Time trends in the male to female ratio for autism incidence: population based, prospectively collected, birth cohort study

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ABSTRACT

OBJECTIVES

To examine changes in the male to female ratio in diagnoses of autism spectrum disorder (ASD) over a 35 year period, providing temporal trends in diagnosis (incidence rate), the male to female ratio, and the age-cohort specific cumulative male to female ratio (cMFR).

DESIGN

Population based, prospectively collected birth cohort study.

PARTICIPANTS

2 756 779 liveborn children recorded in the Swedish medical birth register between 1985 and 2020.

SETTING

Sweden.

MAIN OUTCOME MEASURE

Age-period cohort analysis investigating associations between ASD and age at diagnosis, calendar period, birth cohort, and sex, quantified by incidence rate ratios and associated two sided 95% confidence intervals.

RESULTS

Among 2 756 779 individuals born in Sweden between 1985 and 2020, ASD was diagnosed in 78 522 (2.8%) by the end of follow-up (2022). The incidence rate for ASD increased with each five year age interval throughout childhood, peaking at 645.5 (per 100 000 person years) for male individuals at age 10-14 years and 602.6 for female individuals at age 15-19 years in 2020-2022, and then decreased. Age specific incidence of ASD increased for each calendar period and birth cohort between 1985 and 2020. The male to female ratio decreased with increasing age at diagnosis and, for those older than 10 years, by calendar period. For the final year of follow-up in 2022, the cumulative male to female ratio for incidence of ASD was 1.2 by age 20 years. Further projection of these trends suggested that the cumulative male to female ratio would reach parity at age 20 years by 2024.

CONCLUSION

Findings indicate that the male to female ratio for ASD has decreased over time and with increasing age at diagnosis. This male to female ratio may therefore be substantially lower than previously thought, to the extent that, in Sweden, it may no longer be distinguishable by adulthood. This finding highlights a need to investigate why female individuals receive diagnoses of ASD later than male individuals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The prevalence of autism spectrum disorder has increased over the past three decades, and has been characterised by a high male to female ratio

WHAT THIS STUDY ADDS

The male to female ratio for autism spectrum disorder has decreased over time and with age at diagnosis, demonstrating a pattern of female catch-up

These observations highlight the need to investigate why female individuals receive diagnoses later than male individuals

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterised by differences in social communication, restrictive interests, and repetitive behaviours.[1] ASD prevalence has increased since early 2000, from, for example, 0.7% of 8 year olds in the US in 2002 to 3.3% in 2022, according to Centers for Disease Control and Prevention data.[2 3] The prevalence of ASD (ie, total proportion of the population with a diagnosis of ASD, in the US and western Europe now varies between 1.0% and 3.3%).[2 3] The estimated male to female ratio (MFR) varies between 2.7 and 4.1.[4 5] Many reasons have been put forward for the high MFR of ASD, including a so called female protective effect, whereby female individuals require a higher genetic burden than male individuals for behaviours associated with ASD to become noticeable.[6] Another theory, known as the greater variance in males theory, contends that male individuals have a higher genetic variance for alleles associated with ASD, which randomly places more male than female individuals above the ASD diagnosis threshold.[7] ASD has also been theorised as a manifestation of a the so called extreme male brain, a theory that suggests differences in the ability of male and female individuals to empathise and systemise, and that people with ASD show an extreme version of typical male characteristics.[8] Other factors purported to explain the MFR in people with ASD include camouflaging by female individuals to mask features of ASD (eg, through mimicking peers in social interactions),[9] and diagnostic overshadowing of co-occurring conditions leading to missed ASD diagnosis[10] in female individuals. A potential sex bias in ASD research[4] and the application of diagnostic criteria[9] have also been suggested.

ASD is present from early childhood[1] but may not be diagnosed until later in life (known as the age effect). In Sweden, ASD is often detected by preschool developmental assessments.[11] Recent increases in ASD incidence have been linked to a broadening of diagnostic criteria[12] (incidence in this context refers to the number of people with newly diagnosed

Table 1 | Rate of autism spectrum disorder in study population, by calendar year and age at diagnosis

