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Sex differences in the global burden of autism spectrum disorders: An analysis based on GBD 2021 data

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ABSTRACT

Objective: Autism spectrum disorder (ASD) has become an increasingly serious global public health challenge, with a continuously rising disease burden and marked sex differences. This study aims to evaluate the long-term trends and global distribution patterns of sex differences in the burden of ASD and to project future changes, thereby providing evidence for ASD prevention and management.

Methods: Based on the Global Burden of Disease (GBD) 2021 data, disability-adjusted life years (DALYs) for ASD were extracted for 204 countries and territories. Combined with the sociodemographic index (SDI), the average annual percentage change (AAPC) was used to analyze sex differences in temporal trends and spatial distribution of ASD burden from 1990 to 2021, and to project trends from 2022 to 2050.

Results: From 1990 to 2021, the global age-standardized DALY rate (ASDR) for ASD was significantly higher in males than in females, and this pattern is projected to persist through

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2050. The absolute difference (AD) in ASDR ranged from 103.5 to 105.3 per 100 000, and the relative difference (RD) ranged from 1.0 to 1.1, with the most pronounced sex differences observed in East Asia and high-SDI regions. The male ASDR showed an increasing trend from 1990 to 2021, whereas the female ASDR is projected to increase after 2021, particularly in Africa. In 2021, global DALYs for ASD peaked among children under 5 years of age (221.9 per 100 000 in males and 112.8 per 100 000 in females), and the relative difference in DALYs increased with age. The absolute difference in DALYs during adulthood generally declined but increased among young adults and those aged ≥70 years, consistent with the pattern observed for relative differences. At the national level, sex differences were positively correlated with SDI and universal health coverage (UHC), and negatively correlated with the gender inequality index (GII) (all P<0.001). Spain, Japan, Singapore, South Korea, and China were identified as outliers to these associations.

Conclusion: Sex differences in the burden of ASD persist globally and increase with age. Targeted prevention and control strategies tailored to different sexes and age groups are warranted.

KEY WORDS autism spectrum disorder; sex differences; Global Burden of Disease; disability-adjusted life years; sociodemographic factors

基于GBD 2021数据分析孤独症谱系障碍全球疾病负担的性别差异

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［摘 要］目的：孤独症谱系障碍(autism spectrum disorder，ASD)已成为全球范围内日益严峻的公共卫生挑战，导致的疾病负担持续增加，并伴有显著的性别差异。本研究评估ASD疾病负担性别差异的长期趋势与全球分布模式，并预测其未来变化，旨在为ASD的干预及管理提供依据。**方法：**基于2021年全球疾病负担(Global Burden of Disease，GBD)数据，提取204个国家及地区ASD的伤残调整寿命年(disability-adjusted life years，DALYs)，结合社会人口学指数(sociodemographic index，SDI)，采用平均年度百分比变化(average annual percentage change，AAPC)分析1990—2021年ASD疾病负担时间趋势与空间分布的性别差异，并预测2022—2050年的变化。**结果：**1990—2021年全球ASD年龄标准化DALY率(age-standardized DALY rate，ASDR)男性显著高于女性，预计2022—2050年趋势相同。其中，基于性别的ASDR的绝对差异为103.5/10万~105.3/10万，相对差异为1.0~1.1，且该性别差异在东亚和高SDI

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地区最为显著。男性ASDR在1990—2021年呈上升趋势，女性ASDR预计在2021年后增长，该趋势在非洲尤为明显。2021年，全球ASD的DALYs在5岁以下儿童中达到峰值(男性为221.9/10万；女性为112.8/10万)，且DALYs的相对差异随年龄增长而增加。成年期DALYs的绝对差异整体下降，但在青年及≥70岁人群中呈上升趋势，且与相对差异变化模式一致。在国家层面，性别差异与SDI、全民健康覆盖(universal health coverage，UHC)呈正相关，与性别不平等指数(gender inequality index，GII)呈负相关(均P<0.001)；西班牙、日本、新加坡、韩国及中国偏离此关联。**结论：**ASD疾病负担的性别差异在全球持续存在，并随年龄增长而加剧，需制订针对不同性别与年龄阶段的精准防控策略。

[**关键词**] 孤独症谱系障碍；性别差异；全球疾病负担；伤残调整寿命年；社会人口学因素

Autism spectrum disorder (ASD) encompasses a broad range of genetic neurobehavioral conditions, primarily characterized by developmental challenges in social communication and stereotypical, rigid, or repetitive behaviors[1]. Since its identification in 1943, ASD has garnered increasing attention[2]. It is a complex condition with an unclear etiology and no current cure, typically manifesting in infancy and often becoming evident by the age of three[3]. While individuals with ASD generally have a normal life expectancy, they often require varying levels of lifelong care from their parents or caregivers[4]. Beyond individual challenges, the impact of ASD extends to families, healthcare systems, communities, and society as a whole.

