International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Global Prevalence of Infertility Attributable to Sex Chromosome Abnormalities: Insights from the Global Burden of Disease Study

Ruiyao Zhao[1,*], Wenyu Sun[2,*], Xu Yang[1], Jianwei Wu[1], Yongsheng Li[1], Wenzhong Zheng[1]

[1]Department of Urology, Fujian Medical University Union Hospital, Fuzhou, People's Republic of China; [2]School of Basic Medical Sciences, Fujian Medical University, Fuzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenzhong Zheng; Yongsheng Li, Department of Urology, Fujian Medical University Union Hospital, 29 Xinquan Road, Gulou District, Fuzhou, Fujian Province, 350001, People's Republic of China, Email wenzhong_zheng@yeah.net; Lysdr163@163.com

Background: Klinefelter syndrome (KS) and Turner syndrome (TS) are chromosomal disorders characterized by gonadal dysgenesis, leading to male and female infertility, respectively. There is a significant gap in epidemiological data on infertility related to hereditary gonadal dysgenesis due to sex chromosomal abnormalities in individuals aged 15–49.

Methods: A systematic analysis was conducted to examine the prevalence and Years Lived with Disability (YLD) due to infertility linked to KS and TS across 21 regions and 204 countries from 1990 to 2021. Estimates for cases, age-standardized prevalence rates (ASPR), age-standardized YLDs, and average annual percentage changes (AAPCs) in prevalence and YLDs were calculated, stratified by age and socio-demographic index (SDI).

Results: The global burden of infertility due to gonadal dysgenesis shows significant gender and regional disparities. The prevalence of male infertility linked to KS gradually increased (ASPR rose from 11 to 12/100,000, AAPC=0.09, P<0.05) between 1990 and 2021, with the highest rates in Western and Eastern Europe (ASPR 19–20/100,000) and the fastest growth in East Asia (AAPC=0.44, P<0.05). In contrast, the prevalence of female infertility associated with TS slightly declined globally (ASPR decreased from 6.55 to 6.3/100,000, AAPC=−0.12, P<0.05), particularly in North America and Western Europe. Although absolute YLDs increased due to population growth, age-standardized rates remained stable, indicating no significant worsening of health impacts.

Conclusion: From 1990 to 2021, male infertility from KS increased gradually, while female infertility due to TS decreased slightly. There's an urgent need for better prepubertal identification, fertility preservation, and tailored screening, especially in Europe, East Asia, and North America. Data scarcity in low-SDI regions may distort infertility trend.

Keywords: Klinefelter syndrome, Turner syndrome, infertility, global burden of disease

Introduction

Infertility affects approximately 15–20% of couples worldwide.[1] It is estimated that male factors account for 30% to 50% of infertility cases.[2] In 2021, women with infertility accounted for approximately 66.7% of all global infertility cases.[3] In recent years, the incidence of infertility has been on the rise globally, particularly in industrialized regions. Current etiological research indicates inherited genetic abnormalities as one of causes of infertility,[4] with Klinefelter syndrome (KS,47,XXY) and Turner syndrome (TS,45,X) being critical contributors to gonadal dysgenesis.[5]

KS is the most common sex chromosome disorder leading to male infertility,[6] with an incidence of about 1 in 500 to 1000 males.[7] KS is typically caused by the nondisjunction of the X chromosome during meiosis, although the specific molecular mechanisms are not yet fully understood. Recent studies suggest that mutations in the Ubiquitin Specific Protease 26 (USP26) gene may interfere with the XY body (a specialized meiotic chromatin structure), leading to the production of a high proportion of XY aneuploid sperm and, consequently, the development of KS.[8] Typical clinical

Received: 29 May 2025
Accepted: 23 October 2025
Published: 5 November 2025

manifestations include small testes, gynecomastia, hypogonadism, and azoospermia, and other systemic symptoms, including impaired metabolic features (obesity, dyslipidemia, insulin resistance), thrombotic predisposition, osteoporosis, etc.[9] Patients with KS are usually unable to conceive naturally, and about 3% of male infertility cases are related to KS.[6] About 14% of Azoospermia cases are related to KS.[10] However, some patients may still achieve parenthood through assisted reproductive technologies, such as micro-testicular sperm extraction (m-TESE) combined with intracytoplasmic sperm injection (ICSI).[11,12]

TS is one of the most common causes of hypergonadotropic hypogonadism in females, with an incidence of about 1 in 2000 to 2500 female newborns.[13] Patients with TS typically exhibit gonadal dysgenesis, short stature, premature ovarian failure, and infertility due to the early loss of ovarian function.[14] TS can also lead to increased mortality rates.[15] The molecular mechanism may involve haploinsufficiency of certain genes that normally escape X-chromosome inactivation due to the missing X chromosome. Additionally, the missing X chromosome may cause epigenetic changes in other genes, leading to a wide range of clinical symptoms.[16] There is currently no cure for TS, but hormone replacement therapy can help alleviate symptoms of hypogonadism.[17] Similar to male infertility caused by KS, some patients with TS may also achieve fertility through assisted reproductive technologies.[18]

Quantitative fluorescent polymerase chain reaction (QF-PCR) and karyotype analysis are commonly employed screening methods.[19,20] Early screening is crucial for the treatment of KS. Current evidence indicates that early detection, appropriate medication, and multidisciplinary care are vital to addressing KS-related problems such as infertility and cancer risks.[21] However, only 10% of KS patients are diagnosed before puberty, highlighting a significant screening gap.[22] Therefore, assessing the global infertility burden attributable to KS and TS is urgently needed to inform evidence-based policy-making.

Current research primarily focuses on the prevalence of KS and TS. A Danish study revealed that there are 57 cases of KS per 100,000 newborn males and 59 cases of TS per 100,000 newborn females[23] A UK study of 240,000 women reported a TS prevalence of 88 per 100,000, while a US study of 595,612 males found a KS prevalence of 145 per 100,000.[24] Despite extensive epidemiological investigations into KS and TS, research on the disease burden of infertility caused by these conditions remains notably scarce. As reproductive technologies increasingly enable patients with KS and TS to conceive, therefore, conducting a comprehensive global study on the burden of infertility due to KS and TS is a crucial prerequisite for implementing relevant health policies.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) establishes a comprehensive framework to evaluate the impact of infertility across 204 countries and territories, affording valuable insights into emerging trends. This investigation delves into the global prevalence and years lived with disability (YLDs) lost due to infertility caused by KS in men and TS in women, focusing on the reproductive age group of 15 to 49 years. These data were analyzed by age, Socio-demographic index (SDI), regions, and nations, providing new perspectives and insights for epidemiological research on infertility.

Methods and Materials

The data source for this study is from GBD 2021. The estimates encompassed in the GBD 2021 span 204 countries and territories, grouped into 21 regions and subsequently consolidated into seven super-regions. Estimates for 371 diseases and injuries during the period from 1990 to 2021, including those for females, males, and both sexes combined, are included in the GBD 2021.[25] Based on health data collected from demographic surveillance, administrative reports, scientific research findings, health surveys, medical records, non-medical registries, and numerous other sources, GBD 2021 have conducted detailed estimates for each epidemiological parameter.[25] Other publications have described the methodology used for GBD 2021.[25,26] The SDI serves as a comprehensive indicator, encompassing the social and economic development factors that influence the health outcomes of each nation. On the basis of the SDI scores recorded for each country in 2021, they have been divided into five different quintiles: low, low-medium, medium, high-medium and high. In the SDI, the average years of education for persons over 15 years, the lagged income per capita and the total fertility rate for persons under 25 years were taken into account. Higher SDI values are characterised by regions with more advanced socio-economic and demographic progress.[25]

According to the case definition of KS (47, XXY) provided within GBD 2021, this condition may be described as a disorder characterised by a male patient being born with an extra X chromosome in all or some of his cells. It should be noted that the present study incorporates a number of other genotypes that possess additional X chromosomes. Meanwhile, TS, known as 45,XO, involves a partial or complete absence of an X chromosome in females. Notably, a subset of TS patients may not exhibit any symptoms. Additional details can be found in the supplementary materials.[25]

In GBD 2021, infertility is defined as the inability to conceive a child and subsequently have a live birth through vaginal intercourse without the use of contraceptives. Based on GBD 2021 cause list, several primary causes of infertility were identified, including congenital TS, KS, urogenital anomalies, endometriosis, polycystic ovary syndrome (PCOS), sexually transmitted infections (STIs) and maternal sepsis. Additional details can be found in the appendix of the referenced material.[25]

We extracted final GBD 2021 estimates for "Infertility due to Klinefelter syndrome" and "Infertility due to Turner syndrome" from the online Results Tool (http://ghdx.healthdata.org/gbd-results-tool). Metrics downloaded comprised ASPR, YLD and AAPC with their 95% uncertainty intervals for individuals aged 15–49 years (split into seven 5-year age bands), both sexes, across 204 countries, 21 GBD regions and 5 SDI region from 1990 to 2021. No additional exclusions or re-modelling were applied. We employed four distinct DisMod-MR 2.1 models to estimate the prevalence of infertility by gender and cause. In this study, the prevalence and YLDs were sourced from GBD 2021. Given that infertility caused by Turner and KS does not lead to death, DALYs—a comprehensive measure of disease burden that includes both YLDs and YLLs—are equivalent to YLDs only in this context. Furthermore, binary study-level covariates were used to minimise error. All rates are per 100,000 with 95% UIs of 1000 estimates. We followed the GATHER guidelines for cross-sectional studies and did not need ethical approval because the data were publicly available and anonymous.

