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Male to female ratios in autism spectrum disorders by age, intellectual disability and attention-deficit/hyperactivity disorder

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Abstract

Objective: To examine the gender distribution in ASD in adults compared with children and the impact of comorbid intellectual disability (ID) and attention-deficit/hyperactivity disorder (ADHD) on the male to female ratio (MFR).

Methods: We estimated the MFR and the male prevalence ratio (PR) for ASD in adults and children using the Medical Birth Registry of Norway, including all individuals born during 1967–2011. We examined variation with age, comorbid ID and ADHD as defined by diagnoses in the Norwegian Patient Registry during 2008–2015 and/or a dispensed prescription for ADHD medication.

Results: The sample included 1,701,206 adults and 804,146 children, including 8,995 (0.5%) adults and 8,056 (1.0%) children with ASD, 53,822 (3.2%) adults and 26,967 (3.4%) children with ADHD and 9,178 (0.5%) adults and 5,038 (0.6%) children with ID. The MFR for ASD was 3.67 in children and 2.57 in adults, corresponding to a male PR in ASD of 1.54 (95% CI 1.53–1.56) and 1.41 (1.39–1.24), respectively. Comorbid ID decreased the MFR and the male PR in both adults and children, whereas comorbid ADHD significantly increased the male PR in children. The MFR and the population prevalence of ASD, ADHD and ID decreased from children to younger adults and yet further to older adults.

Conclusion: We found a lower MFR and male PR in adults than in children. Findings suggest the strong male predominance seen in childhood/clinical studies of ASD diminishes in adult samples, possibly reflecting the influence of non-aetiological factors such as later diagnosis in females, diagnostic biases and diagnostic trends.

KEYWORDS

attention deficit disorder with hyperactivity, autism spectrum disorder, intellectual disability, male to female ratio, prevalence

1 | INTRODUCTION

Male predominance is a consistent finding in studies of autism spectrum disorder (ASD), with male to female ratios (MFR) or male: female odds ratio (MFOR; depending on type of study) as high as 4.2–4.3, also in recent studies.[1,2] This strong male predominance has fueled various causal hypotheses of ASD, eg testosterone exposure in utero, the extreme male brain theory[3] and a female protective effect in ASD.[4] The idea of a female protective effect in ASD comes from the finding that the MFR/MFOR seems to increase with level of ability. In samples of individuals with predominantly low ability (intelligence quotient (IQ) below 70), the MFR has been reported as low as 1.8,[5] rising to 4.2 in samples with a majority within the normal range of ability.[1] The interaction between gender difference and ability has been interpreted as females possibly requiring a stronger neurodevelopmental impact to develop ASD. However, there is evidence that some of the male predominance in ASD could be a male ascertainment bias.[1] Studies have shown that females to a larger degree are not being detected and diagnosed with ASD despite large difficulties.[6-9] Under detection of female ASD could be eg gender differences in the clinical presentation of ASD, assessment bias and diagnostic instruments being tailor-made to the male ASD presentation. Girls have different clinical presentations[10] and it has also been shown that diagnostic instruments are not as sensitive to the female phenotype, creating considerably poorer diagnostic precision in females.[11] In line with this, a meta-analysis indicated that the MFR/MFOR in children may be overestimated based on current studies, as studies with lower risk of ascertainment bias had a lower MFOR than studies with a higher risk of ascertainment bias.[1] The same ascertainment bias has been suggested in ADHD, where a lower MFR in adults than in children has been found,[12] possibly caused by later identification and gender barriers to child and adolescent mental health services for girls with ADHD.[13,14] Regarding adult ASD, there are some emerging studies, but we still know little of the natural development of ASD through the life course[15] and even less about the gender distribution in adult ASD. Brugha et al. found an even stronger relationship between the level of ability and gender differences in adult ASD. Using an OR weighted for age, gender, ID and type or residence, they found an OR of 1.35 (95% CI 0.64–2.83) for ASD in males relative to females with moderate to profound intellectual disability (ID) but an OR of 8.97 (95% CI 2.20–36.52) and 8.62 (95% CI 2.2–34.5) in adults with mild ID or borderline/normal intelligence.[16,17] Their large confidence intervals preclude firm conclusions, but the authors hypothesized that the high male OR in adults with normal intelligence could stem partly from assessment bias and difficulties in diagnosing ASD particularly in higher functioning females. In a total population study in the Faroe Island, considerably more females were found in the second assessment, with a MFR of 2.7:1 in their 15–24-year-old sample,[18] which could indicate that the same child-adult gender differences may exist in ASD as found in ADHD. The large differences in the number of females identified in the second vs. the first study in the Faroe Island could be several of the causes mentioned above, eg better identification, increased awareness for female ASD, impairment developing later in females etc.[18] There are thus great discrepancies between the few adult studies that have examined gender and adult ASD, from increased MFR/MFOR to lower MFR/MFOR relative to childhood studies. The cited adult studies included few individuals, and two employed active case-searching methods, producing estimates of MFR and MFOR respectively with very broad confidence intervals and carrying a high risk of ascertainment bias. There is thus a need for larger studies examining the MFR across the lifespan of ASD and how it is influenced by comorbid intellectual disability.