Age at diagnosis (years) by calendar period	No of diagnoses			No of person years (1000s)			Diagnostic rate (per 100 000 person years)			MFR (95% CI)
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female	
1985-1989										
0-4	35	26	9	1047	538	508	3.3	4.8	1.8	2.7 (1.3 to 5.8)
1990-1994										
0-4	152	123	29	2297	1180	1117	6.6	10.4	2.6	4.0 (2.7 to 6.0)
5-9	81	59	22	1042	536	507	7.8	11.0	4.3	2.5 (1.6 to 4.1)
1995-1999										
0-4	163	114	49	2009	1030	980	8.1	11.1	5.0	2.2 (1.6 to 3.1)
5-9	182	136	46	2283	1172	1111	8.0	11.6	4.1	2.8 (2.0 to 3.9)
10-14	83	65	18	1037	533	504	8.0	12.2	3.6	3.4 (2.0 to 5.8)
2000-2004										
0-4	333	248	85	1679	865	814	19.8	28.7	10.4	2.7 (2.1 to 3.5)
5-9	1106	837	269	1994	1021	972	55.5	82.0	27.7	3.0 (2.6 to 3.4)
10-14	1281	926	355	2268	1164	1104	56.5	79.5	32.1	2.5 (2.2 to 2.8)
15-19	550	381	169	1031	530	502	53.3	71.9	33.7	2.1 (1.8 to 2.6)
2005-2009										
0-4	620	467	153	1821	937	884	34.1	49.9	17.3	2.9 (2.4 to 3.5)
5-9	1600	1254	346	1665	856	808	96.1	146.5	42.8	3.4 (3.0 to 3.9)
10-14	2437	1739	698	1978	1011	967	123.2	172.0	72.2	2.4 (2.2 to 2.6)
15-19	2703	1684	1019	2251	1154	1097	120.1	145.9	92.9	1.6 (1.5 to 1.7)
20-24	822	485	337	1013	521	492	81.1	93.0	68.5	1.4 (1.2 to 1.6)
2010-2014										
0-4	1295	1005	290	1876	965	912	69.0	104.2	31.8	3.3 (2.9 to 3.7)
5-9	3558	2776	782	1800	923	877	197.7	300.6	89.2	3.4 (3.1 to 3.6)
10-14	4875	3439	1436	1642	841	801	296.9	409.0	179.3	2.3 (2.1 to 2.4)
15-19	5036	2995	2041	1951	995	956	258.2	301.1	213.5	1.4 (1.3 to 1.5)
20-24	2895	1759	1136	2185	1123	1063	132.5	156.7	106.9	1.5 (1.4 to 1.6)
25-29	981	578	403	976	502	474	100.5	115.0	85.1	1.4 (1.2 to 1.5)
2015-2019										
0-4	1574	1245	329	1822	937	885	86.4	132.9	37.2	3.6 (3.2 to 4.0)
5-9	4939	3787	1152	1851	947	904	266.9	399.8	127.5	3.1 (2.9 to 3.3)
10-14	7817	5060	2757	1764	899	865	443.1	562.8	318.6	1.8 (1.7 to 1.9)
15-19	6293	3233	3060	1606	820	786	392.0	394.4	389.4	1.0 (1.0 to 1.1)
20-24	3071	1743	1328	1903	972	931	161.4	179.4	142.6	1.3 (1.2 to 1.4)
25-29	2657	1537	1120	2119	1089	1030	125.4	141.2	108.7	1.3 (1.2 to 1.4)
30-34	985	558	427	950	488	462	103.7	114.3	92.5	1.2 (1.1 to 1.4)
2020-2022										
0-4	1063	861	202	907	466	441	117.2	184.8	45.8	4.0 (3.5 to 4.7)
5-9	3255	2445	810	1086	556	531	299.6	439.9	152.7	2.9 (2.7 to 3.1)
10-14	6124	3564	2560	1086	552	533	564.1	645.5	479.9	1.3 (1.3 to 1.4)
15-19	5081	2073	3008	1017	518	499	499.4	400.0	602.6	0.7 (0.6 to 0.7)
20-24	1738	788	950	935	478	457	185.9	164.7	208.0	0.8 (0.7 to 0.9)
25-29	1597	810	787	1184	606	579	134.8	133.7	136.0	1.0 (0.9 to 1.1)
30-34	1282	642	640	1222	628	594	104.9	102.2	107.7	0.9 (0.9 to 1.1)
35-37	288	139	149	332	171	161	86.9	81.5	92.5	0.9 (0.7 to 1.1)
Overall	78 552	49 581	28 971	55 629	28 522	27 107	141.2	173.8	106.9	1.6 (1.6 to 1.7)

MFR=male to female rate ratio; CI=confidence interval.

ASD). For example, changes in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV, 1994) and fifth edition (DSM-V, 2013). The incorporation of spectrum conceptualisation allowed for the identification of more symptoms in the updated editions, which may have led to a higher number of people in all age groups simultaneously receiving a diagnosis of ASD (known as the period effect). Societal changes—such as older parental age at birth[2]—can result in differences in rates of ASD diagnosis between generations (ie, a cohort effect). For example, the mean age at childbirth of Swedish mothers increased from 27 years to 33 years between 1970 and 2011,[13 14] with a likely parallel increase for fathers.

Underdiagnosis or delayed diagnosis of female individuals because of typically better social and communication skills (making traits in these domains more difficult to identify) has been hypothesised to be responsible for the higher MFR by age at female diagnosis, rather than there being an actual sex difference.[15] Despite evidence of a downward trajectory in the MFR,[4 5 16] no large population based study has examined trends in the MFR of individuals with ASD that disentangles age at diagnosis, calendar period (ie, overall changes in ASD incidence by year of diagnosis), and birth cohort. Sweden has a publicly funded healthcare system and nationwide population based registers dating back to the 1970s,[17] providing a rare opportunity to detect such changes over the

life course. In this study we analysed and identified these temporal influences on the MFR in people with a diagnosis of ASD.

Methods

Study design

We used a population based, prospectively collected birth cohort study to investigate the influence of age at diagnosis, calendar period, and birth cohort on the MFR for people with a diagnosis of ASD.

Study population

We selected all liveborn children recorded in the Swedish medical birth register between 1985 and 2020 as the study population. Registers are cross linked by a unique personal identification number assigned to all Swedish residents.[18] The medical birth register covers 99% of all births in Sweden since 1973.[19] We obtained parent information through the Swedish multigenerational register, dating back to 1932, and the Swedish population register.[19] To maintain homogeneity across the study period, we only included individuals whose parents were both born in Sweden.

Primary outcome

From the Swedish national patient register, we obtained information on ASD diagnoses in individuals from age 2 years until end of follow-up (1 January 1987 to 31 December 2022). This register uses the ICD-9 (international classification of diseases, ninth revision) from 1987 to 1997 and ICD-10 (international classification of diseases, 10th revision) after 1997 for clinical diagnoses.