Statistical Analysis

We directly extracted data on prevalence cases, YLDs, and their corresponding rates from GBD 2021. The age-standardized prevalence/YLDs rates were directly standardized using the GBD global age-standardized population as the reference. We employed Joinpoint Regression Analysis to identify significant changes in trends and divided the overall trend into multiple segments. Subsequently, AAPC was calculated as a summary measure reflecting the trend over the interval. In addition, the AAPC and its 95% uncertainty interval (UI) were calculated to evaluate the epidemiological trends within each section. If the AAPC and its 95% UI were above or below zero, respectively, the age-standardized rate (ASR) was considered to show an increasing or decreasing trend over time. Furthermore, this study estimated trends across global age groups and health system groups. Given the variations in the distribution of the SDI across countries between 1990 and 2021, we further calculated the distribution of incidence and YLDs for four health system groups and 27 regions. The relationship between AAPC and ASR with SDI was assessed using Spearman correlation analysis. Additionally, the age-standardized prevalence/YLDs distribution and their respective AAPC were analyzed for 204 countries. This study utilized R software (version 4.0.5). A p-value less than 0.05 was considered statistically significant.

Results

Global Burden of Infertility Ascribed to Sex Chromosome Abnormalities in Both Males and Females

At global level, in 1990, there were 329727 prevalent cases (95% UI: 251479–425778) of Kleinfelter syndrome-induced infertility among reproductive-aged men, with an ASPR of 11/100,000 (95% UI: 9–15). By 2021, this number had increased to 473157 (95% UI: 142991–236,948), accompanied by an ASPR of 12/100,000 (95% UI: 9–15) (Table 1). Moreover, there has been a consistent upward trend in the ASPR for infertility over the past 30 years, with an AAPC of 0.09 (95% CI: 0.04–0.13) (Table 1 and Figure S1A), which indicates the prevalence of this infertility condition is slowly increasing globally.

In 1990, the global YLDs due to male infertility caused by KS were 2474 (95% UI: 1087–5351), with an age-standardized YLDs rate of 0.09 /100,000 (95% UI: 0.04–0.19). By 2021, the YLDs increased to 3548 (95% UI: 1595–7525), while the age-standardized YLDs rate remained at 0.09/100,000 (95% UI: 0.04–0.19). From 1990 to 2021, the global AAPC in the age-standardized YLDs rate was 0.08 (95% CI: 0.05–0.12) (Table 2). Although the

https://doi.org/10.2147/IJWH.S542737

Table 1 The Prevalence of Male Infertility Impairment Owing to Klinefelter Syndrome and Their AAPCs from 1990 to 2021 at the Global and Regional Levels

	1990		2021		1990–2021	
	Prevalent Cases No. (95% UI)	ASPR per 100000 No. (95% UI)	Prevalent Cases No. (95% UI)	ASPR per 100000 No. (95% UI)	AAPC No. (95% CI)	P Value
Global	329727 (251,479–425,778)	11 (9–15)	473,157 (362,419–610,585)	12 (9–15)	0.09 (0.04–0.13)	0.000083
Socio-demographic index						
Low SDI	28552 (21,543–37,161)	12 (9–15)	69,167 (52,325–90,364)	12 (9–15)	−0.01 (−0.03–0.00)	0.142798
Low-middle SDI	67780 (51,249–88,224)	11 (9–15)	119,402 (91,218–154,706)	11 (9–15)	−0.03 (−0.05 - −0.01)	0.001246
Middle SDI	95351 (72,153–123,471)	10 (7–13)	132,400 (101,143–170,804)	11 (8–14)	0.29 (0.25–0.32)	0
High-middle SDI	67699 (51,510–87,294)	11 (9–15)	73,285 (55,701–94,776)	12 (9–15)	0.15 (0.05–0.24)	0.001902
High SDI	70064 (53,949–90,700)	15 (12–19)	78,552 (60,318–102,528)	16 (12–21)	0.16 (−0.29–0.62)	0.482121
Region						
Andean Latin America	2113 (1585–2767)	11 (8–14)	3719 (2827–4841)	10 (8–14)	−0.08 (−0.15 - −0.01)	0.033498
Australasia	1114 (843–1463)	10 (8–13)	1501 (1137–1950)	11 (8–14)	0.12 (0.04–0.19)	0.001865
Caribbean	1673 (1268–2169)	9 (7–11)	2146 (1627–2772)	9 (7–12)	0.06 (0.04–0.08)	0
Central Asia	5169 (3926–6694)	15 (11–19)	7269 (5502–9470)	15 (11–19)	0.07 (0.03–0.11)	0.001493
Central Europe	7076 (5379–9109)	11 (9–15)	6215 (4736–8146)	12 (9–16)	0.23 (0.14–0.31)	0
Central Latin America	7541 (5736–9780)	9 (7–11)	11,480 (8716–14,793)	9 (7–11)	0.01 (−0.01–0.02)	0.26845
Central Sub-Saharan Africa	3271 (2441–4371)	12 (9–16)	8629 (6548–11,161)	12 (9–16)	0.01 (−0.04–0.06)	0.670871
East Asia	62599 (46,954–82,129)	8 (6–11)	65,985 (49,588–86,236)	10 (7–13)	0.44 (0.36–0.52)	0
Eastern Europe	20086 (15,204–25,714)	18 (14–23)	16,880 (12,805–21,630)	19 (14–24)	0.13 (0.12–0.15)	0
Eastern Sub-Saharan Africa	11046 (8375–14,399)	12 (9–16)	27,544 (20,858–35,815)	12 (9–16)	−0.02 (−0.03 - −0.00)	0.010129
High-income Asia Pacific	10831 (8408–13,866)	12 (9–15)	9282 (7204–11,982)	12 (9–16)	−0.03 (−0.05 - −0.00)	0.024817
High-income North America	23646 (17,340–31,596)	16 (12–21)	26,373 (19,361–35,549)	16 (12–21)	0.09 (0.07–0.10)	0
North Africa and Middle East	21270 (16,088–27,523)	12 (9–16)	42,026 (32,172–53,987)	12 (9–15)	−0.01 (−0.03–0.00)	0.147334
Oceania	383 (285–506)	11 (8–14)	818 (608–1077)	11 (8–14)	0.02 (−0.00–0.05)	0.081768

South Asia	68979 (52,453–89,631)	12 (9–15)	122,660 (93,150–158,911)	12 (9–15)	−0.06 (−0.09 - −0.03)	0.000048
Southeast Asia	25700 (19,448–33,355)	10 (8–13)	38,601 (29,468–50,144)	10 (8–13)	0.01 (0.01–0.02)	0
Southern Latin America	1397 (1050–1801)	6 (4–7)	1919 (1466–2487)	6 (4–7)	0.11 (−0.39–0.61)	0.663477
Southern Sub-Saharan Africa	3519 (2641–4676)	13 (10–17)	5571 (4178–7325)	13 (10–17)	−0.00 (−0.01–0.01)	0.969756
Tropical Latin America	5496 (4001–7308)	7 (5–9)	8320 (6135–10,972)	7 (5–9)	0.22 (0.17–0.27)	0
Western Europe	35954 (28,493–46,155)	18 (15–24)	37,595 (29,479–48,396)	20 (16–26)	0.32 (0.29–0.35)	0
Western Sub-Saharan Africa	10863 (8202–14,098)	12 (9–16)	28,623 (21,856–37,193)	12 (9–15)	−0.01 (−0.03–0.01)	0.29726

Abbreviations: ASPR, age-standardized prevalence rate; AAPC, average annual percentage change; UI, uncertainty interval; SDI, Socio-demographic index.

https://doi.org/10.2147/IJWH.S542737

https://doi.org/10.2147/IJWH.S542737

Table 2 The YLD of Male Infertility Impairment Owing to Klinefelter Syndrome and Their AAPCs from 1990 to 2021 at the Global and Regional Levels

	1990		2021		1990–2021	
	YLD No. (95% UI)	Age-Standardized YLD Rate per 100000 No. (95% UI)	YLD No. (95% UI)	Age-Standardized YLD Rate per 100000 No. (95% UI)	AAPC No. (95% CI)	P Value
Global	2474 (1087–5351)	0.09 (0.04–0.19)	3548 (1595–7525)	0.09 (0.04–0.19)	0.08 (0.05–0.12)	0.000022
Socio-demographic index						
Low SDI	214 (94–446)	0.09 (0.04–0.19)	517 (230–1059)	0.09 (0.04–0.18)	−0.01 (−0.04–0.02)	0.488486
Low-middle SDI	508 (224–1123)	0.08 (0.04–0.19)	896 (399–1908)	0.08 (0.04–0.18)	−0.06 (−0.06 - −0.05)	0
Middle SDI	715 (312–1553)	0.07 (0.03–0.16)	991 (437–2136)	0.08 (0.03–0.17)	0.28 (0.24–0.32)	0
High-middle SDI	508 (227–1093)	0.09 (0.04–0.19)	550 (245–1188)	0.09 (0.04–0.19)	0.15 (0.06–0.24)	0.000831
High SDI	527 (234–1133)	0.11 (0.05–0.24)	591 (256–1304)	0.12 (0.05–0.26)	0.14 (−0.31–0.60)	0.53218
Region						
Andean Latin America	16 (7–34)	0.08 (0.04–0.17)	28 (12–57)	0.08 (0.03–0.16)	−0.08 (−0.24–0.07)	0.301692
Australasia	8 (3–18)	0.08 (0.03–0.16)	11 (4–24)	0.08 (0.03–0.17)	0.15 (0.02–0.28)	0.02682
Caribbean	12 (5–27)	0.07 (0.03–0.14)	16 (7–35)	0.07 (0.03–0.15)	0.07 (0.02–0.12)	0.003295
Central Asia	39 (17–85)	0.11 (0.05–0.24)	55 (23–114)	0.11 (0.05–0.23)	0.07 (−0.00–0.14)	0.063248
Central Europe	53 (24–117)	0.08 (0.04–0.18)	47 (20–101)	0.09 (0.04–0.2)	0.22 (0.12–0.32)	0.000029
Central Latin America	57 (24–125)	0.07 (0.03–0.14)	86 (36–190)	0.07 (0.03–0.14)	0.02 (−0.02–0.05)	0.375522
Central Sub-Saharan Africa	25 (10–53)	0.09 (0.04–0.19)	64 (27–131)	0.09 (0.04–0.18)	−0.02 (−0.05–0.01)	0.275019
East Asia	470 (202–1024)	0.06 (0.03–0.14)	494 (212–1061)	0.07 (0.03–0.16)	0.43 (0.33–0.53)	0
Eastern Europe	151 (67–318)	0.14 (0.06–0.29)	127 (57–282)	0.14 (0.06–0.31)	0.13 (0.09–0.17)	0
Eastern Sub-Saharan Africa	83 (36–180)	0.09 (0.04–0.2)	205 (91–420)	0.09 (0.04–0.19)	−0.03 (−0.09–0.02)	0.241571
High-income Asia Pacific	82 (33–170)	0.09 (0.04–0.18)	69 (29–149)	0.09 (0.04–0.19)	−0.03 (−0.08–0.02)	0.202932
High-income North America	178 (76–389)	0.12 (0.05–0.26)	199 (86–452)	0.12 (0.05–0.27)	0.09 (0.05–0.12)	0.000004
North Africa and Middle East	160 (70–351)	0.09 (0.04–0.2)	316 (143–646)	0.09 (0.04–0.18)	−0.01 (−0.04–0.02)	0.563786
Oceania	3 (1–6)	0.08 (0.03–0.18)	6 (2–14)	0.08 (0.03–0.18)	0.04 (−0.06–0.15)	0.410525