Significant outcomes:

- We found a lower male to female ratio (MFR) for ASD in adults (2.57) than in children (3.67) in the Norwegian Patient Registry.
- We found a decreasing registered prevalence of autism spectrum disorders (ASD) from children to younger adults and further to older adults in the general population.
- The adult prevalence of ASD in the Norwegian Patient Registry (for individuals aged 18–48 years and alive at the time of the registry linkage) was 0.5%.

Limitations:

- Information on autism spectrum disorders (ASD) and comorbid disorders were based on a national patient registry with clinical diagnoses that were not validated in the current study.
- The study was based on the diagnoses of ASD registered in a limited time window from 2008–2015. Individuals diagnosed before 2008 and not in contact with specialized health services in the years 2008–2015 do not appear in the study as cases.
- The study was based on the Medical Birth Registry of Norway (MBRN) which was established in 1967, and therefore only included adults up to age 48.

1.1 | Aims of the study

The main aim of the present study was to estimate the MFR and the male prevalence ratio (PR) in adults compared with children with ASD in a total population and to examine the impact of comorbid ID and/or ADHD. We furthermore examined the variation of the MFR and male PR with age and ASD subtypes to evaluate possible reasons for ASD MFR variation. Being a total population study, PR was used as the adjusted measure of gender ratio estimates rather than MFOR.[19]

2 | MATERIALS AND METHODS

2.1 | Sample

The study population included all individuals born and registered in the Medical Birth Registry of Norway (MBRN), during 1967–2011, who was living in Norway at record linkage in 2015 (n = 2,486,088). Information from three nationwide population-based registries was linked to obtain information on diagnosis and medication: The MBRN, established in 1967,[20] the Norwegian Prescription Database (NorPD), established in 2004[21] and the Norwegian Patient Registry (NPR),[22] with linkable data from 2008. The NorPD registers all medical prescriptions dispensed to individuals from any Norwegian pharmacy and includes the Anatomical Therapeutic Chemical (ATC) Classification System codes. The NPR includes information about diagnoses and interventions given to patients treated in secondary health care, in hospitals and outpatient clinics. Diagnoses are registered by the International Classification of Diseases (ICD), version 10. Record linkage was performed using the national identification number unique to every Norwegian resident. Individuals born before 1967 are not part of the MBRN and could not be included. The study was approved by the Regional Committees for Medical Research Ethics in Norway (2011/2272) and reported according to guidelines suggested by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative.[23]

2.2 | Variables

2.2.1 | Outcome: ASD with and without comorbid ID and/or ADHD

Diagnoses coded by F84 with subcategories (ICD-10) were analysed jointly under the umbrella term autism spectrum disorders (ASD); defined as individuals registered in the NPR (2008–2015) with the following ICD-10 codes: F84.0–84.1+F84.5+F84.8–84.9 (Table 3). We identified individuals with ADHD if they were registered with an ADHD diagnosis (ICD-10 code F90; NPR 2008–2015) and/or having been dispensed a prescription of ADHD medication during 2004–2015 (NorPD). The ADHD medications identified were the central stimulants methylphenidate (N06B A04), racemic amphetamine (N06B A01) and dexamphetamine (N06B A02) and the non-stimulant drug atomoxetine (N06B A09). Lisdexamphetamine (N06B A12) was not included as it was only introduced on the Norwegian market in the fall of 2014. ID was defined as individuals registered in the NPR with any of the ICD-10 codes: F70-79.

Adults were individuals who were 18 years or more by the time of record linkage, ie born before 1998. In sub-analyses, we further divided adults into older (born 1967–1983) and younger (born 1984–1997) adults. The childhood population was defined as individuals aged 4–17 years (born 1998–2011) at linkage in 2015 and was further divided into younger and older children, age 4–10 years and age 11–17 years.

The remaining population included all individuals who had not been dispensed neither an ADHD medication nor had an ASD, an ADHD nor an ID diagnosis, in the NorPD and NPR, respectively. Any individuals diagnosed with ASD, ADHD or ID before 2008 and not in contact with specialist health services in 2008–2015, nor prescribed any ADHD medication in 2004–2015 were included in the remaining adult population since it was not possible to identify their diagnoses.

2.2.2 | Measures and statistical analyses

We analysed the male to female ratio (MFR) for all ASD (including both ADHD and ID) and then split all ASD by ADHD status to analyse the impact of comorbid ADHD on the MFR. We then reran analyses by ID status, to analyse the impact of comorbid ID. We calculated the male prevalence ratio (PR) as the adjusted measure, which corresponds to the percentage increase in males in the clinical population versus the non-clinical population. A PR of 1.4 equals 40% more males than in the population without the studied diagnoses. As diagnostic practices have changed considerably over the studied decades, we present descriptive statistics of the overall registered prevalence of ASD, ADHD and ID and specifically for Asperger syndrome (AS) that was introduced as a diagnosis in 1994.[24] We analysed the MFR in younger (born 1984–1997) and older adults (born 1967–1983) as well as for all children, children aged 4–10 years and aged 11–17 years separately. Finally, we analysed the MFR in the ASD subtypes separately.