Between 1990 and 2019, the global prevalence of ASD increased from 20.3 million to 28.3 million cases, representing a 39.3% rise and corresponding to 4.3 million disability-adjusted life years (DALYs), a measure of overall disease burden[5-6]. A key feature of this increase is the well-documented sex difference in prevalence, with males diagnosed approximately three to four times more frequently than females[7]. Hypotheses for this disparity point to both biological and social factors. Biologically, sex-specific genetic and hormonal influences are believed to play a significant role in determining susceptibility to ASD[8]. Socially, gender norms may shape how ASD is recognized and treated, often leading to underdiagnosis and insufficient support for females with ASD[9]. Together, these biological and social influences contribute to the overall burden of ASD.

Understanding sex-based differences in ASD burden across diverse socioeconomic contexts and geographic regions is essential for designing effective and equitable interventions. These disparities are shaped by a complex interplay of biological and social determinants of health, both of which evolve with age[10]. As global populations age, it becomes increasingly important to examine how sex differences in ASD manifest across different life stages, particularly in older age groups where research remains limited[11-12]. Moreover, variations in cultural and societal factors across regions and socioeconomic strata may influence patterns of sex difference in ASD[13-14], further complicating the global picture. Addressing these variations through targeted, evidence-based approaches is crucial for reducing inequities and promoting health equity in the management and prevention of ASD.

Several studies have examined the global epidemiology of ASD using data from Global Burden of Disease (GBD) study[6, 15-17]. Yang, et al[6] analyzed GBD 2019 data and found no significant changes in the age-standardized rate over time, with sociodemographic index (SDI)-related disparities persisting from 1990 to 2019. They concluded that the global burden of ASD has remained predominantly in males and disproportionately affects higher-SDI populations. In contrast, Solmi, et al[17] emphasized the need for greater focus on female patients, noting that this group has historically been underrepresented in ASD epidemiological and clinical research. Li, et al[16] conducted a bibliometric analysis to explore potential ASD risk factors in addition to GBD data. Moreover, another study[15] highlighted the burden of ASD among children under 5 years old, underscoring the importance of addressing early-life disparities using GBD 2019 data.

A recent study[18] has presented updated global estimates of ASD prevalence and health burden based on GBD 2021, an in-depth understanding of sex differences in ASD across age groups, socioeconomic strata, and geographic regions over the past and next 30 years remains limited. Using data from the GBD 2021

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and its forecasts, this study aims to evaluate the long-term trends and global distribution patterns of sex differences in the burden of ASD and to project future changes, thereby providing evidence for ASD prevention and management.

1 Materials and methods

1.1 Ethics statements

All data used in this study were sourced from publicly accessible databases and adhered to relevant ethical standards and data usage permissions. The study did not involve any personally identifiable information, and thus, no additional ethical approval was required.

1.2 Data sources

We used estimates from GBD 2021 and GBD Foresight studies to quantify sex differences in the global burden of ASD across the lifespan. The GBD 2021 Results Database, publicly accessible through the GBD Collaborative Network website, reports the estimates of disease burdens (e. g., mortality and morbidity) from 1990 to 2021 for 371 diseases and injuries across 204 countries and territories. For ASD, the epidemiological systematic literature review was initially conducted for GBD 2017 and updated in April 2021 for the GBD 2021 study. The GBD foresight study provides cause-specific forecasts of mortality, years of life lost, years lived with disability, and DALYs by age and sex through 2050 for 204 countries and territories under 5 scenarios: 1 reference scenario (the most likely future, based on historical trends) and 4 alternative scenarios in which specific risk factors are eliminated by 2050 (Safer environment scenario, improved childhood nutrition and vaccination scenario, improved behavioral and metabolic risks scenario, and a combination of these 3 scenarios) [19]. This study used the GBD Foresight reference scenario.

1.3 Methods

The GBD study provides a range of estimates for disease burdens by the Institute for Health Metrics and Evaluation (IHME, 2024). This study retrieved age-standardized, age-specific, and sex-specific GBD estimates to assess DALY rates (per 100 000 population) for males and females with ASD. DALY accounts for both the severity of a condition and its impact on quality of life, offering a comprehensive and comparable measure of disease burden across populations. One DALY represents the loss of one year of full health. We extracted age-standardized DALY rate (ASDR) and 95% uncertainty interval (*UI*; representing the 2.5th and 97.5th percentiles) for ASD globally[20], disaggregating them by sex, age group, region, and income group from 1990 to 2050.

To evaluate sex-based disparities, we calculated the absolute difference (AD) in DALYs by subtracting female DALYs from male DALYs and the relative difference (RD) by dividing the AD by the female DALY rate. Additionally, we assessed changes in DALY between 1990 and 2021 and between 2021 and 2050 by calculating relative change (RC) for each sex.