The process for diagnosing ASD in Sweden evolved over the course of the study period in line with changes in the DSM. For example, in 1987 only autistic disorder (AD)—which typically requires higher levels of support—was included in the DSM. The introduction of ICD-10 broadened diagnostic criteria to include a wider range of subtypes (hereafter referred to as autism spectrum) from 1997 onwards (supplementary materials, table 1). The national patient register provides nationwide coverage of hospital inpatients receiving an ASD diagnosis from 1987, and diagnoses received by people in outpatient care were included incrementally between 2001 and 2005.[20] The national patient register has been subject to extensive validation efforts, including for ASD diagnosis.[18]

In Sweden, child health centres provide routine preventive child healthcare, attended by all Swedish children from birth to 5 years of age. Usually, specialist nurses and doctors evaluate children 12 times during their first year of life, and thereafter two to six times yearly. Comprehensive developmental assessment of motor skills, language, cognitive skills, and social development are performed when children reach 18 months, 2.5 years, 4 years, and 5 years of age. When in school, from 6 years of age, the school's medical team evaluate children with problems related to cognition, social skills, or attention. Specialised teams then refer children with suspected developmental disorders for further assessment.[21] Diagnosis may be received (in children and adults) while under the care of psychiatric services as a result of concerns from themselves or their care givers about feelings and behaviours (eg, temper tantrums, anxiety, depression, eating disorders, or obsessive-compulsive disorder). A diagnosis of ASD among individuals younger than 18 years in Sweden is given after assessment by a specialised team—for example, in a child psychiatry unit or paediatric neurology/habilitation service in younger age groups.[21] For adults, specialised assessment teams exists within psychiatry clinics. According to the recommendations by the Swedish National Board of Health and Welfare, assessment of adults with suspected ASD are conducted jointly by a psychologist and a physician.

Exposure variables: age at diagnosis, calendar period, birth cohort, and sex

We extracted birth date and sex assigned at birth from the medical birth register. Calendar period and age at diagnosis of ASD was obtained by linking the medical birth register with the national patient register.

Statistical analysis

We followed each individual from birth until the ASD diagnosis, death, emigration from Sweden, or the end of the study period.

For descriptive purposes, we grouped the continuous time scales into five year intervals for age and calendar period, and the corresponding overlapping 10 year intervals for birth cohort (supplementary materials). To explore how ASD incidence and the MFR vary over time, we summarised the number of ASD diagnoses, person years at risk, incidence rates (number of diagnoses divided by person years), and the MFR. The uncertainty of the MFR was quantified by 95% Wald-type confidence intervals (CI).

Temporal patterns were assessed by fitting a sequence of log-linear rate models of increasing complexity, defined by the covariates (age, age and drift, age and period, age and cohort, and age, period, and cohort). Drift refers to a linear time trend that can be arbitrarily attributed to period or cohort.[22] Estimation was performed using Poisson regression, as the likelihood under a constant rate model is proportional to the Poisson likelihood. We then extended the models by adding interactions with sex to all covariates. Age, period, and cohort was modelled using natural cubic splines with eight knots, equivalent to one knot every five years,[23] placed so that the number of events between knots was about equal.[24] We estimated age effects as age specific rates for a reference period, adjusted for cohort effects. Period effects, with drift included, were estimated relative to the reference period, and cohort effects were estimated relative to the age-period effect.[24] We selected 2016 as the reference year, corresponding to the median diagnosis year among all people with a diagnosis of ASD. Fitted models were compared using the Akaike

Information Criterion, which balances goodness-of-fit and model complexity; lower values indicate better supported models.[25]

To better understand how changes in diagnostic patterns have affected rates of ASD diagnosis, we used the estimated age, period, and cohort effects to compute age-cohort specific ASD rates and the MFR for selected calendar periods: 2016 (the reference year), 2022 (the final year of follow-up), and 2024 (the current year at time of analysis). For the observed age range and specified period, we obtained the corresponding cohorts by calculating the identity cohort as period minus age. The age-cohort specific rates of ASD diagnosis were then computed by multiplying the age specific rates by the corresponding cohort specific rate ratios and the period specific rate ratio. We also computed cumulative ASD rates and cumulative MFR (cMFR), along with associated 95% CIs using the delta method.[25] When periods and cohorts extended beyond the observed range, we obtained estimates by linear extrapolation, as implied by the natural cubic spline formulation.[26] We used SAS version 9.1 and R version 4 for the statistical analysis.

Supplementary analysis

To explore specificity of outcomes, we repeated the analysis for the main ASD subtype: autistic disorder. Autistic disorder differs from other forms of ASD