We used the STATA command 'binreg' for the calculation of PR with gender as the exposure and with adjustment for birth year (5-year periods, from 1967 to 1997, with 1967–1973 as the reference). Statistical differences were based on evaluation of confidence intervals (CI), using 95% intervals as the range to evaluate significance.

3 | RESULTS

3.1 | Study groups

A total of 1,701,206 adult individuals born during 1967–1997 and living in Norway at linkage in 2015 were included. We identified 8,995 adults with any ASD (0.5%), 53,822 adults with any ADHD (3.2%) and 9,178 adults with any ID (0.5%). There were 5,300 adults with ASD only (0.3%), 49,908 adults with ADHD only (2.9%), 2,512 adults with ADHD+ASD (0.1%) and 1,183 adults with ASD+ID (0.1%) in our study population (no ADHD). Very few had all three disorders, ASD+ADHD+ID, n = 328 (0.2‰), see Table 1. The adult population with no ASD, ADHD nor ID consisted of 1,684,543 individuals, 823,546 (49%) women. The mean age in 2015 for adults (born before 1998) for the ASD only group was 26.2 years, for the ASD+ADHD 24.1 years and the remaining adults 33.1 years.

We identified 804,146 children (391,751 (48.7%) females), born 1998–2011. We identified 8,056 (1.0%) children with any ASD, 26,967 with any ADHD (3.4%) and 5,038 with any ID (0.6%). The number of children with ASD only was 5,459 (0.7%), ADHD only 24,370 (3.0%) and 2,597 had ADHD+ASD (0.3%). Only 357 (0.4‰) had all three disorders (ASD+ADHD+ID) (0.04%). The remaining children with no ASD, ADHD nor ID consisted of 792,314 individuals (388, 409 (49.6%) females).

3.2 | Gender ratios in adults – impact of ADHD and ID

Table 1 and Figure 1 show the MFR and the male prevalence ratio in ASD with and without comorbid ADHD and ID as compared with males in the population without ASD, ADHD and ID (Table 1 and Figure 1). The overall MFR for adult ASD was 2.57 and the PR 1.41 (95% confidence interval (CI) 1.39–1.42). The overall MFR for ASD only (excluding ADHD and ID) was 2.62 with a PR of 1.41 (1.39–1.44). The group with comorbid ADHD but no ID had an MFR of 2.75 with a PR of 1.43 (1.39–1.47). The lowest MFR of 1.93, PR 1.31 (1.25–1.37) was seen in the group with ID and ASD (no ADHD) whereas the highest MFR among adults was found in the group with ASD+ADHD+ID: 3.61, PR 1.52 (1.43–1.62).

3.3 | Older versus younger adults and prevalence trends

The registered prevalence of ASD, ADHD and ID all increased from older (born 1967–1983) to younger (born 1984–1997) adults (Table 2). Figure 2 shows the population prevalence of ASD with and without comorbid ADHD and/or ID in males and females by birth year cohorts (Figure 2). ASD was the diagnosis with the largest change, increasing from 0.2% in adults born 1967–1983 to 0.9% in adults born 1984–1997. The rise was mainly accounted for by increasing prevalence of Asperger syndrome (AS) that was registered almost nine times as often in individuals born in the last 5-year period (1994–1997) compared with the reference birth years (1967–1973) (Figure 3). Older adults with ASD had a lower MFR than younger adults: 2.36, PR 1.38 (1.34–1.42) vs. 2.63, PR 1.41 (1.39–1.43), although with overlapping confidence intervals.

3.4 | Comparison with children

The MFR in the childhood population (4–17 years old) with any ASD of 3.67, PR 1.54 (1.53–1.56) was higher than in adults (Table 1). Similarly, younger children (4–10 years old) had a higher MFR than older (11–17 years old) children, 4.46, PR 1.60 (1.57–1.63) and 3.36, PR 1.52 (1.49–1.54), respectively. In the age group 4–10 years old, the effect of concurrent ID was notable, with an MFR of 2.72, PR 1.26 (1.17–1.35) in ASD with ID compared with 5.05, PR 1.63 (1.60–1.66) for ASD without ID. However, in both age groups (and in the total population of children), the MFRs and the PRs were higher in cases without concurrent ID.

3.5 | Variance in gender ratio according to ASD subtypes

The MFRs for different ASD subtypes (adults and children combined) are shown in Table 3. The highest MFR of 4.49, PR 1.60 (1.57–1.63) was seen for childhood autism without ID and the lowest MFR of 2.25, PR 1.22 (1.15–1.29) was found for pervasive developmental disorder-not otherwise specified (PDD-NOS) with ID (Table 3). The MFR for Asperger syndrome (AS) without ID was 2.98, PR 1.46 (1.45–1.55) (very few individuals overall were diagnosed with AS with ID (Table 3)).