Subgroup analyses were conducted to explore specific variations. We categorized age groups based on the disease profile of ASD: <5 years (toddler/preschool children), 5－14 years (school-aged children), 15－49 years (young adults), 50－69 years (middle-aged adults), and ⩾70 years (older adults) [17, 21]. Furthermore, we analyzed data based on the World Bank income classifications (low, lower-middle, upper-middle, and high groups) and World Bank regions (Sub-Saharan Africa, East Asia, South Asia, North Africa & Middle East, Latin America & Caribbean, High-income North America, and Cetral Europe & Easter Europe & Central Asia).

Additionally, we extracted data for 5 SDI groups from 1990 and 2021. SDI, published by IHME, measures a country's sociodemographic development based on income, education, and fertility, with 5 levels ranging from low to high (low, low-middle, middle, high-middle, and high). Furthermore, we explored the relationships between sex differences in the ASD burden and SDI, universal health coverage (UHC), and the gender inequality index (GII). UHC, provided by the World Health Organization (WHO), tracks progress in health service coverage using 23 indicators, with values ranging from 0 to 100[22]. GII, published by the United Nations Development Programme, measures gender inequality in reproductive health, empowerment, and the labor market, with lower values indicating greater equality[23].

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1.4 Statistical analysis

All analyses were conducted using R software (version 4.3.1). We analyzed the ADs and RDs in DALY between females and males across age groups, socioeconomic strata, and geographic regions. We calculated the average annual percentage change (AAPC) and its 95% confidence interval (*CI*) to describe temporal trends in sex differences in the ASD burden from 1990 to 2050 using the Joinpoint regression models. AAPC with a 95% *CI* >0 indicates an increasing trend, an AAPC with a 95% *CI* <0 indicates a decreasing trend, and an AAPC with a 95% *CI* including 0 indicates a stable trend[24].

We performed Pearson correlation tests to estimate the associations between ADs/RDs of ASD and GII, SDI, and UHC. The correlation coefficient (r^2) and its 95% *CI* were reported. Polynomial curves were also modeled. A two-sided *P* value <0.05 was considered statistically significant.

2 Results

2.1 Sex differences in ASDR at global, regional, and national levels

Globally, the ASDR was 195.9 per 100 000 (95% *UI* 133.7 to 274.9) for males and 92.4 (95% *UI* 63.7 to 130.1) for females in 1990, yielding an AD of 103.5 per 100 000. By 2021 the ASDR increased to 199.8 per 100 000 (95% *UI* 136.3 to 282.0) in males and 94.5 per 100 000 (95% *UI* 64.5 to 133.0) in females (AD=105.3) (Table 1). The ASDRs are projected to rise further by 2050, reaching 203.7 (95% *UI* 138.7 to 286.4) in males and 99.7 (95% *UI* 68.5 to 140.2) in females (AD= 104.0). Despite these increases, the global RD remained between 1.0 and 1.1 over the 60 years.

Table 1 Sex differences in ASDR for ASD per 100 000 population in 1990, 2021, and 2050, stratified by global level, World Bank income groups, SDI level, and World Bank regions

Year and characteristics	ASDR (95% *UI*)		AD	RD
	Males	Females		
1990				
Global	195.9(133.7 to 274.9)	92.4(63.7 to 130.1)	103.5	1.1
World Bank income levels				
Low	202.2(139.2 to 284.1)	107.4(74.8 to 150.6)	94.8	0.9
Lower-middle	173.2(118.6 to 243.3)	91.4(63.3 to 128.4)	81.8	0.9
Upper-middle	177.9(121.3 to 250.9)	76.6(52.6 to 107.3)	101.3	1.3
High	270.8(187 to 380.5)	118.3(81.2 to 165.1)	152.5	1.3
SDI level				
Low	189.6(131.8 to 266.5)	102.2(70.9 to 143.1)	87.4	0.9
Low-middle	169.6(116.7 to 238.2)	88.7(61.6 to 124.4)	80.9	0.9
Middle	171.1(116.1 to 240.9)	78.5(54.2 to 110.8)	92.6	1.2
High-middle	202.7(139.4 to 286.6)	89.0(60.9 to 124.4)	113.7	1.3
High	270.6(187.0 to 380.3)	119.0(81.7 to 165.9)	151.6	1.3
World Bank regions				
Sub-Saharan Africa	212.3(146.1 to 297.7)	114.3(79.6 to 160.3)	98.0	0.9
East Asia	170.0(116.0 to 240.2)	60.4(41.2 to 85.4)	109.6	1.8
South Asia	164.2(113.1 to 230.7)	85.5(59.3 to 119.5)	78.7	0.9
North Africa and Middle East	183.6(126.8 to 256.5)	96.8(66.6 to 135.7)	86.8	0.9
Latin America and Caribbean	168.0(115.5 to 235.2)	86.5(59.9 to 121.9)	81.5	0.9
High-income North America	271.6(188.4 to 381.6)	130.2(90.3 to 180.1)	141.4	1.1
Central Europe, Eastern Europe, and Central Asia	222.6(151.7 to 312.9)	120.5(82.2 to 167.7)	102.1	0.8

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Table 1 (to be continued)