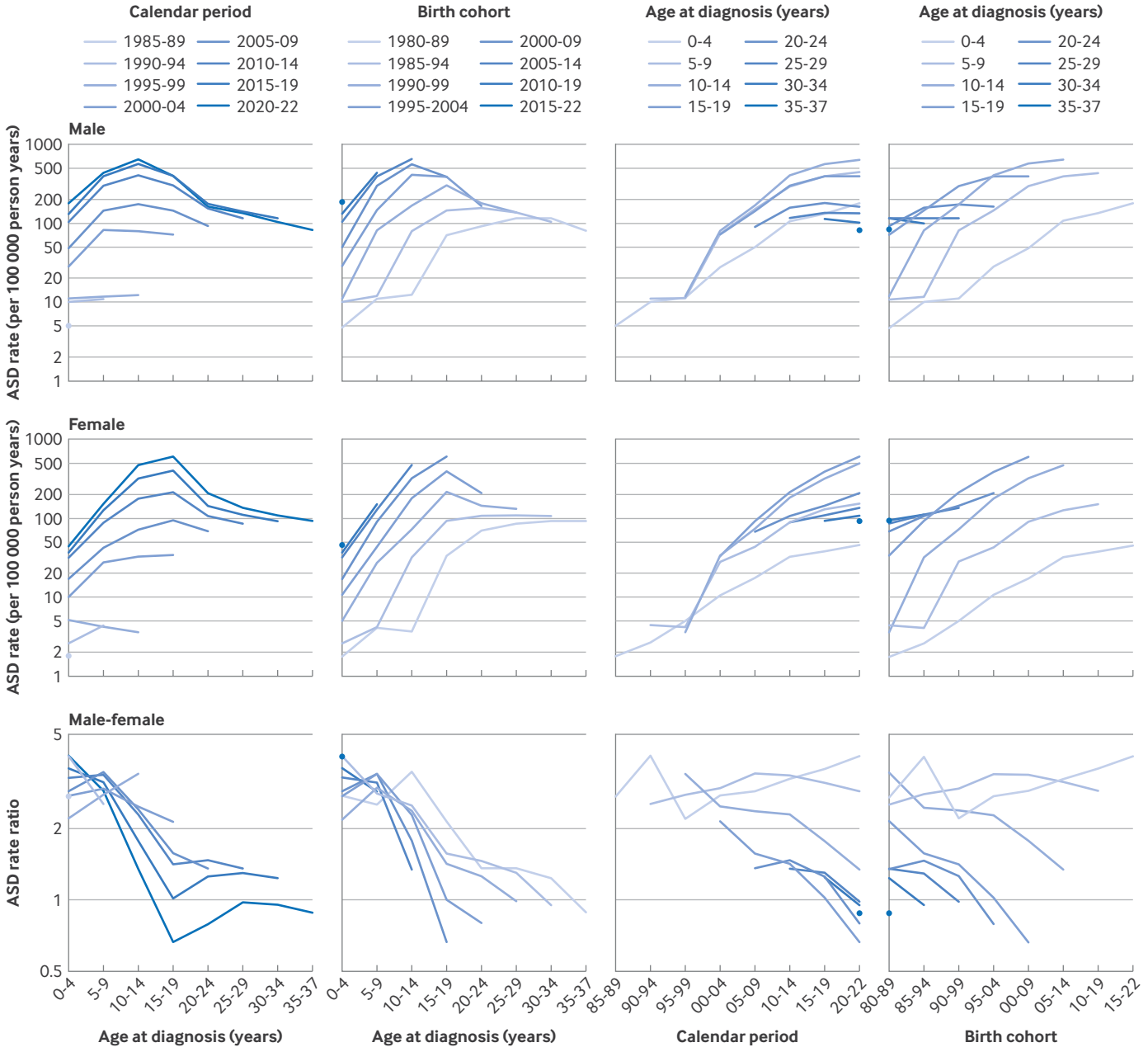

Fig 1 | Incidence rate and male to female ratio of autism spectrum disorder during study period. Incidence rate shown by male sex, female sex, and male to female rate ratio. Stratified by age at diagnosis and calendar period, age at diagnosis and birth cohort, calendar period and age at diagnosis, and birth cohort and age at diagnosis. ASD=autism spectrum disorder

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Table 2 | Model fit statistics for models with age at diagnosis of autism spectrum disorder, calendar period, and birth cohort, with and without sex interaction

Model	Akaike information criterion*	Degrees of freedom	Deviance
Without sex interaction			
Age	70 910	2872	58 898
Age+drift	32 976	2871	20 963
Age+period	29 902	2865	17 877
Age+cohort	32 264	2865	20 239
Age+period+cohort	29 681	2859	17 643
With sex interaction			
Age	62 855	2864	50 828
Age+drift	24 488	2862	12 456
Age+period	20 957	2850	8901
Age+cohort	23 813	2850	11 758
Age+period+cohort	20 637	2838	8558

Drift refers to a linear time trend that can be arbitrarily attributed to period or cohort.
*Comparing the Akaike information criterion for the age+drift model to the Akaike information criterion for the age+period model or age+cohort model contrasts a strictly linear trend in calendar period or birth cohort with a model allowing for non-linear effects.

in that the characteristics of autism are noticeable earlier in life and occur in all three diagnostic domains (reciprocal social interaction, communication—particularly in terms of language acquisition—and specific behavioural traits).

Patient and public involvement

No patients or members of the public were involved in this study. At the time of study inception, no mechanisms were in place for patient and public involvement, which is being rectified.

Results

Our final study population size included 2 756 779 people, having excluded 3216 (0.1%) individuals with incomplete records, 36 748 (1.0%) who emigrated or died before 2 years of age, and 980 405 (26.0%) with parents born outside Sweden (supplementary file, supplementary fig 1). We followed individuals to a maximum of 37 years of age (median 20.1 years, interquartile range (IQR) 8.8 to 29.4 years). ASD was diagnosed in 78 522 (2.8%) of the study population.