4 | DISCUSSION

We found a lower male to female ratio (MFR) for ASD in adults than in children. The highest MFR was found in

TABLE 1 Male/female ratio (MFR) and male prevalence ratio (PR) in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) with and without intellectual disability (ID) compared with males among individuals without ASD, ADHD and ID, Norway, all born 1967–2011

Group		N (%)	MFR	PR (95% CI)	Comorbid ID, N (%)	MFR	PR (95%CI)	No ID, N (%)	MFR	PR (95%CI)
ADULTS, born 1967–1997										
Reference pop.	M	864,856 (51.1)	1.05	Reference	3,857 (50.3)	1.01	Reference	860,997 (51.1)	1.05	Reference
	F	827,355 (48.9)			3,809 (49.7)			823,546 (48.9)		
Any ASD	M	6,474 (72.0)	2.57	1.41 (1.39–1.42)	1,036 (68.6)	2.18	1.36 (1.30–1.41)	5,438 (72.7)	2.66	1.42 (1.40–1.44)
	F	2,521 (28.0)			475 (31.4)			2,046 (27.3)		
ASD (no ADHD)	M	4,617 (71.2)	2.47	1.39 (1.37–1.41)	779 (65.9)	1.93	1.31 (1.25–1.37)	3,838 (72.4)	2.62	1.41 (1.39–1.44)
	F	1,866 (28.8)			404 (34.2)			1,462 (27.6)		
ASD+ADHD	M	1,857 (73.9)	2.83	1.44 (1.41–1.48)	257 (78.4)	3.61	1.52 (1.43–1.62)	1,600 (73.3)	2.75	1.43 (1.39–1.47)
	F	655 (26.1)			71 (21.7)			584 (26.7)		
ALL CHILDREN, born 1998–2011										
Reference pop.	M	406,063 (51.0)	1.04	Reference	2,158 (57.2)	1.33	Reference	403,905 (51.0)	1.04	Reference
	F	390,027 (49.0)			1,618 (42.9)			388,409 (49.0)		
Any ASD	M	6,332 (78.6)	3.67	1.54 (1.53–1.56)	913 (72.4)	2.62	1.26 (1.21–1.32)	5,419 (79.8)	3.94	1.57 (1.55–1.59)
	F	1,724 (21.4)			349 (27.7)			1,375 (20.2)		
ASD (no ADHD)	M	4,229 (77.5)	3.44	1.52 (1.50–1.54)	650 (71.8)	2.55	1.25 (1.19–1.32)	3,579 (78.6)	3.67	1.54 (1.52–1.57)
	F	1,230 (22.5)			255 (28.2)			975 (21.4)		
ASD+ADHD	M	2,103 (81.0)	4.26	1.59 (1.56–1.62)	263 (73.7)	2.80	1.29 (1.01–1.39)	1,840 (82.1)	4.6	1.62 (1.58–1.65)
	F	494 (19.0)			94 (26.3)			400 (17.9)		
CHILDREN, aged 4–10, born 2005–2011										
Reference pop.	M	209,374 (51.1)	1.05	Reference	738 (58.1)	1.39	Reference	208,636 (51.1)	1.05	Reference
	F	200,104 (48.9)			532 (41.9)			199,572 (48.9)		
Any ASD	M	2,170 (81.7)	4.46	1.60 (1.57–1.63)	337 (73.1)	2.72	1.26 (1.17–1.35)	1,833 (83.5)	5.05	1.63 (1.60–1.66)
	F	487 (18.3)			124 (26.9)			363 (16.5)		
ASD (no ADHD)	M	1,669 (80.9)	4.23	1.58 (1.55–1.62)	272 (72.2)	2.59	1.24 (1.15–1.34)	1,397 (82.8)	4.82	1.62 (1.59–1.66)
	F	395 (19.1)			105 (27.9)			290 (17.2)		
ASD+ADHD	M	501 (84.5)	5.45	1.65 (1.60–1.71)	65 (77.4)	3.42	1.33 (1.17–1.51)	436 (85.7)	5.97	1.68 (1.62–1.74)
	F	92 (15.5)			19 (22.6)			73 (14.3)		

(Continues)

TABLE 1 (Continued)

Group		N (%)	MFR	PR (95% CI)	Comorbid ID, N (%)	MFR	PR (95%CI)	No ID, N (%)	MFR	PR (95%CI)
CHILDREN, aged 11–17, born 1998–2004										
Reference pop	M	196,689 (50.9)	1.04	Reference	1,420 (56,7)	1.31	Reference	195,269 (50.8)	1.03	Reference
	F	189,923 (49.1)			1,086 (43.3)			188,837 (49.2)		
Any ASD	M	4,162 (77.1)	3.36	1.52 (1.49–1.54)	576 (71.9)	2.56	1.27 (1.20–1.34)	3,586 (78.0)	3.54	1.53 (1.51–1.56)
	F	1,237 (22.9)			225 (28.1)			1,012 (22.0)		
ASD (no ADHD)	M	2,560 (75.4)	3.07	1.48 (1.45–1.51)	378 (71.6)	2.52	1.26 (1.18–1.34)	2,182 (76.1)	3.19	1.50 (1.47–1.53)
	F	835 (24.6)			150 (28.4)			685 (23.9)		
ASD+ADHD	M	1,602 (79.9)	3.99	1.57 (1.54–1.61)	198 (72.5)	2.64	1.28 (1.18–1.39)	1,404 (81.1)	4.29	1.60 (1.56–1.63)
	F	402 (20.1)			75 (27.5)			327 (18.9)		