Year and characteristics	ASDR (95% *UI*)		AD	RD
	Males	Females		
2021				
Global	199.8(136.3 to 282.0)	94.5(64.5 to 133.0)	105.3	1.1
World Bank income levels				
Low	208.3(142.1 to 293.6)	110.3(76.6 to 155.6)	98.0	0.9
Lower-middle	179.3(121.4 to 251.3)	93.1(64.2 to 131.1)	86.2	0.9
Upper-middle	188.1(128.7 to 265.8)	77.9(52.7 to 109.7)	110.2	1.4
High	275.2(191.1 to 386.8)	119.5(81.0 to 167.8)	155.7	1.3
SDI level				
Low	197.0(133.8 to 276.8)	104.9(73.0 to 147.7)	92.1	0.9
Low-middle	176.2(119.4 to 247.2)	91.2(62.9 to 128.7)	85.0	0.9
Middle	180.3(122.6 to 254.8)	82.8(56.1 to 117.6)	97.5	1.2
High-middle	210.0(144.6 to 297.2)	87.3(59.2 to 122.5)	122.7	1.4
High	273.4(189.3 to 384.9)	119.5(81.0 to 167.9)	153.9	1.3
World Bank regions				
Sub-Saharan Africa	218.1(148.1 to 306.9)	116.3(80.8 to 164.1)	101.8	0.9
East Asia	184.2(125.4 to 259.8)	61.2(40.6 to 86.8)	123.0	2.0
South Asia	167.9(114.2 to 235.6)	86.2(59.6 to 121.2)	81.7	0.9
North Africa and Middle East	187.9(127.0 to 265.0)	97.1(66.5 to 136.8)	90.8	0.9
Latin America and Caribbean	172.6(116.8 to 243.8)	86.4(58.7 to 121.0)	86.2	1.0
High-income North America	277.1(192.5 to 388.2)	130.6(89.2 to 182.8)	146.5	1.1
Central Europe, Eastern Europe, and Central Asia	228.7(157.2 to 321.8)	120.1(81.6 to 166.7)	108.6	0.9
2050				
Global	203.7(138.7 to 286.4)	99.7(68.5 to 140.2)	104.0	1.0
World Bank income levels				
Low	214.3(146.3 to 302.7)	114.0(79.3 to 161.5)	100.3	0.9
Lower-middle	186.6(126.6 to 261.4)	97.3(66.9 to 136.7)	89.3	0.9
Upper-middle	190.8(130.6 to 270.5)	82.0(55.8 to 115.2)	108.8	1.3
High	273.2(189.3 to 384.4)	118.3(80.2 to 166.2)	154.9	1.3
SDI level				
Low	209.9(141.9 to 295.0)	111.8(77.7 to 157.3)	98.1	0.9
Low-middle	186.8(127.2 to 262.0)	97.4(67.0 to 137.0)	89.4	0.9
Middle	181.1(123.6 to 256.0)	85.2(58.0 to 120.6)	95.9	1.1
High-middle	232.0(159.8 to 327.8)	94.1(64.0 to 132.2)	137.9	1.5
High	259.5(179.6 to 365.4)	117.7(79.9 to 165.0)	141.8	1.2
World Bank regions				
Sub-Saharan Africa	222.5(151.1 to 313.0)	118.6(82.4 to 167.5)	103.9	0.9
East Asia	187.4(127.8 to 264.3)	62.2(41.3 to 88.5)	125.2	2.0
South Asia	169.7(115.6 to 238.3)	87.3(60.4 to 122.9)	82.4	0.9
North Africa and Middle East	189.2(128.1 to 267.1)	98.0(67.4 to 137.8)	91.2	0.9
Latin America and Caribbean	174.0(117.6 to 245.8)	87.1(59.4 to 121.7)	86.9	1.0
High-income North America	278.1(193.0 to 390.3)	131.1(89.6 to 183.6)	147.0	1.1
Central Europe, Eastern Europe, and Central Asia	228.6(156.8 to 321.9)	120.3(81.9 to 167.3)	108.3	0.9

ASD: Autism spectrum disorder; SDI: Sociodemographic index; DALY: Disability-adjusted life year; ASDR: Age-standardized DALY rate; *UI*: Uncertainty interval; AD: Absolute difference; RD: Relative difference.

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Regionally, the largest sex differences were consistently observed in World Bank upper-middle and high-income countries, high-middle and high-SDI regions, and in high-income North America and East Asia across 1990, 2021, and 2050 (Table 1). East Asia exhibited the highest RD, ranging from 1.8 to 2.0 across all 3 time points. National-level analyses yielded consistent findings were in Supplementary Table 1 (https://doi.org/10.57760/sciencedb.xbyxb.00099).