Age at diagnosis

Across all age groups, we observed the highest rate of ASD diagnoses (ie, incident cases per 100 000 person years) in the period 2020 to 2022, ranging from 184.8 diagnoses in male individuals and 45.8 in female individuals aged 0-4 years to 645.5 for male individuals aged 10-14 years and 602.6 for female individuals aged 15-19 years (table 1). The median age at diagnosis was 14.3 years (IQR 9.9 to 17.6 years; supplementary file, supplementary table 2).

The MFR was approximately 3 until individuals reached 10 years of age; rate of ASD diagnosis was highest for male individuals at 10-14 years and 15-19 years for female individuals (fig 1). We observed the highest MFR in individuals aged 10 years and younger. In individuals older than 10 years, the MFR decreased with increasing age across all calendar periods. For children with a diagnosis of ASD between 2020 and 2022 (the most recent period for which data were available), the MFR was no longer >1 for individuals older than 15 years (fig 1; table 1). The age specific change in rates of ASD diagnosis was similar across birth cohorts from the 1995-2004 birth cohort onwards (fig 1). The MFR was ≤1 for individuals older than 15 years in birth cohorts from 2000 onwards (fig 1).

Calendar period (year of diagnosis)

A constant increase in ASD rates was observed in all age groups from 1995 to 2022. For example, between the periods 2000-2004 and 2020-2022, the ASD rate for individuals aged 0-4 years increased from 19.8 to 117.2, and for those aged 10-14 years, from 56.5 to 564.1 (table 1). The increase in ASD rates over time was greater for male individuals aged 0-4 years than for female individuals of the same age, but greater for female individuals aged 10-14 years or older. The MFR fluctuated between 2 and 4 for age groups 0-4 and 5-9 years across all calendar periods but decreased over time in all other age groups (fig 1).

Birth cohort (year of birth)

For individuals born in the 1995-2004, 2000-2009, and 2005-2015 cohorts, the rate of ASD diagnosis was highest at 15-19 years of age. For individuals born from 1985 to 1994, the rate of ASD diagnosis increased until 20-24 years of age and plateaued thereafter. With the exception of the 10-14 years and 15-19 years age groups, the change in rates of ASD diagnosis between birth cohorts was similar for male and female individuals (fig 1).

Relative impact of age at diagnosis, calendar period, birth cohort, and sex

When comparing the models with different combinations of timescale, those that included all three (age, period, and cohort) were best supported by the Akaike information criterion. Among the less complex models, those with age and calendar period were better supported than models using age and cohort. When we added an interaction with sex, the model fit improved across all specifications (table 2).

The model with the lowest Akaike information criterion (which included age, calendar period, birth cohort, and their interactions with sex) revealed a cohort adjusted, age specific pattern of the high MFR up to age 10 years, followed by a decline to reach a plateau at around age 15 years. The period specific effect, with drift included, increased monotonically until 2010 and then declined. The (residual) cohort specific effect remained nearly constant until 1995, decreased until 2005, and then increased again to the end of the study period in 2022 (fig 2).

To illustrate how changes in diagnostic patterns have affected the rate of ASD diagnosis, we used the estimated age, period, and cohort effects (fig 2) to compute age-cohort-specific ASD rates and the MFR, including their cumulative versions, for calendar periods 2016, 2022, and 2024 (fig 3). These estimates were obtained by multiplying the age specific rates by the corresponding cohort specific rate ratios