South Asia	517 (225–1144)	0.09 (0.04–0.2)	919 (406–1926)	0.09 (0.04–0.18)	−0.06 (−0.08 - −0.05)	0
Southeast Asia	192 (82–420)	0.08 (0.03–0.17)	289 (125–627)	0.08 (0.03–0.17)	0.02 (−0.03–0.07)	0.462038
Southern Latin America	11 (4–22)	0.04 (0.02–0.09)	14 (6–32)	0.04 (0.02–0.09)	0.12 (−0.13–0.38)	0.330388
Southern Sub-Saharan Africa	26 (11–57)	0.1 (0.04–0.21)	42 (18–87)	0.1 (0.04–0.2)	−0.01 (−0.02 - −0.00)	0.029048
Tropical Latin America	41 (17–88)	0.05 (0.02–0.11)	63 (27–137)	0.05 (0.02–0.12)	0.22 (0.13–0.31)	0.000001
Western Europe	270 (120–571)	0.14 (0.06–0.29)	283 (124–617)	0.15 (0.07–0.33)	0.34 (0.28–0.41)	0
Western Sub-Saharan Africa	81 (35–172)	0.09 (0.04–0.19)	215 (96–451)	0.09 (0.04–0.19)	−0.02 (−0.07–0.04)	0.526833

Abbreviations: YLD, years lived with disability; AAPC, average annual percentage change; UI, uncertainty interval; SDI, Socio-demographic index.

https://doi.org/10.2147/IJWH.S542737

absolute value of YLDs increased, the age-standardized YLDs rate remained relatively stable, indicating that the impact of male infertility caused by KS on population health did not significantly worsen in the context of overall population growth (Table 2 and Figure S1B).

Meanwhile, female infertility associated with TS shows an opposite trend. In 1990, there were 181173 prevalent cases of TS-induced female infertility among reproductive-aged women, with an ASPR of 6.55/100,000 persons (95% UI: 5.16–8.55). By 2021, this number had significantly increased to 245550 cases, accompanied by an ASPR of 6.3/100,000 (95% UI: 4.93–8.24) (Table 3). There has been a continuous downward trend in the ASPRs for infertility, with an AAPC of −0.012 (95% CI: −0.13 - −0.11) (Table 3). Although the number of prevalent cases has increased, the decline in ASPR indicates that the age-standardized prevalence rate of female infertility is slowly decreasing on a global scale (Table 3 and Figure S1C).

In 1990, the global YLDs due to female infertility caused by TS were 1358 years (95%UI: 557–2750), with an age-standardized YLDs rate of 0.05/100,000 (95% UI: 0.02–0.1). By 2021, the YLDs increased to 1840 years (95% UI:769–3736), while the age-standardized YLDs rate remained at 0.05/100,000 (95% UI:0.02–0.1). From 1990 to 2021, the global AAPC in the age-standardized YLDs rate was −0.12 (95% UI: −0.13 - −0.11) (Table 4). Despite the increase in the absolute number of YLDs, the significant decline in the age-standardized YLDs rate indicates that the impact of female infertility caused by TS on population health has improved in the context of overall population growth (Table 4 and Figure S1D).

Global Burden of Infertility Attributable to Sex Chromosome Abnormalities in Both Males and Females by Age

Overall, the prevalence of male infertility induced by KS gradually decreases with increasing age, and there is a slight increase in prevalence when comparing the rates from 2021 to 1990. In terms of age structure, high-middle SDI regions show a trend of reduced proportion among young people (aged 15–29). There are no significant changes in the age structure of prevalence in other SDI regions. In contrast, there was a noticeable increase in the proportion of younger patients (15–29 years) in the region with low SDI (Figure 1A). However, the YLDs within the same SDI region showed no significant change between 1990 and 2021 (Figure S2A).

For women infertility attributed to TS, The prevalence gradually decreases with increasing age. Overall, there has been a slight increase in the global prevalence rates between 1990 and 2021 (Figure 1B). Similar to male infertility induced by KS, the high-middle SDI regions also show a trend of decreasing proportion of prevalence among younger patients (aged 15–29), while there are no significant changes in the age distribution of prevalence in the remaining SDI regions, and when comparing the YLDs across all age groups in 2021 to those in 1990, there are no significant changes (Figure S2A).

Global Burden of Infertility Attributable to Sex Chromosome Abnormalities in Both Males and Females by SDI

For KS-induced male infertility, we found there is a clear positive correlation between SDI and both incidence rates and YLDs when SDI is between 0.6 and 0.8. But this correlation becomes negative when SDI exceeds 0.8 (Figures 2A and S3A). High SDI areas typically have a higher number of prevalent cases and ASPR, but the rate of increase is slower. In 2021, the ASPR in high SDI areas was 16/100,000. Compared to the data from 1990, the low-middle SDI region demonstrated a slight decline in the ASPR, with an AAPC of −0.03 (95% CI: −0.05 - −0.01). In the meanwhile, the middle and the middle-high SDI region demonstrated a significant increase in the ASPR, with an AAPC of 0.29 (95% CI: 0.25–0.32) and 0.15 (95% Cl: 0.05–0.24) respectively during the same period (Table 1). Similar, the YLDs in various regions exhibited comparable trends. There was a slight decrease in YLDs in low-middle SDI regions, with an AAPC of −0.06 (95% CI: −0.06 - −0.05). In contrast, YLDs in middle SDI and middle-high SDI regions showed a more pronounced increase, with AAPCs of 0.28 (95% CI: 0.24–0.32) and 0.15 (95% CI: 0.06–0.24), respectively (Table 2). By analyzing the annual prevalence and YLDs of male infertility caused by KS from 1990 to 2021, we found that

Table 3 The Prevalence of Female Infertility Impairment Owing to Turner Syndrome and Their AAPCs from 1990 to 2021 at the Global and Regional Levels

	1990		2021		1990–2021	
	Prevalent Cases No. (95% UI)	ASPR per 100000 No. (95% UI)	Prevalent Cases No. (95% UI)	ASPR per 100000 No. (95% UI)	AAPC No. (95% CI)	P Value
Global	181173 (142,991–236,948)	6.55 (5.16–8.55)	245,550 (192,054–321,103)	6.3 (4.93–8.24)	−0.12 (−0.13 - −0.11)	0
Socio-demographic index						
Low SDI	13692 (10,516–17,954)	5.6 (4.27–7.33)	33,236 (25,350–43,782)	5.58 (4.25–7.32)	−0.00 (−0.01–0.01)	0.939598
Low-middle SDI	32257 (24,999–42,442)	5.5 (4.27–7.24)	57,326 (44,025–75,632)	5.49 (4.22–7.23)	−0.01 (−0.02 - −0.01)	0
Middle SDI	46754 (35,824–62,098)	4.94 (3.78–6.56)	63,473 (49,139–83,555)	5.21 (4.03–6.86)	0.17 (0.16–0.18)	0
High-middle SDI	36835 (28,921–48,395)	6.48 (5.09–8.53)	37,636 (29,569–49,215)	6.39 (5.03–8.36)	−0.00 (−0.01–0.00)	0.21818
High SDI	51470 (40,910–65,794)	11.34 (9.01–14.49)	53,694 (42,684–69,097)	11.32 (9.01–14.55)	−0.06 (−0.08 - −0.04)	0
Region						
Andean Latin America	999 (773–1295)	4.95 (3.83–6.43)	1688 (1296–2164)	4.79 (3.68–6.15)	−0.11 (−0.11 - −0.10)	0
Australasia	826 (650–1080)	7.66 (6.02–10.01)	1102 (864–1436)	7.76 (6.09–10.1)	0.05 (0.03–0.06)	0
Caribbean	1019 (801–1341)	5.21 (4.09–6.87)	1234 (963–1634)	5.12 (4–6.78)	−0.06 (−0.07 - −0.04)	0
Central Asia	2753 (2161–3586)	7.77 (6.1–10.13)	3919 (3005–5135)	8.11 (6.22–10.66)	0.14 (0.13–0.15)	0
Central Europe	4374 (3449–5713)	7.12 (5.62–9.3)	3700 (2903–4820)	7.44 (5.88–9.69)	0.14 (0.11–0.17)	0
Central Latin America	4558 (3542–5970)	5.11 (3.97–6.7)	6821 (5323–8909)	4.98 (3.89–6.5)	−0.08 (−0.12 - −0.03)	0.000665
Central Sub-Saharan Africa	1571 (1182–2069)	5.76 (4.33–7.6)	4048 (3046–5361)	5.7 (4.26–7.53)	−0.02 (−0.04–0.01)	0.254381
East Asia	30388 (23,384–40,526)	4.37 (3.36–5.83)	30,546 (23,820–40,392)	4.79 (3.74–6.31)	0.29 (0.27–0.31)	0
Eastern Europe	10490 (8164–13,726)	9.52 (7.4–12.48)	8708 (6850–11,443)	9.56 (7.5–12.58)	0.01 (−0.00–0.03)	0.075171
Eastern Sub-Saharan Africa	5621 (4264–7406)	5.79 (4.4–7.63)	13,731 (10,407–18,074)	5.81 (4.44–7.62)	0.01 (0.00–0.02)	0.018938
High-income Asia Pacific	8722 (6997–11,196)	9.55 (7.65–12.26)	6881 (5520–8803)	9.36 (7.5–11.99)	0.02 (0.02–0.03)	0
High-income North America	21801 (17,134–28,253)	14.7 (11.56–19.03)	24,608 (19,372–31,959)	14.8 (11.64–19.24)	−0.05 (−0.06 - −0.04)	0
North Africa and Middle East	5985 (4617–7921)	3.6 (2.78–4.77)	11,383 (8807–15,006)	3.55 (2.75–4.68)	−0.04 (−0.06 - −0.03)	0
Oceania	181 (138–240)	5.42 (4.12–7.17)	390 (295–514)	5.42 (4.11–7.15)	−0.01 (−0.03–0.02)	0.546957