2.2 RCs in ASDR (1990—2021 and 2022—2050) by sex

From 1990 to 2050, the increase in ASD-related disease burden among males mainly occurred in 1990—2021, whereas for females, most of the rise is projected to occur between 2022 and 2050. Between 1990 and 2021, South Korea, Japan, Singapore, the United Kingdom, Equatorial Guinea, Spain, China, and the Maldives exhibited RCs in male ASDR>12 (Supplementary Figure 1A, Supplementary Table 2; https://doi. org/10.57760/sciencedb. xbyxb. 00099). During the same period, female ASDR declined in over 80 countries (RC<0) (Supplementary Figure 1C, Supplementary Table 2; https://doi.org/10.57760/sciencedb.xbyxb.00099). From 2022 to 2050, female ASDR is projected to increase in nearly all countries except Venezuela (Supplementary Figure 1D, Supplementary Table 2; https://doi. org/10.57760/sciencedb. xbyxb. 00099), with the largest increases for both sexes expected in African countries (Supplementary Figure 1B and 1D, Supplementary Table 2; https://doi.org/10.57760/sciencedb.xbyxb.00099).

2.3 Sex disparities in age-specific DALY rates

In 2021, age-specific DALY rates were consistently higher in males than females. The highest rates were observed in the <5 years age group (males: 221.9 per 100 000; females: 112.8 per 100 000; Figure 1). DALY rates decreased with age for both sexes, from 221.9 (<5 years) to 131.1 (≥70 years) in males and from 112.8 to 48.5 in females. Conversely, RDs increased steadily with age, reaching 1.7 in the ≥70 years group (Supplementary Table 3, https://doi.org/10.57760/sciencedb.xbyxb.00099). Regionally, East Asia consistently exhibited the most pronounced disparities, with RDs ranging from 2.0 (<5 years) to 2.5 (≥70 years) (Figure 1; Supplementary Table 3, https://doi.org/10.57760/sciencedb. xbyxb.00099). Comparable patterns were seen in 1990 and are projected for 2050 (Supplementary Figure 2 and 3, Supplementary Table 3; https://doi.org/10.57760/sciencedb.xbyxb.00099).

2.4 Trends in age-specific DALY rates disparities (1990—2050)

Globally, ADs in DALY rates decreased over time in the 15－49 years (AAPC=－0.057, 95% *CI* －0.062 to －0.051, *P*<0.001) and 50－69 years groups (AAPC=－0.052, 95% *CI* －0.083 to －0.022, *P*=0.001), but increased in the <5 years (AAPC=0.063, 95% *CI* 0.057 to 0.070, *P*<0.001), 5－14 years (AAPC=0.029, 95% *CI* 0.022 to 0.035, *P*<0.001) and ≥70 years (AAPC=0.114, 95% *CI* 0.056 to 0.172, *P*<0.001) from 1990 to 2050 (Figure 2A; Supplementary Table 4－5, https://doi.org/10.57760/sciencedb.xbyxb.00099). Similarly, RDs declined in the <5 years (AAPC=－0.135, *P*<0.001), 5－14 years (AAPC=－0.167, *P*<0.001), and 15－49 years (AAPC=－0.185, *P*<0.001), remained stable in 50－69 years (AAPC=－0.021, *P*=0.250), and increased in the ≥70 years (AAPC=0.254, *P*<0.001) (Figure 2B; Supplementary Table 4－6, https://doi.org/10.57760/sciencedb.xbyxb.00099). Region- specific analyses showed similar patterns, with age groups declining in high SDI regions (Supplementary Figure 4; Supplementary Table 4－5; https://doi.org/10.57760/sciencedb.xbyxb.00099) and RDs increasing in most regions except for middle and high SDI settings (Supplementary Figure 5, Supplementary Table 4－6; https://doi.org/10.57760/sciencedb.xbyxb.00099).

2.5 Correlations of sex differences with SDI, GII, and UHC

At the country level, both RD and AD were positively correlated with SDI (RD: *r*=0.514, *P*<0.001; AD: 0.508, *P*<0.001; Figure 3A and 3B) and UHC (RD: *r*=0.532, *P*<0.001; AD: *r*=0.517, *P*<0.001; Figure 3C and 3D), but negatively correlated with GII (RD: *r*=－0.574, *P*<0.001; AD: *r*=－0.634, *P*<0.001; Figure 3E and 3F). Spain, Japan, Singapore, South Korea, and China displayed outlier levels of sex differences, deviating from the model-predicted trends (Figure 3; Supplementary Table 7, https://doi.org/10.57760/sciencedb.xbyxb.00099).