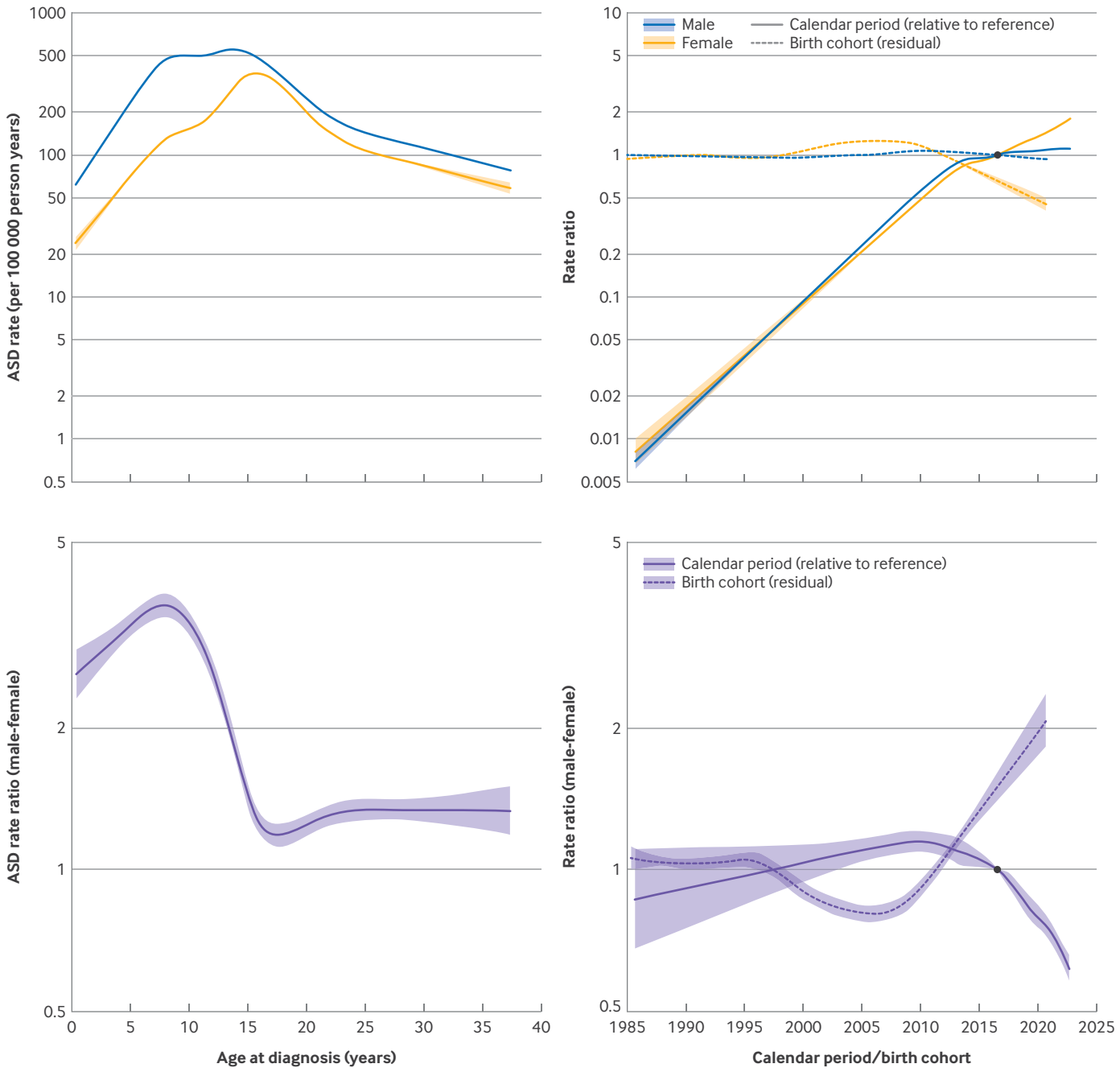

Fig 2 | Estimated effects of age at diagnosis, calendar period, and birth cohort on the rate of autism spectrum disorder for male and female individuals and the associated male to female ratio from the best fitting model that included variables for age, period, cohort, and their interactions with sex, along with 95% confidence intervals (shaded regions). Upper left panel shows the estimated cohort adjusted, age specific, population averaged rates of autism spectrum disorder for male and female individuals who received diagnoses in 2016. Upper right panel shows the estimated period specific rate ratios relative to the reference period 2016 (black dot) and the cohort specific rate ratios relative to the age period effect. Lower left panel shows the corresponding age specific male to female ratios. Lower right panel shows the period specific and cohort specific male to female ratios. For example, the male to female ratio for 15 year olds who received a diagnosis in 2022 and therefore born in 2007 is about 1.5×0.6×0.8=0.7. ASD=autism spectrum disorder

and the period-specific rate ratio, applying linear extrapolation where periods or cohorts extended beyond the observed range (fig 2). For diagnoses received in 2016, the age-cohort-specific MFR remained >1 for all age groups, whereas for 2022 it was <1 after 14 years of age (fig 3). Up to age 20 years, the cMFR declined from about 1.9 in 2016 to about 1.2 in 2022, while at age 10 years the cMFR remained stable at around 3 (fig 3). To investigate how recent trends might influence future MFRs and cMFRs, we included a projection beyond 2022—the final year of follow-up—showing that, under projected diagnostic patterns for 2024, the cMFR decreased to 1 by age 20 years (fig 3).

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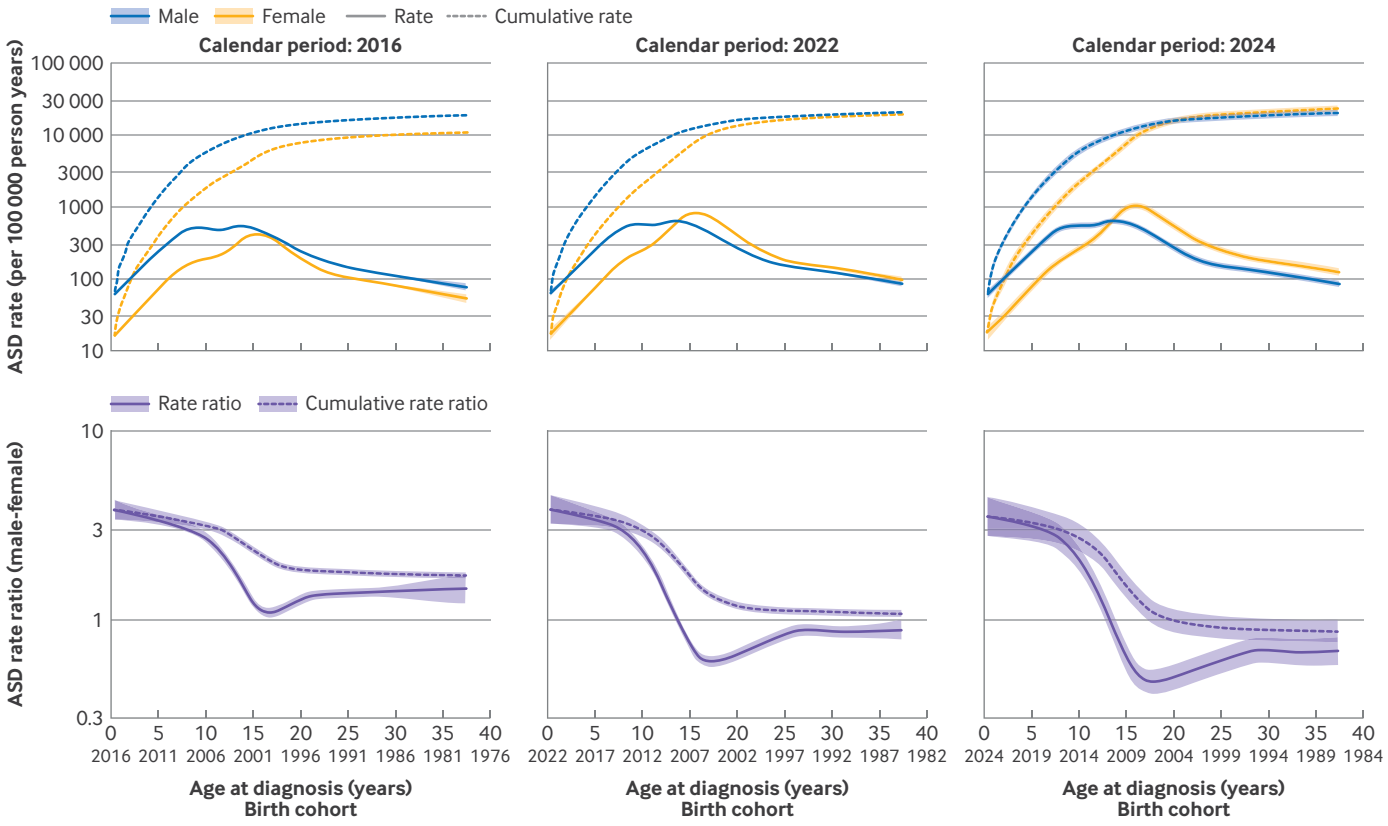

