricted interests and behaviors and stereotypes. This may primarily be the case in boys. More research on this issue is warranted.

In sum the main result of the present meta-analysis is that females with ASD show less repetitive and stereotyped behavior than males, whereas there appear to be no gender differences in the domain of social behavior and communication. These findings imply that according to the studies analyzed to date there are no major differences in the core symptoms of ASD between males and females according to the defining criteria thus far.

But in the discussion we raised the question why men would have more stereotype movements. This is biologically yet unclear and definitely needs more investigation. Other possible confounding factors are intellectual disability and the ascertainment bias. So it could be that many females with normal to high intelligence could be overlooked or misdiagnosed because they do not present the male phenotype of autism. Therefore more research is will be needed with instruments better adapted or more fit to help defining and identifying a female phenotype of ASD.

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