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence intervalF, female; ID, intellectual disability; M, male; MFR, male/female ratio; PR, prevalence ratio.

the youngest children (4–10 years old), decreasing to the lowest MFR in older adults. Children with concurrent ID had a lower MFR than children with ASD alone, whereas children with ADHD and ASD had a higher MFR than in children with ASD alone, independent of concurrent ID. In adults, the presence of ID and ADHD had less impact on the MFR. We found higher registered prevalence of ASD, ADHD and ID in younger than in older adults, with a registered ASD prevalence of 0.2% in older adults compared with 0.9% in younger adults.

Adult ASD is little studied, but childhood studies typically report more males with ASD than females, with an MFR of 4.25 in a meta-analysis from 2017.[1] In the present study, we found a considerably lower MFR in adults than in children, in line with a small population study in the Faroe Island, but contrary to Brugha et al.[16-18] This was also true for Asperger syndrome (AS) where we found an MFR of 2.96 in adults, similar to a clinical study screening for ASD in adult psychiatric outpatients.[25] AS has previously been thought of as a predominantly male disorder, with reports of up to ten males per female with AS in children.[26] In the current study, the MFR for AS was similar to other ASD diagnoses, indicating that some of the previously reported gender difference in AS may have been ascertainment bias and under detection in females [1] in older studies. We found an equally steady increase in registered prevalence of AS with increasing 5-year age groups for both genders, with males being diagnosed 2–3 times more frequently across all age groups, not supporting a better recognition of AS in females in the younger age groups. However, we were not able to discern from our data when the diagnosis was made, so it is still possible that recognition of female AS has improved.

Several findings in the current study indicate the presence of a gender bias in ASD diagnostic practice. Studies have shown that the MFR increases with increasing intellectual level.[1,17,27,28] In the current study, all but F84.8 (PDD-OS) ASD diagnoses had a higher male PR for individuals without ID than with ID with the largest difference for childhood autism. This gender ratio gradient has led to the hypothesis that females may be protected against developing ASD and that a stronger developmental/genetic impact is needed for females to develop symptomatic ASD than for males.[4] However, in the present study, we found larger differences in the MFR depending on ID in children than in adults, so that the difference in the MFR for ASD with ID compared to without ID was largest in the youngest group, while there was no significant difference in MFR for adults. The smaller impact of concurrent ID on the male predominance in the older age groups could be because of later identification of ASD in females without ID. The pattern of MFR variation according to ASD subtypes and ID also indicates that female ASD may still

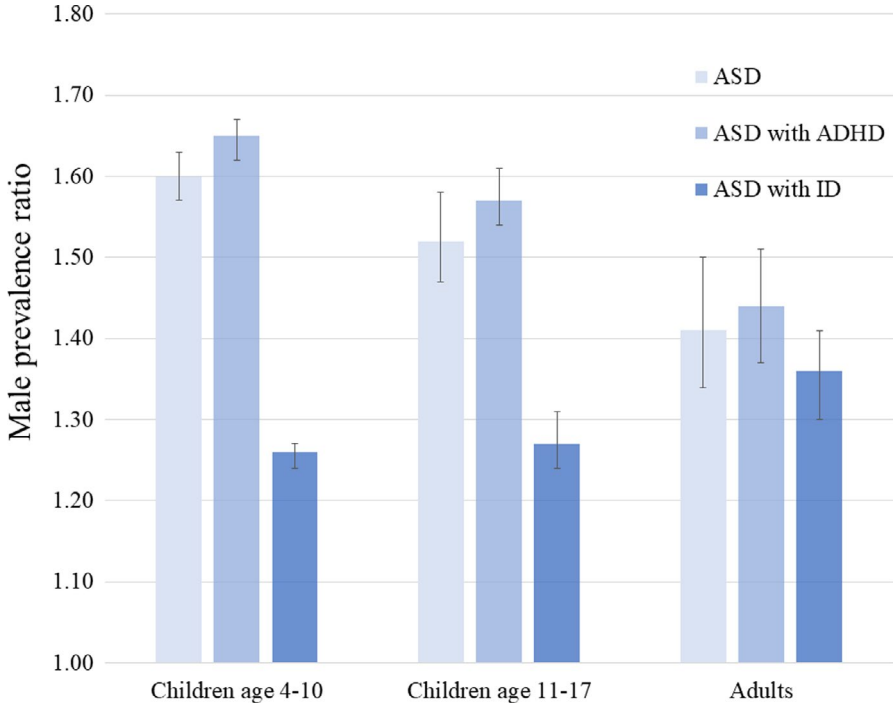

FIGURE 1 Male prevalence ratio for children and adults with autism spectrum disorder (ASD), ASD with ADHD and ASD with intellectual disability (ID) compared with the corresponding reference population without these diagnoses