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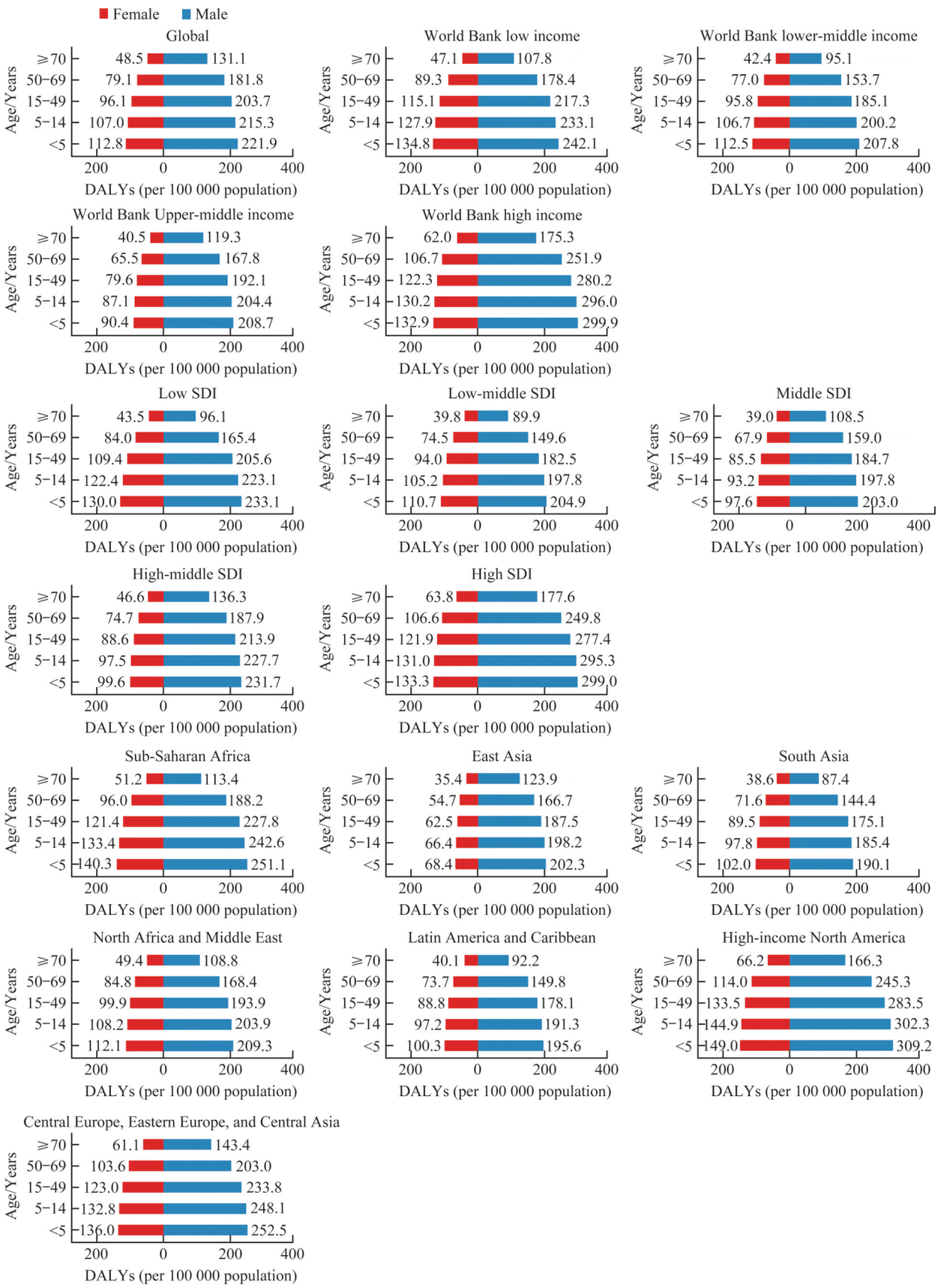


Figure 1 Sex differences in age-specific DALY rates for ASD across age groups in 2021, stratified by global level, World Bank income groups, SDI, and World Bank regions

ASD: Autism spectrum disorder; DALY: Disability-adjusted life year; SDI: Sociodemographic index.

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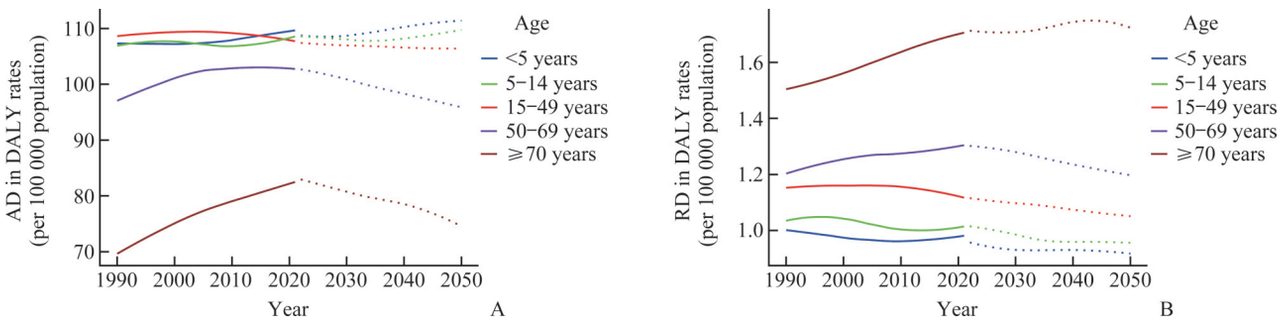


Figure 2 Global trends in sex differences in age-specific DALY rates for ASD from 1990 to 2021 and projected to 2050

A: AD. B: RD. AD: Absolute difference; RD: Relative difference.