(*Continued*)

Table 3 (Continued).

	1990		2021		1990–2021	
	Prevalent Cases No. (95% UI)	**ASPR per 100000 No. (95% UI)**	**Prevalent Cases No. (95% UI)**	**ASPR per 100000 No. (95% UI)**	**AAPC No. (95% CI)**	**P Value**
South Asia	30186 (23,333–39,675)	5.55 (4.3–7.28)	56,168 (43,127–73,815)	5.54 (4.26–7.29)	0.00 (−0.02–0.03)	0.654162
Southeast Asia	15438 (12,091–20,353)	6.05 (4.73–8)	21,119 (16,385–27,712)	5.79 (4.49–7.59)	−0.14 (−0.18 - −0.10)	0
Southern Latin America	2525 (1952–3330)	9.99 (7.72–13.17)	3550 (2771–4650)	10.23 (7.98–13.39)	0.07 (0.04–0.10)	0.000004
Southern Sub-Saharan Africa	1771 (1357–2315)	5.99 (4.6–7.81)	2661 (2053–3514)	6.02 (4.65–7.96)	0.02 (0.02–0.03)	0
Tropical Latin America	5360 (4098–7090)	6.41 (4.92–8.46)	8031 (6242–10,644)	6.72 (5.23–8.93)	0.15 (0.13–0.17)	0
Western Europe	21073 (16,939–26,326)	11 (8.84–13.74)	20,361 (16,081–26,248)	11.16 (8.83–14.41)	0.05 (0.03–0.06)	0
Western Sub-Saharan Africa	5532 (4276–7290)	5.73 (4.41–7.55)	14,902 (11,405–19,588)	5.7 (4.37–7.5)	−0.02 (−0.05–0.00)	0.079283

Abbreviations: ASPR, age-standardized prevalence rate; AAPC, average annual percentage change; UI, uncertainty interval; SDI, Socio-demographic index.

https://doi.org/10.2147/IJWH.S542737

Table 4 The YLD of Female Infertility Impairment Owing to Turner Syndrome and Their AAPCs from 1990 to 2021 at the Global and Regional Levels

	1990		2021		1990–2021	
	YLD No. (95% UI)	Age-Standardized YLD Rate per 100000 No. (95% UI)	YLD No. (95% UI)	Age-Standardized YLD Rate per 100000 No. (95% UI)	AAPC No. (95% CI)	P Value
Global	1358 (557–2750)	0.05 (0.02–0.1)	1840 (769–3736)	0.05 (0.02–0.1)	−0.12 (−0.13 - −0.11)	0
Socio-demographic index						
Low SDI	103 (42–211)	0.04 (0.02–0.09)	249 (105–515)	0.04 (0.02–0.09)	0.00 (−0.02–0.02)	0.996903
Low-middle SDI	242 (97–505)	0.04 (0.02–0.09)	430 (185–884)	0.04 (0.02–0.08)	−0.02 (−0.06–0.02)	0.379058
Middle SDI	351 (144–697)	0.04 (0.02–0.07)	476 (201–957)	0.04 (0.02–0.08)	0.16 (0.15–0.18)	0
High-middle SDI	276 (114–560)	0.05 (0.02–0.1)	282 (116–564)	0.05 (0.02–0.1)	−0.01 (−0.04–0.02)	0.573862
High SDI	385 (160–780)	0.08 (0.04–0.17)	402 (170–808)	0.08 (0.04–0.17)	−0.08 (−0.16 - −0.00)	0.043046
Region						
Andean Latin America	7 (3–15)	0.04 (0.02–0.07)	13 (5–26)	0.04 (0.01–0.07)	−0.11 (−0.15 - −0.06)	0.000002
Australasia	6 (3–13)	0.06 (0.02–0.12)	8 (3–17)	0.06 (0.02–0.12)	0.01 (−0.08–0.10)	0.89337
Caribbean	8 (3–15)	0.04 (0.02–0.08)	9 (4–19)	0.04 (0.02–0.08)	−0.06 (−0.08 - −0.05)	0
Central Asia	21 (8–42)	0.06 (0.02–0.12)	29 (12–59)	0.06 (0.02–0.12)	0.12 (0.05–0.19)	0.000421
Central Europe	33 (13–65)	0.05 (0.02–0.11)	28 (11–56)	0.06 (0.02–0.11)	0.14 (0.09–0.19)	0
Central Latin America	34 (14–70)	0.04 (0.02–0.08)	51 (21–103)	0.04 (0.02–0.08)	−0.07 (−0.12 - −0.03)	0.000596
Central Sub-Saharan Africa	12 (5–26)	0.04 (0.02–0.09)	30 (12–67)	0.04 (0.02–0.09)	−0.02 (−0.03 - −0.00)	0.010452
East Asia	229 (94–457)	0.03 (0.01–0.07)	230 (96–463)	0.04 (0.02–0.07)	0.29 (0.27–0.32)	0
Eastern Europe	78 (33–162)	0.07 (0.03–0.15)	65 (27–131)	0.07 (0.03–0.14)	0.02 (−0.03–0.07)	0.500545
Eastern Sub-Saharan Africa	42 (17–84)	0.04 (0.02–0.09)	103 (44–214)	0.04 (0.02–0.09)	0.02 (−0.02–0.05)	0.335575
High-income Asia Pacific	65 (27–134)	0.07 (0.03–0.15)	51 (22–105)	0.07 (0.03–0.14)	0.02 (−0.01–0.06)	0.198772
High-income North America	163 (67–330)	0.11 (0.05–0.22)	184 (75–369)	0.11 (0.04–0.22)	−0.05 (−0.08 - −0.02)	0.002405
North Africa and Middle East	45 (19–91)	0.03 (0.01–0.06)	86 (36–172)	0.03 (0.01–0.05)	−0.05 (−0.06 - −0.03)	0
Oceania	1 (1–3)	0.04 (0.02–0.08)	3 (1–6)	0.04 (0.02–0.09)	−0.02 (−0.11–0.07)	0.67193

(*Continued*)

Table 4 (Continued).

	1990		2021		1990–2021	
	YLD No. (95% UI)	Age-Standardized YLD Rate per 100000 No. (95% UI)	YLD No. (95% UI)	Age-Standardized YLD Rate per 100000 No. (95% UI)	AAPC No. (95% CI)	P Value
South Asia	226 (92–472)	0.04 (0.02–0.09)	421 (179–869)	0.04 (0.02–0.09)	−0.00 (−0.03–0.03)	0.963456
Southeast Asia	116 (48–232)	0.05 (0.02–0.09)	158 (66–320)	0.04 (0.02–0.09)	−0.15 (−0.21 - −0.10)	0
Southern Latin America	19 (8–39)	0.08 (0.03–0.16)	27 (10–53)	0.08 (0.03–0.15)	0.04 (−0.08–0.17)	0.491612
Southern Sub-Saharan Africa	13 (5–27)	0.04 (0.02–0.09)	20 (9–41)	0.05 (0.02–0.09)	0.03 (−0.01–0.07)	0.167013
Tropical Latin America	40 (16–82)	0.05 (0.02–0.1)	60 (25–121)	0.05 (0.02–0.1)	0.15 (0.11–0.20)	0
Western Europe	158 (68–327)	0.08 (0.04–0.17)	152 (65–312)	0.08 (0.04–0.17)	0.04 (−0.04–0.11)	0.306093
Western Sub-Saharan Africa	41 (17–86)	0.04 (0.02–0.09)	112 (48–224)	0.04 (0.02–0.09)	−0.02 (−0.05–0.00)	0.059054

Abbreviations: YLD, years lived with disability; AAPC, average annual percentage change; UI, uncertainty interval; SDI, Socio-demographic index.