Fig 3 | Population averaged, age-cohort specific rates of autism spectrum disorder and male to female ratios for calendar periods 2016, 2022, and 2024. Figure presents estimates from the model best supported by the Akaike information criterion, which included terms for age, period, cohort, and their interactions with sex, using diagnoses of autism spectrum disorder between 1987 and 2022 and projected diagnoses in 2024. ASD=autism spectrum disorder

Supplementary analysis: autism disorder

We identified 43 146 individuals with a diagnosis of autism disorder. Post hoc summary statistics suggest similar rates of autism disorder and ASD in childhood and adolescence (0-19 years) but with a much sharper decrease in autism disorder rates during adulthood (>20 years) (supplementary files, supplementary fig 2). The overall MFR ratio for autism disorder was (1.7, 95% CI 1.7 to 1.7) (supplementary file, supplementary table 3).

Discussion

Principal findings

Among the 2.7 million children born in Sweden between 1985 and 2020, the rate of ASD diagnoses increased about 10-fold over the study period (follow-up to 2022). For example, from 56.5 to 564.1 cases per 100 000 person years between 2000 and 2022, in individuals aged 10-14 years. The well known high MFR for ASD declined steadily for those with a diagnosis of ASD after 10 years of age, and for people with a more recent diagnosis (after 2010). A model based projection found a cMFR (sex difference in cumulative ASD incidence) close to 1 in Sweden for the 2022 calendar period, suggesting a similar lifetime rate of ASD diagnosis in male and female individuals.

Our analyses of the MFR showed a substantial catch-up effect for ASD in female individuals relative to male individuals, over time and especially as age increased. This effect began at age 10 years, when the cMFR was about 3, and plateaued at age 20 years, after a rapid decline in the age specific MFR to <1 during adolescence.

Comparison with other studies

Earlier studies have linked changes in ASD incidence to period effects (eg, the broadening of diagnostic criteria). ASD is diagnosed based on the fulfilment of descriptive criteria,[15] thus the ASD rate and the MFR may have been affected by changes in the diagnostic manuals.[12] While in post hoc analysis, we did not observe any abrupt alterations in either rates of ASD diagnosis or the MFR after the introduction of DSM-V in Sweden in 2013, new criteria can take several years to be implemented in a nuanced and consistent way. In addition, DSM-V was implemented at a time of growing awareness of ASD and formalised ASD as a spectrum. A Danish study found greatest increases in ASD diagnosis rates between the ages of 4 and 20 years, which the authors linked to increased diagnosis of autism spectrum after the introduction of ICD-10.[27] A Norwegian population based register study of individuals born from 1967 to 2011 similarly

found a higher MFR in children (3.7) than in adults (2.6).[28]

Several factors may have influenced the higher than previously reported peak age of diagnosis for male and female individuals in our study—for example, a longer follow-up period and increased awareness of ASD can both lead to more adults receiving an ASD diagnosis.[2 27 29] The inclusion of outpatients in the Swedish national patient register from 2001 onwards also inflated the age of ASD diagnosis, as it led to late inclusion of people who had already received a diagnosis as outpatients. However, we also identified a higher peak age at diagnosis for female individuals (15-19 years) compared with male individuals (10-14 years). Two British studies that followed a birth cohort to age 25 years gave similar results: these studies found that children assessed as having a high likelihood of ASD at 6 months to 9 years old were predominantly male (73%), while no significant difference explained by sex was found among people identified as having late emerging ASD traits.[30 31]