TABLE 2 Prevalence of Norwegian Patient Registry diagnoses of ASD, ADHD and ID in older (born 1967–1983) versus younger adults (born 1984–1997), Norway, diagnoses from 2008–2015

	ASD (incl ADHD/ID) N (%)	ADHD (incl ASD/ID) N (%)	ID (incl ADHD/ASD) N (%)
All older adults	1,991 (0.2)	17,270 (1.9)	3,356 (0.4)
Men	1,399 (0.3)	9,433 (2.0)	1,701 (0.4)
Women	592 (0.1)	7,837 (1.7)	1,655 (0.4)
All younger adults	7,004 (0.9)	36,552 (4.7)	5,822 (0.7)
Men	5,075 (1.3)	22,662 (5.7)	3,193 (0.8)
Women	1,929 (0.5)	13,890 (3.7)	2,629 (0.7)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, Autism spectrum disorder; ID, intellectual disability.

be undiagnosed in the current sample, especially in higher functioning individuals,[29] despite the relatively low MFR in the present study. The highest MFR was surprisingly found for childhood autism when excluding ID, while the lowest MFR was found for PDD-NOS including ID. This means that females are relatively more often diagnosed with the less specific diagnoses, ie that females are less often identified as having typical autism. Taken together, these findings indicate that although there may be a true gender difference, core ASD symptoms are also less well recognized in females, especially when not having comorbid intellectual disability. The pattern of registered ASD in childhood further supports this, as very few females in the youngest age group were diagnosed with ASD without ID. The overall highest MFR of 6 times more males than females was found in the age group 4–10 years old, for the combination ASD+ADHD without ID, indicating few girls are diagnosed early with neuropsychiatric symptoms unless they have concurrent ID. As found in other studies, these patterns indicate that a female with social difficulties is less likely to be perceived as having a classic autism phenotype in the absence of ID[10] also in adult populations. Thus, despite a lower male to female ratio compared with previous studies, our findings still support the existence of a gender bias in this sample, where males are more easily diagnosed than females. It has been suggested that the standard for assessing ASD performs worse in females than in males as the items are modelled on the male phenotype.[11] Brugha et al. also suspected assessment and ascertainment bias to be part of the explanation for their high ASD gender ratio among able adults, as they had a very low ASD ascertainment rate in females of normal intelligence and a very strong IQ gradient with ASD and gender.[16,17] For ADHD, it has been shown that

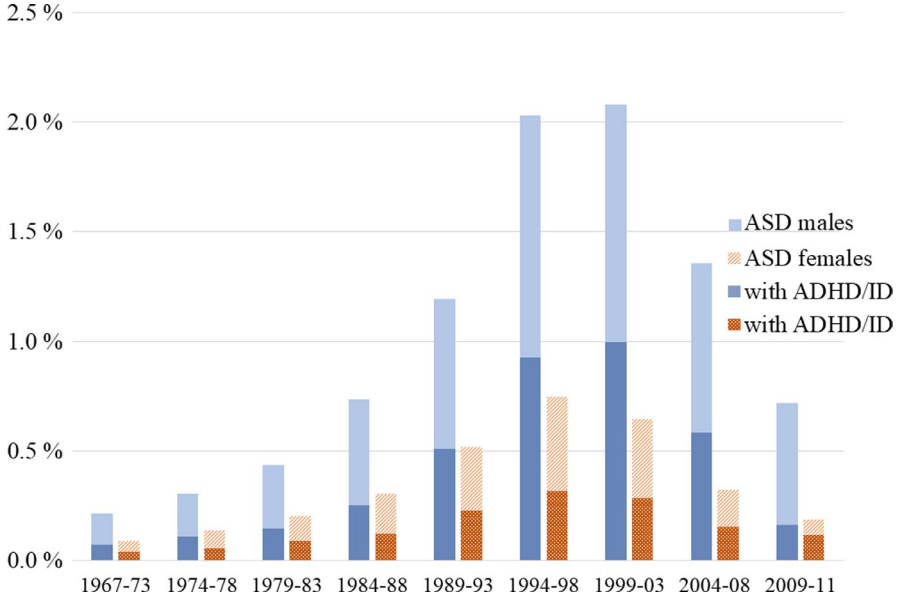

FIGURE 2 Population prevalence of ASD with and without comorbid ADHD and/or ID in males and females by birth year cohorts