https://doi.org/10.2147/IJWH.S542737

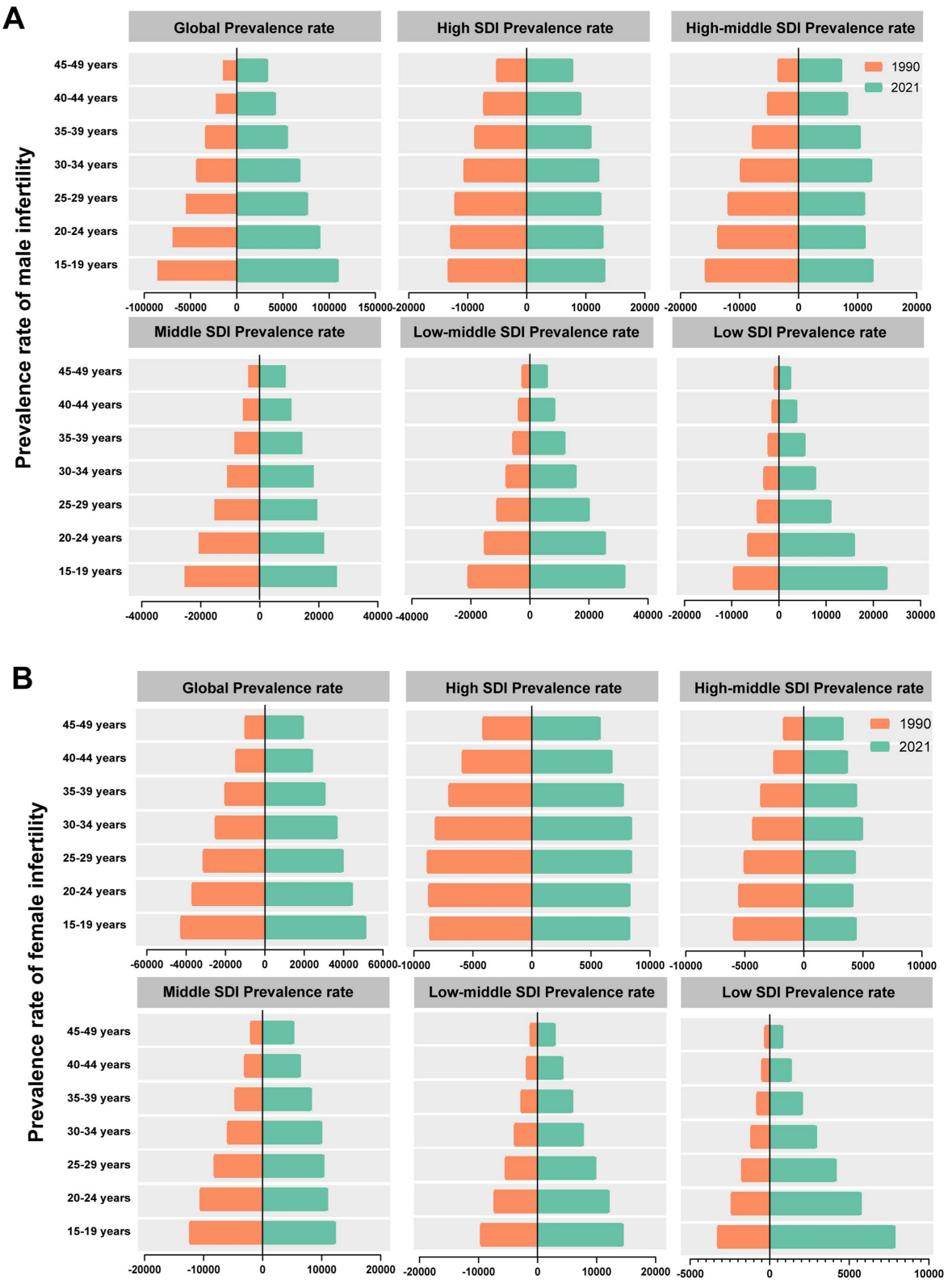

Figure 1 The changes in the prevalence rates of male infertility globally and across different levels of the SDI from 1990 to 2021. (**A**) Prevalence rates of male infertility. (**B**) Prevalence rates of female infertility.

Abbreviations: ASPR, age-standardized prevalence rate; SDI, Socio-demographic index.

https://doi.org/10.2147/IJWH.S542737

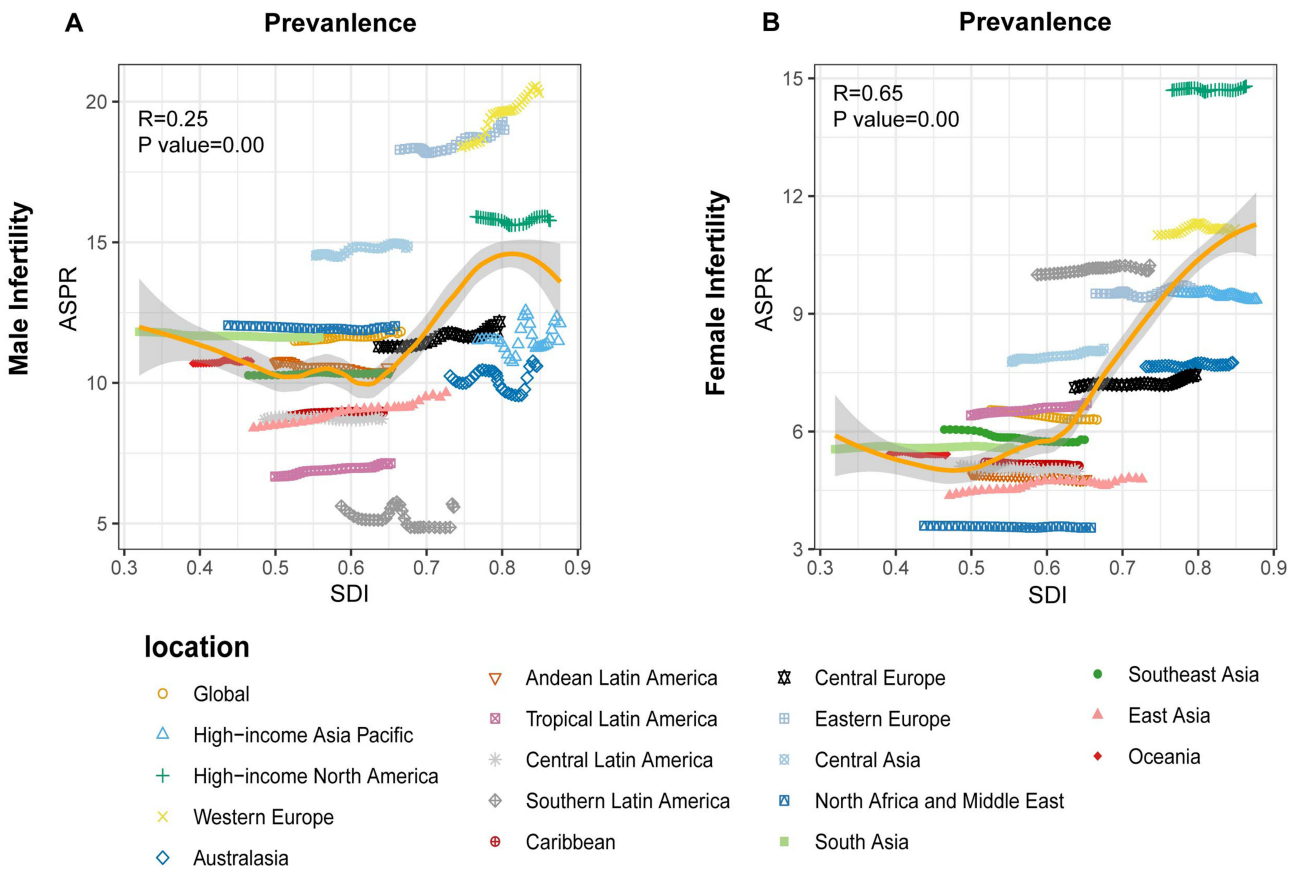

Figure 2 Global and Regional Relationships between SDI and YLDs of Infertility. (**A**) Relationship between male infertility prevalence and SDI. (**B**) Relationship between female infertility prevalence and SDI.
Abbreviations: ASPR, age-standardized prevalence rate; SDI, Socio-demographic index.

between 2000 and 2010, there was a peak in the prevalence and YLDs of male infertility in high SDI regions. After falling back to previous levels in 2010, the figures began to rise gradually again (Figure S1A).

For TS-induced female infertility, Similar to male infertility, there is a clear positive correlation between SDI and both incidence rates and YLDs when SDI is bigger than 0.5 (Figures 2B and S3B), High SDI regions had a higher ASPR (11.32/100,000, 95% UI:9.01–14.55) than the other SDI regions. Compared to the data from 1990, the low-middle SDI regions demonstrated a slight decline in the ASPR, with an AAPC of −0.12 (95% CI: −0.13 - −0.11). In the meanwhile, the middle SDI region demonstrated a significant increase in the ASPR, with an AAPC of 0.17 (95% Cl: 0.16–0.18) during the same period (Table 3). In regions with high SDI and high-middle SDI levels, the proportion of younger patients has significantly decreased, and the peak prevalence age group tends to shift towards middle-aged populations (Figure 1B). Similar, the YLDs in various regions exhibited comparable trends. There was a slight decrease in YLDs in high SDI regions, with an AAPC of −0.08 (95% CI: −0.16 - −0.00). In contrast, YLDs in middle SDI regions showed a notable increase, with AAPC of 0.16 (95% CI:0.15–0.18) (Table 4). Similar to men infertility induced by KS, we noticed a significant decrease in the proportion of younger patients (15–29 years) suffered women infertility induced by TS in the region with middle to high SDI, and there was also a noticeable increase in the proportion of younger patients (15–29 years) in the region with low SDI. The peak prevalence age group tends to shift towards the middle-aged population. The YLDs within the same SDI region showed no significant change between 1990 and 2021 (Figure S2B).