Our results may provide a more comprehensive understanding of the findings of earlier studies. For example, a meta-analysis of 54 studies reported a cMFR for ASD of 4.2 (95% CI 3.8 to 4.6), compared with 1.6 (1.6 to 1.7) in our study, but with substantial variability between studies (I^2=90.9%). Only one of the 54 studies included in the meta-analysis examined the MFR by age at diagnosis, and none considered calendar period or birth cohort. This, in addition to variations in the age range of participants (0-18 years, mean 7.4 (standard deviation 2.9) years), may explain part of the differences between the studies. The cMFR was lower when ASD was ascertained from screening the general population to identify rather than being identified through diagnostic records: odds ratio 3.2 (95% CI 2.9 to 3.8).[4] Many epidemiological studies rely on questionnaire based screening data, which may also contribute to the variability in reported cMFRs.[4 5 9 32]

The high MFR may be linked to the so called female protective effect,[6] whereby female individuals show greater genetic resilience, enabling them to carry more alleles contributing to ASD before reaching the threshold for an ASD diagnosis.[6 8] However, compelling evidence for this theory is mixed. Greater heritability (ie, higher genetic contribution) was also identified as contributing to greater prevalence of ASD in male individuals.[21] The greater heritability in these individuals may have been observed because non-genetic factors contribute more to ASD in female individuals, including diagnostic ascertainment and differences in clinical presentation.[21]

Lower rates of ASD diagnosis in female individuals have also been attributed to a sex bias in both case ascertainment and clinical diagnosis, potentially resulting from differences in clinical presentation by sex and assessments and criteria favouring detection in male individuals.[4 9 28] For example, recent increases in rates of ASD diagnoses in female individuals have been linked to the widening of diagnostic criteria.[33] Camouflaging of traits associated with ASD (ie, taking behavioural cues from peers, including mimicking speech or expressions[9]) may also be more common in this group.[33] In such cases, ASD-like behaviours may only become detectable during adolescence, when social interactions become more complex.[9 27] These characteristics can lead to a later age at diagnosis that only becomes visible with sufficiently long follow-up.[29] In addition, because comprehensive screening occurs at younger ages in Sweden, adolescents and adults are more likely to access mental health services through self-referral. Earlier data suggest that women are more likely to seek general healthcare,[34] suggesting more complex social and cultural factors also lead to the increase in diagnosis in young female adults. The clear increase in ASD diagnoses received by adolescent female individuals documented in our study could thus be interpreted in several ways. Firstly, differences in presentation or application of diagnostic criteria by sex and age, or some relatively later manifestation of biological traits in female individuals (ie, a sex-by-age interaction on the impact of biological traits). Lastly, differences in how individuals come to clinical attention that vary by age and by sex.

The misattribution of symptoms to a previously identified condition has been recognised in the diagnosis of psychiatric conditions since the 1980s.[10] This phenomenon may have influenced the age of ASD diagnosis and variations in the MFR with age at diagnosis. During the past decade, the burden of co-occurring psychiatric conditions in individuals with ASD has been increasingly identified both in epidemiological studies and in clinical practice.[35] Studies suggest that nearly 70% of individuals with a diagnosis of ASD have at least one additional psychiatric condition.[35 36] Recent studies, one of which had a population partly overlapping with ours, found that female individuals are more likely than male individuals to have an earlier psychiatric diagnosis before receiving a diagnosis of ASD, and ASD is generally diagnosed at a later age.[37 38] In the past, diagnosis of co-occurring conditions has led to ASD being missed. However, greater recognition of ASD in recent years could now be having the opposite effect, leading to an increase in rates of ASD diagnosis among those presenting with co-occurring conditions. This may partly explain the change in the MFR by age at diagnosis.

Strengths and limitations of this study

A major strength of this study is the size and availability of clinically ascertained ASD. Clinical ascertainment of ASD using internationally recognised diagnostic criteria (DSM-V) allows outcomes to be generalised to similar populations. The ability to link data for a whole population to childhood medical and developmental assessment records in a publicly funded and operated healthcare system almost eliminated selection bias. Longer term studies allowed us to disentangle the effects of different time scales. However, using register data restricted our assessment of ASD type to specific ICD-10 coded categories, meaning we had

less information about specific traits or clinical details, which could have enhanced the granularity of the study and provided a clinical perspective. Furthermore, the study does not specifically address comorbid conditions associated with ASD, such as co-occurring intellectual disability, attention deficit/hyperactivity disorder, depression and anxiety, or syndromic ASD. We also did not consider potential modifiers of the MFR, such as preterm birth. These conditions and variables require specific studies that were beyond the scope of our current research. In addition, measuring time dependent effects limited our ability to control for within cohort confounders, such as shared genetic and environmental conditions like parental mental health. These factors may increase the likelihood of ASD diagnosis within families and have been shown to unequally affect male individuals.[8] The lack of outpatient data before 2001 led to later age at ASD diagnosis in the earlier cohorts, which may have led to the difference in age at diagnosis between male and female individuals being underestimated. It should be noted that the statistical modelling used in figure 3 to evaluate the effects of changes in diagnostic intensities from 2016 to 2022 and project them to 2024 were partially based on data that do not fully cover the target years. This limitation is reflected in the much wider confidence intervals for the projections in 2024.

Conclusions

The findings, involving analysis of the Swedish population over a period of more than 35 years, indicate that the MFR for ASD has decreased over time, and that diagnosis of ASD has increased. This suggests that the MFR for ASD may be significantly lower than previously thought—to the extent that, in Sweden, it may no longer be distinguishable by adulthood. The decreasing MFR over time highlights the need to investigate why female individuals receive a diagnosis of ASD later than male individuals. Further research should focus on phenotypic differences in how ASD manifests by sex and the implications for screening and diagnostic practices.

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Web appendix: Supplementary materials