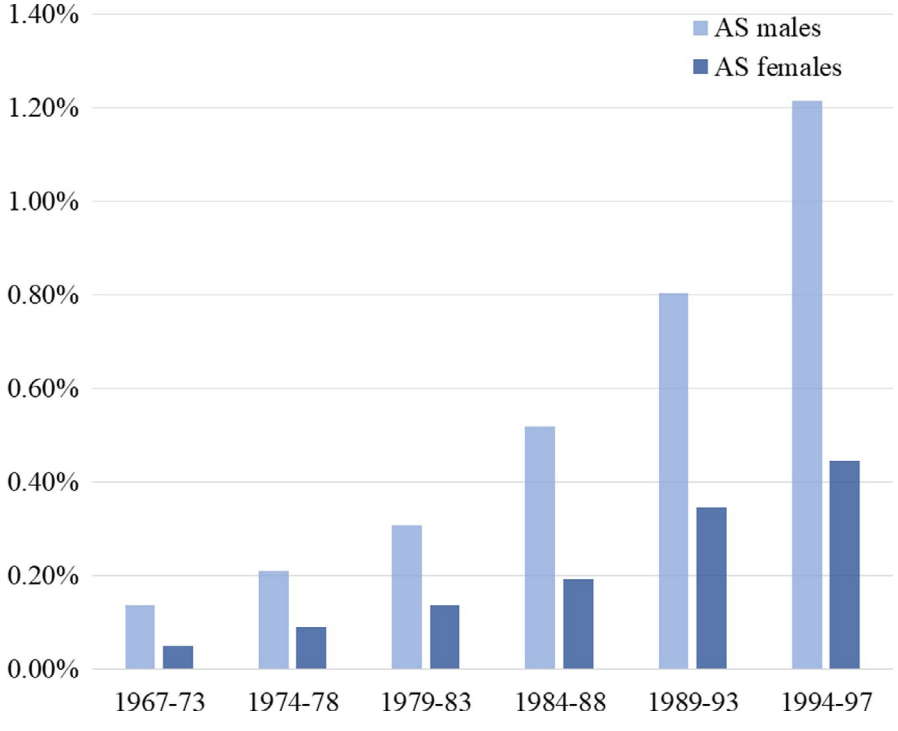

FIGURE 3 Population prevalence of Asperger syndrome (AS) in adult males and females by birth year cohorts

female gender is a strong barrier to child mental health services, assessment and adequate management for neuropsychiatric disorders at every level among children and adolescents, whereas adult studies show an almost equal MFR and even lower than 1 in some cases,[12,30] suggesting that females receive the ADHD diagnosis later in adolescence and adulthood. Childhood studies have also found that females with mental health problems have lower chances for being in contact with mental health services,[31] and in autism symptom high scorers, girls required a much higher symptom load to be viewed as impaired.[32] The findings of the present study and the study from the Faroe Islands where they found more females with ASD in the second assessment (older adolescents and adults) than in the first assessment suggest the same diagnostic delay could apply for females with ASD. Furthermore, as impairment is crucial to the diagnosis, females may first seek help and/or fulfil diagnostic criteria when encountering more complex demands in adulthood requiring social skills (eg childrearing). It is also well known that in adulthood, females seek health services more often than males, which could contribute to a reversal of the diagnostic bias in adulthood.[33-35] The somewhat surprising finding in the present study of a relatively lower MFR for AS than for childhood autism could support this hypothesis, as first-time diagnosed adults would preferentially

TABLE 3 Male/female ratio (MFR) and male prevalence ratio (PR) for ASD subtypes as compared with males in the population without ASD, ADHD and ID, Norway, all individuals born 1967–2011

	All ASD, N (%)	MFR	PR (95% CI)	Comorbid ID, N (%)	MFR	PR (95% CI)	No ID, N (%)	MFR	PR (95% CI)
F84.0 (Childhood autism, 27.0% of all ASD)									
Men	3,578 (77.6)	3.46	1.51 (1.49–1.54)	1,290 (71.2)	2.47	1.29 (1.25–1.34)	2,288 (81.80)	4.49	1.60 (1.57–1.63)
Women	1,031 (22.4)[a]			522 (28.8)			509 (18.20)		
F84.1 (Atypical autism, 13.5% of all ASD)									
Men	1,665 (72.2)	2.60	1.41 (1.37–1.44)	680 (70.6)	2.40	1.26 (1.20–1.31)	985 (73.3)	2.75	1.43 (1.39–1.48)
Women	641 (27.8)			283 (29.4)			358 (26.7)		
F84.5 (Asperger syndrome, 53.3% of all ASD)									
Men	6,797 (74.8)	2.96	1.46 (1.44–1.48)	178 (69.5)	2.28	1.28 (1.18–1.39)	6,619 (74.9)	2.98	1.46 (1.45–1.48)
Women	2,296 (25.3)			78 (30.5)			2,218 (25.1)		
F84.8 (Pervasive developmental disorder, otherwise specified, 2.2% of all ASD)									
Men	289 (73.7)	2.80	1.44 (1.35–1.52)	60 (70.6)	2.39	1.22 (1.06–1.40)	229 (74.6)	2.94	1.45 (1.36–1.55)
Women	103 (26.3)			25 (29.4)			78 (25.4)		
F84.9 (Pervasive developmental disorder, not otherwise specified, 15.2% of all ASD)									
Men	2,588 (74.5)	2.92	1.45 (1.42–1.48)	418 (69.2)	2.25	1.22 (1.15–1.29)	2,170 (75.6)	3.10	1.48 (1.44–1.51)
Women	887 (25.5)			186 (30.8)			701 (24.4)		

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval, MFR, male/female ratioID, intellectual disability; PR, prevalence ratio.