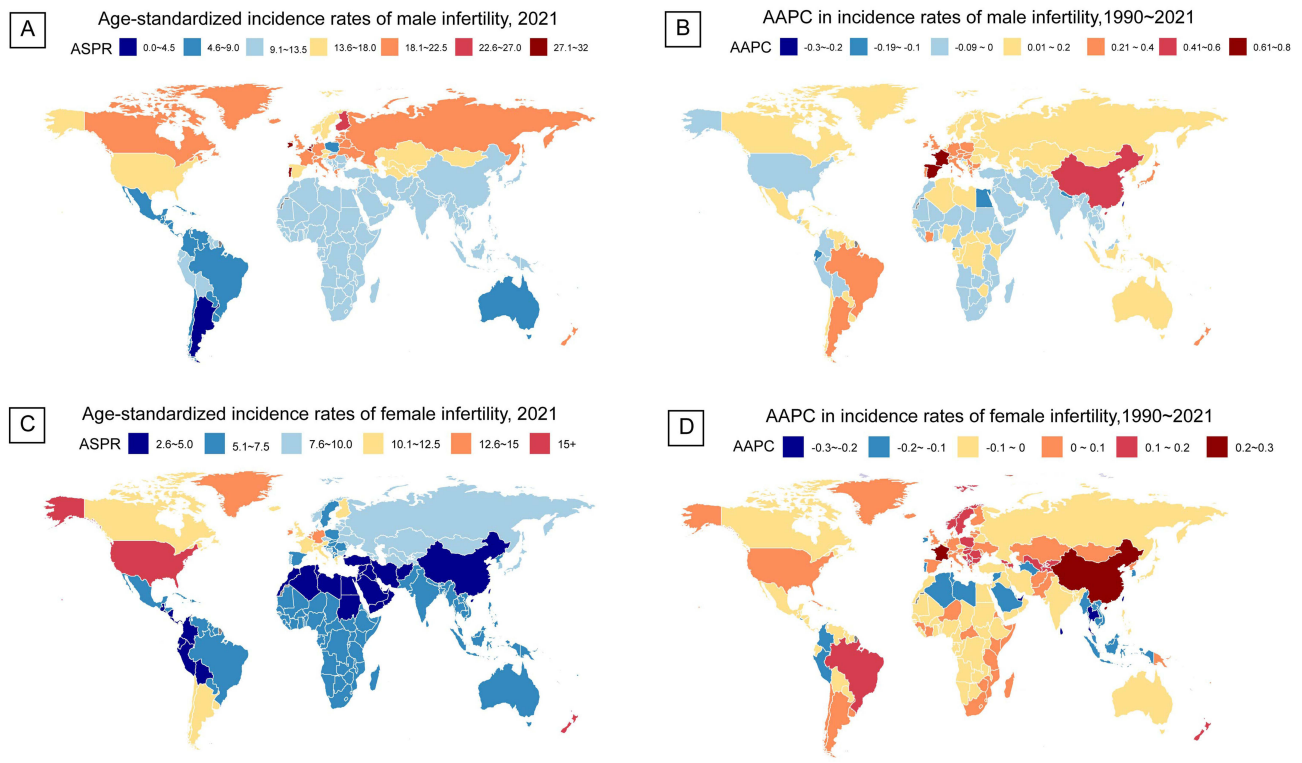

Figure 3 Global map of 2021 age-standardized rates and corresponding average annual percentage changes from 1990 to 2021 for male infertility attributable to Klinefelter syndrome. (**A**) The ASPR of male infertility attributable to Klinefelter syndrome in 2021. (**B**) The AAPC of ASPR from 1990 to 2021. (**C**) The ASPR of female infertility attributable to Turner syndrome in 2021. (**D**) The AAPC of ASPR from 1990 to 2021.
Abbreviations: ASPR, age-standardized prevalence rate; AAPC, average annual percentage change.

Regional Burden of Infertility Attributable to Sex Chromosome Abnormalities in Both Males and Females

Epidemiological analysis of GBD 2021 data revealed distinct SDI-related stratification in sex chromosome disorder-associated infertility. In 2021, for KS-related male infertility burden, middle SDI regions exhibited the highest prevalence concentration, with Western Europe (37,595 cases; 95% UI: 29,479–48,396), Eastern Europe (16,880; 95% UI:12,805–21,630), and High-income North America (26,373; 95% UI:19,361–35,549) representing the most affected areas (Table 1 and Figure S4A). Conversely, TS-mediated female infertility displayed parallel geographic disparities, though with differential regional gradients. Despite similar SDI stratification patterns, the predominant burden localized to High-income North America (24,608; 95% UI:19,372–31,959), Western Europe (20,361; 95% UI:6081–26,248), and Southern Latin America (3550; 95% UI:2771–4650), collectively accounting for 61.3% of global female cases (Table 3 and Figure S4A).

Based on the data from 2021, the regions with the highest prevalence of male infertility induced by KS are Western Europe (20/100,000,95% UI:16–26), Eastern Europe (19/100,000,95% UI:14–24) and High-income North America (16/100,000,95% UI:12–21), while the lowest prevalence is in Southern Latin America (6/100,000, 95% UI:4–7), Tropical Latin America (7/100,000, 95% UI:5–9) and the Caribbean (9/100,000, 95% UI:7–12). The regions with the fastest increase in prevalence are East Asia (0.44, 95% UI:0.36–0.52), Western Europe (0.32, 95% UI:0.29–0.35) and Central Europe (0.23, 95% UI:0.14–0.31), whereas the region with the fastest decrease is Andean Latin America (−0.08, 95% UI:-0.15 - −0.01) (Table 1). The highest YLDs are Western Europe (0.15, 95% UI: 0.07–0.33) and Eastern Europe (0.14,95% UI: 0.06–0.31), while the lowest YLDs are in Tropical Latin America (0.05,95%UI:0.02–0.12), the Caribbean (0.07, 95% UI: 0.03–0.15), and East Asia (0.07, 95%UI: 0.03–0.16) (Table 2 and Figure S4B).

For female infertility induced by TS, the regions with the highest prevalence are High-income North America (14.8, 95% UI: 11.64–19.24) and Western Europe (11.16, 95% UI: 8.83–14.41), while the lowest prevalence is in North Africa and the

Middle East (3.55, 95% UI: 2.75–4.68), East Asia (4.79, 95% UI: 3.74–6.31), and Andean Latin America (4.79, 95% UI: 3.68–6.15). The region with the fastest increase in prevalence is East Asia (0.29, 95% CI: 0.27–0.31), whereas the region with the fastest decrease is Southeast Asia (−0.14, 95% CI: −0.18 - −0.10) (Table 3). The highest YLDs are in High-income North America (0.11; 95% UI: 0.04–0.22), while the lowest YLDs are in North Africa and the Middle East (0.03, 95% UI: 0.01–0.05), and East Asia (0.04, 95% UI: 0.02–0.07). The fastest increase in YLDs is in East Asia (0.29, 95% CI:0.27–0.32), and the fastest decrease is in Andean Latin America (−0.11, 95% CI:-0.15 - −0.06) (Table 4 and Figure S4B).

National Burden of Infertility Attributable to Sex Chromosome Abnormalities in Both Males and Females

According to 2021 data, countries with the highest prevalence of male infertility caused by KS are primarily located in Netherlands (31.47), Portugal (29.53), Belgium (29.44). Countries with the lowest prevalence include Argentina (4.25), Uruguay (6.08) and Paraguay (7.1) (Table S1 and Figure 3A). The fastest-growing prevalence rates are observed in France (0.79), Spain (0.65), China (0.46). While, the lowest-growing prevalence rates are observed in Taiwan (Province of China) (−0.22), Nepal (−0.15), Ecuador (−0.13) (Table S2 and Figure 3B). The highest YLDs due to male infertility are concentrated in Netherlands (0.24), Belgium (0.22) and Ireland (0.22). The lowest YLDs due to male infertility are concentrated in Argentina (0.03), Paraguay (0.05) and Brazil (0.05) (Table S3 and Figure S5A). The fastest increases in YLDs are seen in France (0.77), Spain (0.65) and China (0.45), while the most significant declines occur in the Nepal (−0.22), Taiwan (Province of China)(−0.21) and Palestine (−0.15) (Table S4 and Figure S5B).

Regarding female infertility caused by TS, highest-prevalence areas are concentrated in New Zealand (15.55), United States of America (15.15), and Belgium (14.81). Moreover, lowest-prevalence areas are concentrated in Iran (Islamic Republic of)(3.39), Tunisia (3.42) and Kuwait (3.42) (Table S5 and Figure 3C. The prevalence rates are increasing most rapidly in China (0.3), followed by France (0.22) and Montenegro (0.2). The prevalence rates are decreasing most rapidly in Taiwan (Province of China)(−0.27), Bermuda (−0.26) and Maldives (−0.25) (Table S6 and Figure 3D). The highest YLDs linked to female infertility are found in New Zealand (0.12), Belgium (0.11), United States of America (0.11). The lowest YLDs linked to female infertility are found in Sudan (0.03), Yemen (0.03) and Afghanistan (0.03) (Table S7 and Figure S5C). The most rapid increases in YLDs occur in China (0.3), Montenegro (0.22) and France (0.21). The most rapid declines in YLDs occur in Taiwan (Province of China)(−0.27), Viet Nam (−0.26), and Bermuda (−0.26) (Table S8 and Figure S5D).