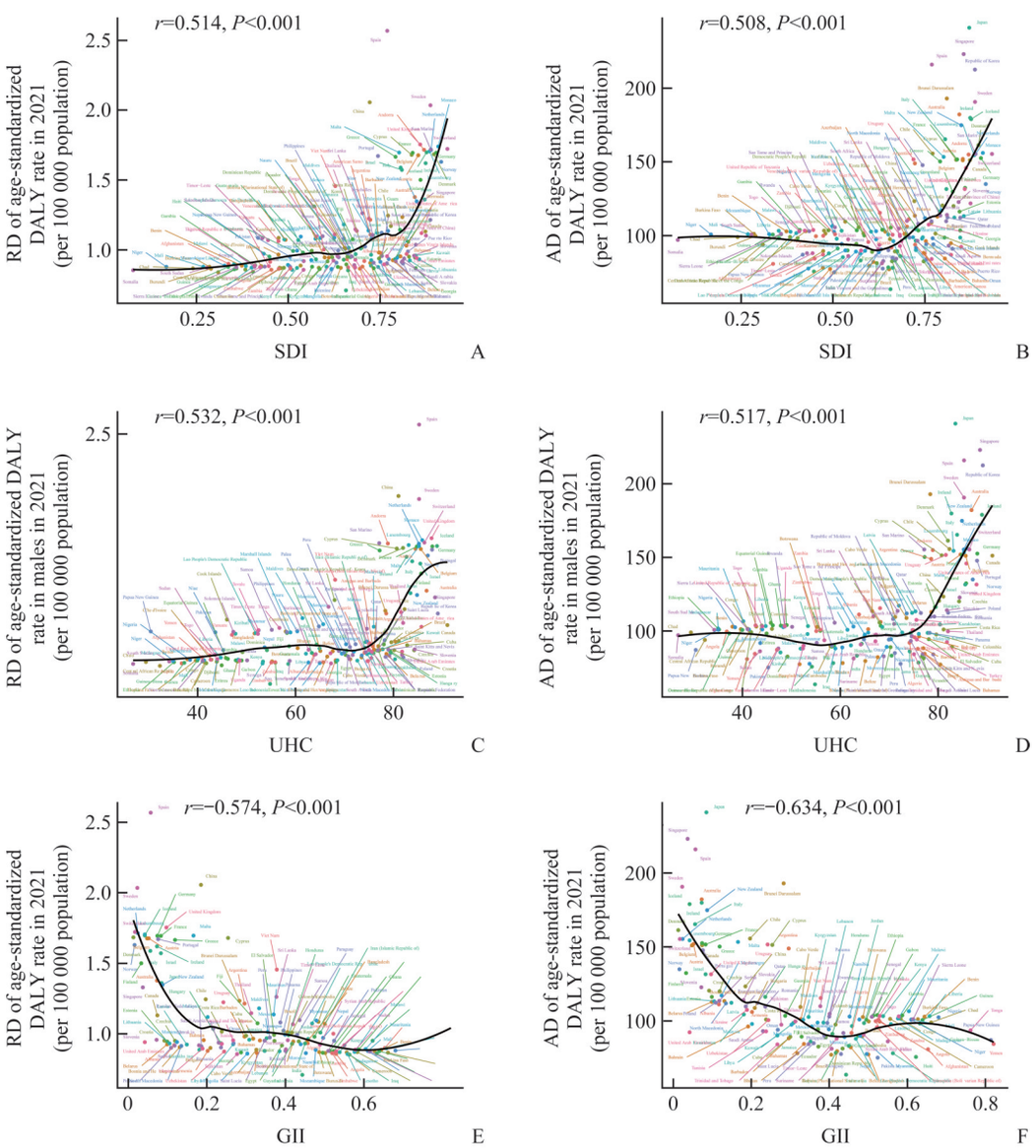


Figure 3 Associations between sex differences in ASD and SDI, UHC, and GII across countries and territories in 2021

A: RD and SDI; B: AD and SDI; C: RD and UHC; D: AD and UHC; E: RD and GII; F: AD and GII. UHC: Universal health coverage index; GII: Gender inequality index

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3 Discussion

To the best of our knowledge, this is the first study to use the most recent GBD data to analyze sex differences in DALY rates for ASD from 1990 to 2050. Consistent with earlier GBD estimates[6, 16], our findings confirm that males consistently bear a higher ASD burden than females. This study extends previous findings by analyzing sex differences across different countries, regions, age groups, and trends over time, while also examining correlations with the SDI, UHC, and GII.