[a]The sum of individuals here exceeds the total number of ASD individuals as some have been registered with more than one ASD diagnosis.

be diagnosed with AS (a diagnosis of childhood autism requires established developmental deviances before the age of three).

The increase of registered ASD from older to younger adults was quite dramatic but is in line with the changes in diagnostic practice in the last decades, with increasingly higher prevalence rates of ASD registered in later years.[36] The increase was mainly accounted for by the addition of Asperger syndrome (AS) as a separate diagnosis in 1994, with a very clear effect on the registered prevalence of AS diagnoses. It was also by far the most common diagnosis of the ASD spectrum, accounting for 60% of all ASD cases (Table 3 and Figure 3). The overall registered prevalence and the increase of AS diagnoses indicate that ASD should not be considered an uncommon disorder in adulthood, nor a disorder limited to childhood. The registered prevalence of 0.9% ASD among younger adults stands in contrast to the paucity of research on this condition in adulthood. Viewed as a childhood condition, adults with ASD are standing with unmet healthcare needs and few evidence-based interventions to resort to.[37,38] The 0.9% prevalence is probably a low estimate of the prevalence worldwide as Norwegian studies often report lower prevalence rates than other countries.[39] In the current study, the child ASD prevalence was 1.4% while recent USA and UK studies report prevalence rates above 2%.[2,36] However, the gender distribution in this study was almost identical to the findings in Roman-Urrestarazu et al., indicating that the gender discrepancy is present regardless of diagnostic restrictive or liberal practice.[2]

4.1 | Strengths and limitations

A strength of our study is that we used data from nationwide health registries of good quality and with mandatory, prospective reporting, minimizing selection bias and loss to follow-up and eliminating recall bias. However, this study also has some limitations. Analyses were cross-sectional and for ASD and ID, these were based on diagnoses registered in the NPR from 2008–2015, limiting the study of temporal relations. ASD and ID are both neurodevelopmental disorders where diagnoses are usually given in childhood. Since the NPR was established in 2008, adults with stable disorders, who were diagnosed and treated for ASD and ID entirely before 2008 and not in contact with specialized health services after that, will not appear in the clinical population. It is therefore impossible to draw any firm conclusions as to the magnitude of prevalence difference between older and younger adults. Further, we could only determine the date of the registered diagnosis in NPR in the 2008–2015 interval, so to construct the 'adult population' we based this on the individuals' age in 2015 (at record linkage) instead of their age at diagnosis. This means that an adult born in 1997 would have been counted in the present study as an adult with ASD even if diagnosed in childhood. However, since ASD and ID are stable diagnoses across the lifespan,[40,41] the majority will have retained their diagnosis as adults. For ADHD however, the adult prevalence may have been overestimated because of this limitation, but as adult ADHD was also based on age at dispensed ADHD medication, this should not be a large problem. The lack of information on other comorbidities, eg epilepsy, is another limitation.

Only including diagnoses registered on individuals who were in contact with specialist health services at any point in time 2008–2015 (or a prescription for ADHD medicine 2004–2015) may furthermore cause some specific biases in the male to female ratio estimates and prevalence registered. For individuals where the diagnostic assessment of ASD was before 2008, the NPR will only capture the ASD diagnosis when individuals seek specialist health care for later concerns, and health-seeking behaviours in males and females are known to differ. Secondly, we were not able to consider the increased mortality associated with ASD, ID and ADHD, which has also been found to be differential between males and females.[42] Furthermore, less disabled individuals may not have their ASD diagnosis registered when seeking health care for other matters, underestimating the registered prevalence of ASD especially in older well-functioning individuals. Thus, the overall registered ASD prevalence of 0.5% in this adult sample is probably an underestimation of the ASD prevalence in adults. Furthermore, although the register has national coverage only includes formal diagnoses made in the specialized health services, thus individuals with subthreshold or unrecognized ASD is not part of the register.

According to DSM-IV and ICD-10, a diagnosis of ASD precludes ADHD. This may have affected the diagnostic procedures and hindered the clinician to give both disorders whether the criteria were fulfilled. This diagnostic practice has changed gradually even before the advent of DSM-5 and is likely to explain the far lower number of individuals with comorbid ADHD and ASD disorder in older adults.

The adult ASD male to female ratio (MFR) was lower than the MFR in children and less affected by comorbid ID. Females were more likely to be diagnosed with atypical autism and PDD-NOS, and in childhood, if they had concurrent ID, supporting the existence of a male phenotype bias in the diagnosing of ASD. An overall registered prevalence of ASD of 0.9% among younger adults shows that ASD is becoming relatively common, warranting further research on this condition in adulthood.

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CONFLICT OF INTERESTS

JH has served as a speaker for Eli-Lilly, HB Pharma, Biocodex and Shire. MP is a member of the Scientific Advisory Board for Slenyto® at Takeda/Neurim. The other authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13368.

DATA AVAILABILITY STATEMENT

The data used in this study are available from the Norwegian Medical Birth Registry, the Norwegian Prescription Database and the Norwegian Patient Registry. Restrictions during ethical considerations apply to the availability of these data as required by the Norwegian Data Inspectorate.

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