Discussion

To investigate the global prevalence of infertility linked to KS and TS, our study was conducted at global, regional, and national levels, with stratification by age and the SDI. Our findings indicated a modest rise in the global burden of infertility due to KS, whereas the burden of infertility due to TS exhibited a decline during the period from 1990 to 2021. Additionally, both KS and TS exhibited a consistent pattern of decreasing incidence as age increased. It is worth mentioning that the burden of infertility due to both KS and TS increased in regions with middle to high SDI, with particularly higher incidence rates observed in Europe and the United States.

The global number of KS cases slightly increased from 1990 to 2021. Prior epidemiological investigations have reported comparable patterns in the worldwide distribution of KS, aligning with our findings.[27] However, in the context of female infertility, a contrary phenomenon can be observed. The global number of TS cases slightly decreased from 1990 to 2021. Previous study observed a similar trend in the global trend of TS.[28] The prevalence of KS is increasing every year due to advances in technology. It has been suggested that a possible explanation for the increased prevalence of KS is the increased frequency of paternal sex chromosome nondisjunction in the MI compartment of spermatogenesis.[27] Given the correlation between GBD data and diagnoses of KS and TS, this rising trend may be attributed to improved screening protocols and rapid expansion of assisted reproductive technology (ART). This pattern aligns with our finding of high KS/TS prevalence in Europe and the United States, while in underdeveloped countries, comparable patient proportions likely remain underdiagnosed due to lack of treatment, resulting in data gaps rather than

truly low incidence. Moreover, the majority of TS embryos or fetuses are spontaneously aborted in early and mid-pregnancy[29,30] and there is a decreasing trend in the prevalence of TS due to an increase in the rate of induced abortions.[23] Additionally, The differing incidence rates between KS and TS may also correlate with their distinct phenotypic presentations. KS often remains clinically asymptomatic until adulthood, while typical features of TS are typically identified in childhood or even prenatally.[31] This phenotypic asymmetry further widens the observed prevalence gap between the two syndromes.

In our study, patients with infertility caused by TS and KS tended to be younger. This is consistent with the fact that the average age at TS diagnosis is around 15 years.[16] One explanation for the trend towards younger age at onset of prevalence is that while the majority of patients with KS and TS are diagnosed during adulthood, symptoms can actually manifest during infancy, childhood, or adolescence.[32] Furthermore, studies have indicated that age has emerged as a potential predictor for successful sperm extraction, with higher retrieval rates observed in patients undergoing m-TESE before the age of 35. This enhances the possibility of treating infertility in patients with KS.[33] Considering the median age of diagnosis for KS is 27,[14] this also offers an explanation for the comparatively rare occurrence of infertility in elderly patients with the condition. At the social level, the relationship between delayed childbearing and infertility merits attention.[34] Particularly for patients with KS, diagnosis often only occurs when they are preparing for pregnancy. The current trend of delayed childbearing may further push back the diagnosis age of KS patients, causing them to miss the optimal window for fertility preservation.

A positive relationship between SDI and ASPR was observed in this study, aligning with previous research findings.[28] In countries with higher levels of socioeconomic development, there is an enhanced capacity to identify previously undetected cases of KS within the population.[28] Even in developed regions, assisted reproductive technology (ART) treatments for infertility, like in vitro fertilization (IVF), are still underfunded and hard to access due to high costs, social stigma, and limited availability. For fertility preservation in patients with KS, timely screening and diagnosis are crucial. Although technologies for addressing KS-related infertility are advancing, screening for KS remains inadequate, with the average diagnosis age at 27.[14] This often means many KS patients miss the optimal treatment window, further highlighting the importance of early screening for preserving their fertility. Additionally, TS is frequently associated with impairments in social-cognitive processing and executive function. These cognitive abnormalities, coupled with various physical differences, can adversely impact social communication skills, typically leading to a decline in quality of life during early adolescence.[35] Research has shown that individuals diagnosed with TS exhibit a higher incidence and more severe depressive symptoms compared to those without a TS diagnosis.[36] Furthermore, for individuals with TS, notable physical differences such as short stature, shield-like chest, webbed neck, and edema can pose risks stemming from self-perception and fear of others' reactions. These factors collectively heighten their sense of social shame and hinder their likelihood of seeking medical help.[36] In addition, individuals diagnosed with TS frequently encounter infertility as a prevalent issue. Therapeutic interventions utilising ART are, however, significantly constrained. A matter of significant concern involves the reported potential elevation in mortality rates stemming from aortic dissection or rupture in women with TS who successfully conceive through oocyte donation-facilitated IVF.[37] Notably, our findings indicate that while the global incidence of infertility related to TS is generally declining in most regions, there is a notable increase in the burden of infertility due to TS in middle SDI areas. This trend may suggest that for developing countries, the capacity for early diagnosis is crucial for the management of girls with TS.[38] However, notably, numerous data gaps persist in environments with limited resources.[39] This may also account for the virtually unchanged prevalence rates observed in low and lower-middle SDI countries.

It is noteworthy that the burden of infertility linked to TS is primarily concentrated in Europe and the United States. A recent research report underscores that countries with higher ASPRs for TS are similarly clustered in North America and Europe. This could be due to the advanced healthcare systems in these regions, which are more likely to identify cases of TS.[28] As for KS, Europe also bears a significant brunt of infertility associated with this condition. It is noteworthy that in 2021, the European Society of Endocrinology established the first guidelines on KS, offering recommendations tailored to cater to KS patients across various developmental stages, ranging from childhood and adolescence to adulthood.[32]

Early intervention is vital for preserving fertility in patients with KS and TS, highlighting the necessity of enhanced early screening. Yet, underdiagnosis is prevalent in KS, with only around a quarter of patients diagnosed in their lifetime.[40] High-income countries, equipped with advanced diagnostic technologies, can comprehensively identify cases. If undiagnosed prenatally, the condition is rarely identified within the first decade of life, with 75% of cases remaining undiagnosed indefinitely.[41] Currently, karyotype analysis remains the gold standard for prenatal diagnosis,[19] while non-invasive prenatal testing (NIPT) serves as a non-invasive screening alternative. Cell-free fetal DNA, isolated from maternal peripheral blood, forms the analytical basis of NIPT.[42] While the use of NIPT for sex chromosome aneuploidy detection remains controversial, a recent large-scale retrospective study demonstrated that NIPT-based SCA screening has significantly increased population-level prenatal diagnosis rates, particularly for KS.[43] Meanwhile, the rapid growth in middle-income countries highlights the need to balance healthcare advancement with disease prevention. Apart from establishing a tiered screening and diagnosis pathway, family support plays a vital role in holistic KS and TS management, from screening to treatment.[44] Given the current focus on multidisciplinary care, strengthening genetic counseling services is urgently needed.[45] Particularly, low-income countries necessitate the widespread adoption of low-cost screening strategies. QF-PCR is a widely adopted prenatal diagnostic method for detecting common chromosomal abnormalities in recent years. It enables rapid diagnosis of common aneuploidies within hours post-sampling, featuring high throughput, low error rates, and cost-effectiveness.[46] A study proposes a possible cost-effective prenatal diagnosis strategy for low-SDI countries: initial rapid QF-PCR screening for common aneuploidies, followed by targeted chromosomal microarray analysis when indicated.[47]

This study is based on the authoritative GBD 2021 database, systematically analyzing data from 204 countries/regions from 1990 to 2021, enhancing the universality and comparability of the results. It comprehensively reveals the global burden differences of KS and TS on infertility across multiple dimensions, including gender (male/female infertility), age (grouped by 15–49 years), region (stratified by SDI), and economic development level (high/medium/low SDI), providing key evidence-based insights for reproductive medicine and public health policies. But a limitation of this study is that the true prevalence and YLDs in low-SDI regions may not be fully captured due to inadequate screening methods. Additionally, factors such as environmental exposures, cultural practices related to childbirth, and racial differences were not accounted for, which could provide new perspectives for studying infertility caused by sex chromosome disorders. As GBD estimates are model-derived, their accuracy is inherently limited by data completeness and diagnostic practices that differ widely across countries; in many low- and middle-income settings the absence of cytogenetic confirmation likely leads to under-estimation of true prevalence.

Conclusions

From 1990 to 2021, male infertility attributable to Klinefelter syndrome rose steadily, whereas female infertility linked to Turner syndrome declined slightly. This divergence underscores the urgent need for effective prepubertal detection, fertility-preservation counselling, and targeted screening in Europe, East Asia and North America. In low-SDI regions, priority should be given to establishing low-cost screening strategies that secure equitable first-step care for individuals with KS or TS.

Data Sharing Statement

The underlying data for this article are accessible within the Global Burden of Disease Study 2021 (https://ghdx.healthdata.org/).

Ethics Approval and Consent to Participate

This study is exempt from ethical review according to Items (1) and (2) of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (promulgated on February 18, 2023, China).

Acknowledgments

The authors express their gratitude for the participants and numerous researchers contributing to the GBD 2021.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (No. 82101673). The authors declare no conflict of interest.

Disclosure

The authors declare no competing interests in this work.