Our findings indicate that higher sex differences have consistently occurred in high-income and high-SDI regions from 1990 to 2050, with East Asia showing particularly pronounced disparities. In this region, the ASDR for ASD in males was more than twice that of females, with pronounced disparities across all age groups. These disparities may partly result from the exceptionally high prevalence of ASD in countries such as South Korea and Japan, where rates are particularly high in males[25-26]. Moreover, deeply ingrained cultural norms, such as ‘son preference’[11], may contribute to these disparities. This preference, rooted in profound social, economic, and cultural traditions in countries like China, Japan, and South Korea[27], has led to imbalanced sex ratios[28] and restricted access to rehabilitation and education for females with ASD[29]. A study[25] in South Korea further reinforces this, showing that in 2015, 87.5% of the total economic cost burden of ASD was associated with male patients, while only 12.5% was attributed to female patients[25].

The analysis of sex-specific trends in ASD-related disease burden from 1990 to 2050 shows that while the increase in burden for males was concentrated between 1990 and 2021, females are projected to experience a more pronounced rise between 2021 and 2050. These rising trends are likely driven by factors such as improvements in awareness, detection and diagnosis of ASD, as well as greater financial investment in support services since ASD was first reported in 1943[2]. Consequently, the number of individuals with ASD and the associated disease burden has surged[30-31]. The difference in sex-specific trends may be due to improvements in the identification and support of females with ASD[32-33], which could help reduce the sex-based disparity in growth trends in the future. Over the next 30 years, the growing ASD burden for both sexes is projected to be most pronounced in Africa. Despite progress in raising awareness and improving access to services, significant gaps remain in ensuring timely diagnosis, appropriate treatment, and adequate support for individuals with ASD in Africa[34]. Addressing these challenges necessitates enhanced efforts in screening, diagnosis, and intervention to bridge these gaps and achieve better outcomes for individuals with ASD in the region.

Globally, the DALY rates for ASD were consistently higher in males than in females across all age groups in 2021, with the highest rates observed in children under 5 years for both sexes. This finding aligns with previous studies[6, 21], reinforcing the importance of providing early support to children with ASD[15, 17]. Interestingly, sex differences in DALY rates were most pronounced in individuals aged 70 and older, and this disparity is projected to continue growing from 1990 to 2050. The exact reasons for this pronounced disparity in the older age group are not fully understood, but several factors may contribute. First, the significant sex disparity among older individuals may stem from a large number of undiagnosed cases in females before the 1990s[35]. Additionally, higher mortality rates among older females with ASD may contribute to the underrepresentation of their long-term disease burden[36]. Second, aging-related disease burdens and health vulnerabilities, which are more pronounced in males[8], could further exacerbate the disease burden for males. However, these results should be interpreted with caution, as they do not account for demographic shifts such as increasing life expectancy, declining fertility rates, and the longer lifespan of women[37-38]. Given the expected growth of the elderly population and the widening sex differences, these findings underscore the need to consider both age- and sex-specific patterns in ASD care to ensure equitable support, particularly for the elderly.

Notably, sex differences in the ASD burden increased with higher SDI and UHC but decreased with

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greater GII. Higher SDI and UHC generally indicate greater awareness, improved understanding, and better access to healthcare services for ASD[39-41]. However, this progress may not equally benefit both sexes. For instance, issues such as delayed and missed diagnoses, mismatched rehabilitation and educational support, and disproportionately economic investment continue to have larger influences on female than male ASD patients[25, 42-43]. In contrast, the negative correlation between sex differences and GII may be misleading. This is because the GII primarily reflects gender-based disadvantage in areas such as reproductive health, empowerment, and the labor market[44]. This may not fully capture the biological and social difference of ASD by sex. Furthermore, a lower GII signifies greater gender equality, which is typically associated with higher sociodemographic development, including improved access to healthcare and education[45]. Therefore, the negative relationship between sex differences in the ASD burden and GII aligns with its positive association with SDI and UHC, reflecting broader trends in gender equality and health resource distribution. The exceptionally high sex differences in ASD burden observed in Spain, Japan, Singapore, South Korea, and China, which deviated from the model-predicted trends, may be attributed to factors such as low total fertility rates[46], high ASD prevalence[17], and cultural factors like son preference in these countries[47-48].

Several limitations of this study warrant mention. First, the accuracy of GBD 2021 estimates depends on data availability and quality; data from low-income countries may be less reliable due to limited epidemiological studies and healthcare infrastructure, potentially leading to underestimation or misclassification of ASD cases. Second, variations in diagnostic methods across data sources and changes in diagnostic criteria over time (e.g., DSM-IV to DSM-5) may affect the consistency of burden estimates and observed trends. Third, this study did not analyze risk factors contributing to ASD burden, which warrants future investigation. Fourth, although this study identified significant sex differences in high-income/high-SDI regions, especially East Asia, attributing these solely to cultural factors like son preference is insufficient; further research is needed to understand these disparities.

In conclusion, sex differences in the burden of ASD persist globally and increase with age, highlighting the need for gender- and age-sensitive policies and interventions.

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