References

1. Mazzilli R, Rucci C, Vaiarelli A, et al. Male factor infertility and assisted reproductive technologies: indications, minimum access criteria and outcomes. *J Endocrinol Invest*. 2023;46(6):1079–1085. doi:10.1007/s40618-022-02000-4
2. Eisenberg ML, Esteves SC, Lamb DJ, et al. Male infertility. *Nat Rev Dis Primers*. 2023;9(1):49. doi:10.1038/s41572-023-00459-w
3. Liang Y, Huang J, Zhao Q, et al. Global, regional, and national prevalence and trends of infertility among individuals of reproductive age (15-49 years) from 1990 to 2021, with projections to 2040. *Hum Reprod*. 2025;40(3):529–544. doi:10.1093/humrep/deae292
4. Karimian M, Parvaresh L, Behjati M. Genetic variations as molecular diagnostic factors for idiopathic male infertility: current knowledge and future perspectives. *Expert Rev Mol Diagn*. 2021;21(11):1191–1210. doi:10.1080/14737159.2021.1985469
5. Breuil V, Euller-Ziegler L. Gonadal dysgenesis and bone metabolism. *Joint Bone Spine*. 2001;68(1):26–33. doi:10.1016/S1297-319X(00)00235-9
6. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet*. 2004;364(9430):273–283. doi:10.1016/S0140-6736(04)16678-6
7. Bonomi M, Rochira V, Pasquali D, et al. Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. *J Endocrinol Invest*. 2017;40(2):123–134. doi:10.1007/s40618-016-0541-6
8. Liu C, Zhang H, Liu H, et al. Paternal USP26 mutations raise Klinefelter syndrome risk in the offspring of mice and humans. *EMBO J*. 2021;40(13):e106864. doi:10.15252/embj.2020106864
9. Kanakis GA, Nieschlag E. Klinefelter syndrome: more than hypogonadism. *Metabolism*. 2018;86:135–144. doi:10.1016/j.metabol.2017.09.017
10. Tuttelmann F, Werny F, Cooper TG, Kliesch S, Simoni M, Nieschlag E. Clinical experience with azoospermia: aetiology and chances for spermatozoa detection upon biopsy. *Int J Androl*. 2011;34(4):291–298. doi:10.1111/j.1365-2605.2010.01087.x
11. Sharma A, Minhas S, Dhillo WS, Jayasena CN. Male infertility due to testicular disorders. *J Clin Endocrinol Metab*. 2021;106(2):e442–e459. doi:10.1210/clinem/dgaa781
12. Fullerton G, Hamilton M, Maheshwari A. Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009? *Hum Reprod*. 2010;25(3):588–597. doi:10.1093/humrep/dep431
13. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91(10):3897–3902. doi:10.1210/jc.2006-0558
14. Gravholt CH, Viuff M, Just J, et al. The changing face of Turner syndrome. *Endocr Rev*. 2023;44(1):33–69. doi:10.1210/endrev/bnac016
15. Singh I, Duca LM, Kao D, Chatfield KC, Khanna AD. Outcomes in hospitalisations of women with Turner syndrome compared to women without Turner syndrome. *Cardiol Young*. 2021;31(10):1667–1674. doi:10.1017/S1047951121000858
16. Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: mechanisms and management. *Nat Rev Endocrinol*. 2019;15(10):601–614. doi:10.1038/s41574-019-0224-4
17. Klein KO, Rosenfield RL, Santen RJ, et al. Estrogen replacement in Turner Syndrome: literature review and practical considerations. *J Clin Endocrinol Metab*. 2018;103(5):1790–1803. doi:10.1210/jc.2017-02183
18. Viuff M, Gravholt CH. Turner syndrome and fertility. *Ann Endocrinol*. 2022;83(4):244–249. doi:10.1016/j.ando.2022.06.001
19. Radicioni AF, De Marco E, Gianfrilli D, et al. Strategies and advantages of early diagnosis in Klinefelter's syndrome. *Mol Hum Reprod*. 2010;16(6):434–440. doi:10.1093/molehr/gaq027
20. Cirigliano V, Ejarque M, Canadas MP, et al. Clinical application of multiplex quantitative fluorescent polymerase chain reaction (QF-PCR) for the rapid prenatal detection of common chromosome aneuploidies. *Mol Hum Reprod*. 2001;7(10):1001–1006. doi:10.1093/molehr/7.10.1001
21. Mehmet B, Dwyer AA, Jayasena CN, Gillard S, Llahana S. Update on physical, psychological, and quality of life management in Klinefelter syndrome. *J Clin Endocrinol Metab*. 2025;110(8):e2435–e2445. doi:10.1210/clinem/dgaf261
22. Forti G, Corona G, Vignozzi L, Krausz C, Maggi M. Klinefelter's syndrome: a clinical and therapeutical update. *Sex Dev*. 2010;4(4–5):249–258. doi:10.1159/000316604
23. Berglund A, Viuff MH, Skakkebaek A, Chang S, Stochholm K, Gravholt CH. Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. *Orphanet J Rare Dis*. 2019;14(1):16. doi:10.1186/s13023-018-0976-2
24. Berglund A, Chang S, Lind-Holst M, Stochholm K, Gravholt CH. The epidemiology of disorders of sex development. *Best Pract Res Clin Endocrinol Metab*. 2025;39(4):102002. doi:10.1016/j.beem.2025.102002

25. Diseases GBD, Injuries C. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2024;403(10440):2133–2161.
26. Collaborators GBDD. Global age-sex-specific mortality, life expectancy, and population estimates in 204 countries and territories and 811 subnational locations, 1950-2021, and the impact of the COVID-19 pandemic: a comprehensive demographic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403(10440):1989–2056.
27. Morris JK, Alberman E, Scott C, Jacobs P. Is the prevalence of Klinefelter syndrome increasing? *Eur J Hum Genet*. 2008;16(2):163–170. doi:10.1038/sj.ejhg.5201956
28. Shen L, Li J, Zhang H, Zhao Y. Global, regional and national burdens of reproduction-related congenital birth defects, 1990-2019. *Front Public Health*. 2024;12:1328282. doi:10.3389/fpubh.2024.1328282
29. Ranke MB, Saenger P. Turner's syndrome. *Lancet*. 2001;358(9278):309–314. doi:10.1016/S0140-6736(01)05487-3
30. Hook EB. Spontaneous deaths of fetuses with chromosomal abnormalities diagnosed prenatally. *N Engl J Med*. 1978;299(19):1036–1038. doi:10.1056/NEJM197811092991903
31. Berglund A, Stochholm K, Gravholt CH. The epidemiology of sex chromosome abnormalities. *Am J Med Genet C Semin Med Genet*. 2020;184(2):202–215. doi:10.1002/ajmg.c.31805
32. Zitzmann M, Aksglaede L, Corona G, et al. European academy of andrology guidelines on Klinefelter Syndrome Endorsing Organization: European Society of Endocrinology. *Andrology*. 2021;9(1):145–167. doi:10.1111/andr.12909
33. Kang C, Punjani N, Kashanian JA, Schlegel PN. Age, sperm retrieval, and testicular histology in Klinefelter Syndrome. *J Urol*. 2024;211(1):163–169. doi:10.1097/JU.0000000000003737
34. Brugo-Olmedo S, Chillik C, Kopelman S. Definition and causes of infertility. *Reprod Biomed Online*. 2001;2(1):41–53. doi:10.1016/S1472-6483(10)62187-6
35. Wolstencroft J, Skuse D. Social skills and relationships in Turner syndrome. *Curr Opin Psychiatry*. 2019;32(2):85–91. doi:10.1097/YCO.0000000000000472
36. Morris LA, Tishelman AC, Kremen J, Ross RA. Depression in Turner syndrome: a systematic review. *Arch Sex Behav*. 2020;49(2):769–786. doi:10.1007/s10508-019-01549-1
37. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. *Fertil Steril*. 2003;80(3):498–501. doi:10.1016/S0015-0282(03)00974-9
38. Wonkam A, Veigne SW, Abass A, et al. Features of Turner syndrome among a group of Cameroonian patients. *Int J Gynaecol Obstet*. 2015;129(3):264–266. doi:10.1016/j.ijgo.2014.11.025
39. Murray CJL, Collaborators GBD. Findings from the global burden of disease study 2021. *Lancet*. 2024;403(10440):2259–2262. doi:10.1016/S0140-6736(24)00769-4
40. Nieschlag E. Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. *Dtsch Arztebl Int*. 2013;110(20):347–353. doi:10.3238/arztebl.2013.0347
41. Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat Diagn*. 1997;17(4):363–368. doi:10.1002/(SICI)1097-0223(199704)17:4<363::AID-PD79>3.0.CO;2-O
42. Alberry MS, Aziz E, Ahmed SR, Abdel-Fattah S. Non invasive prenatal testing (NIPT) for common aneuploidies and beyond. *Eur J Obstet Gynecol Reprod Biol*. 2021;258:424–429. doi:10.1016/j.ejogrb.2021.01.008
43. Loughry L, Pynaker C, White M, Halliday J, Hui L. State-wide increase in prenatal diagnosis of klinefelter syndrome on amniocentesis and chorionic villus sampling: impact of non-invasive prenatal testing for sex chromosome conditions. *Prenat Diagn*. 2023;43(2):156–161. doi:10.1002/pd.6103
44. Close S, Sadler L, Grey M. In the dark: challenges of caring for sons with Klinefelter syndrome. *J Pediatr Nurs*. 2016;31(1):11–20. doi:10.1016/j.pedn.2015.05.002
45. Rigamonti C, Vizziello P, Monti F, et al. Klinefelter Syndrome in preschool children: the importance of an early multidisciplinary approach for patients and families. *Minerva Pediatr*. 2019;71(5):395–403. doi:10.23736/S0026-4946.16.04412-1
46. Onay H, Ugurlu T, Aykut A, et al. Rapid prenatal diagnosis of common aneuploidies in amniotic fluid using quantitative fluorescent polymerase chain reaction. *Gynecol Obstet Invest*. 2008;66(2):104–110. doi:10.1159/000128598
47. Pan M, Han J, Zhen L, et al. Prenatal diagnosis of fetuses with increased nuchal translucency using an approach based on quantitative fluorescent polymerase chain reaction and genomic microarray. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:164–167. doi:10.1016/j.ejogrb.2015.12.024