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Global, regional, and national burden of female infertility and trends from 1990 to 2021 with projections to 2050 based on the GBD 2021 analysis

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Female infertility represents a significant reproductive health issue that critically affects global fertility rates. In this study, we utilized the most recent data from the Global Burden of Disease (GBD) study 2021. Initially, we assessed the global burden by the number of female infertility prevalence and disability-adjusted life years (DALYs), along with the age-standardized rate (ASR) per 100,000 individuals, stratified by age, sociodemographic index (SDI), nationality, and region. Furthermore, linear regression models were employed to examine the temporal trends of disease burden from 1990 to 2021. Cluster analysis facilitated the evaluation of disease burden change patterns across different GBD regions. Lastly, the autoregressive composite moving average model was applied to forecast future disease burdens. In 2021, the global prevalence of female infertility was estimated at 110,089,459, contributing to 6,210,145 DALYs, there was an observed increase of 84.44% in prevalence and 84.43% in DALYs since 1990. The highest burden occurred among individuals aged 35–39, with the most rapid increase observed in the 30–34 age group. The burden of female infertility displayed considerable variability across GBD regions and countries, with areas of high-medium SDI facing elevated risks. Projections indicate a continuing rise in the ASR of prevalence and DALYs for female infertility over the next 2 decades. The global burden of female infertility has intensified from 1990 to 2021, with notable disparities across different SDI regions and countries. Women aged 35–39 face the highest risk, and there is a trend toward earlier onset of infertility.

Keywords Female infertility, Global Burden of Disease, Age-standardized prevalence rate, Disability-adjusted life years, Age-standardized DALYs rate, Estimated annual percentage change

Female infertility represents a significant public health concern globally, defined as the inability to conceive after more than 12 months of regular unprotected intercourse without contraception through WHO[1,2], which is different from the definition of GBD2021. This condition is categorized into primary and secondary infertility. In the United States, an estimated 7–15.5% of women of childbearing age are afflicted with infertility[3,4]. And the economic cost of ART treatment for infertile women is high, for example: The cost (in 2006 United States dollars) of a standard IVF cycle ranged from $12,513 in the United States to $3956 in Japan[5]. Worldwide, infertility impacts millions of families, affecting approximately one in seven couples in developed countries and one in four in developing countries[6]. In China, over 50 million women of childbearing age suffer from infertility, constituting 15% of this demographic[7]. In many developing countries, Infertility is common and often linked to negative psychosocial effects. In Morocco, even with increasing knowledge about the causes and treatments

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of infertility, women continue to face social stigma and marital issues, such as divorce or polygamy, due to infertility being associated with them[8].

The predominant cause of female infertility is fallopian tube obstruction, while secondary causes include ovulatory disorders related to diminished ovarian reserve, endocrine disruptions, and delayed childbearing. Genetic factors also contribute, with 5–10% of affected women displaying chromosomal anomalies, gene mutations, or polymorphisms[9]. Additionally, environmental influences, endocrine dysfunctions, and hormonal imbalances explain a considerable portion of infertility cases. Emerging research suggests that infertile women may face an elevated risk of gynecological cancers[10]. Moreover, conditions such as endometriosis are linked with higher incidences of melanoma, asthma, autoimmune disorders, allergic diseases, cardiovascular diseases, and ovarian cancer[11]. The multifaceted impact of female infertility underscores the necessity for a comprehensive understanding of its complexities and implications.

Current epidemiological research on female infertility is notably sparse. One pivotal study analyzed data from 277 demographic and reproductive health surveys, uncovering variations in the prevalence of primary and secondary infertility across 190 countries and territories from 1990 to 2010[12]. Notably, regions such as North Africa and the Middle East, particularly Morocco and Yemen, exhibited high rates of primary infertility but low rates of secondary infertility. Conversely, Central and Eastern Europe along with Central Asia showed higher prevalence of secondary infertility and lower incidence of primary infertility. A separate analysis on the disease burden associated with polycystic ovary syndrome (PCOS) revealed a significant increase in infertility cases linked to PCOS among women aged 15 to 49 years—from 6 million cases in 1990 to 12.13 million in 2019[13]. Research on endometriosis-related infertility indicated a slight decrease in the global burden from 1990 to 2019, though substantial regional, age-related, temporal, and cohort-based disparities persist[14].

Differences in the burden of female infertility among countries may stem from several factors, including widespread preconception testing, complexity in diagnostic processes, the adoption of assisted reproductive technologies, and disparities in medical resource distribution.

The Global Burden of Disease (GBD) Study serves as a crucial resource for understanding the epidemiological status of various diseases, encompassing data on prevalence, incidence, mortality, and disability-adjusted life years (DALYs). We derived specific data (prevalence and DALYs) on female infertility from the most recent 2021 GBD study. This study also offers a detailed breakdown of the prevalence, and DALYs of female infertility by age, geographic region, and the sociodemographic index (SDI), emphasizing SDI distribution and the temporal patterns and trends in disease burden. Projecting the disease burden from 2020 to 2050, this analysis is aimed at aiding clinicians, epidemiologists, and health policymakers in devising and evaluating effective public health strategies to mitigate the substantial disease burden, offering considerable benefit and value.

Results

The disease burden attributable to female infertility in 2021

In 2021, the global prevalence of female infertility was estimated at 110,089,459 cases, with a 95% uncertainty interval (UI) of 58,608,815–195,025,585. The ASPR (age-standardized prevalence rate, ASPR) was 1367.36 per 100,000 population. DALYs (Disability-adjusted life years, DALYs) associated with female infertility totaled 601,134, with an age-standardized rate of 7.48 per 100,000 population (95% UI 2.65–18.23) (Tables 1 and 2).

The ASPR and DALYs were highest in the 35–39 age group, showing a peak before declining. Both the number of prevalence cases and DALYs followed similar age-related patterns as the age-standardized DALYs rates (Fig. S1). In 2021, the prevalence and DALYs in the 35–39 age group were 1.14 and 1.13 times higher, respectively, than those in the 30–34 age group (Fig. S1). The corresponding age-standardized rates were 1.23-fold and 1.21-fold higher, respectively (Fig. S1, Tables 1 and 2).

At the regional level, based on the sociodemographic index (SDI), the Middle SDI region recorded the highest numbers of female infertility cases at 39,038,802 and DALYs at 211,708 in 2021. However, the highest corresponding ASRs (age-standardized rate) were observed in the high-middle SDI region (Fig. 1, Tables 1 and 2). The relationship between SDI levels and disease burden remained consistent across countries and regions. As illustrated in Fig. S2, the relationship between the ASPR and sociodemographic index (SDI) manifests as a "wave". Age-Standardized DALYs Rate and SDI have the same relationship. In different territories and countries where the SDI is under 0.50, the trend is predominantly stable and tends to decrease slightly. For SDI levels between 0.50 and 0.75, the trend shows mild fluctuations, whereas regions with an SDI above 0.75 experience a rapid decline in both ASPR and age-standardized DALY's rate across territories and countries.

Among the GBD regions, Asia reported the highest prevalence (80,708,741, 95% UI 44,013,820–140,273,972) and DALYs (440,253, 95% UI 160,445–1,076,577), while Australasia had the lowest (prevalence: 23,946, 95% UI 5,824–97,727; DALYs: 135, 95% UI 22–593). For age-standardized rates, East Asia showed the highest prevalence (1979.77 per 100,000, 95% UI 1020.52–3458.07) and DALYs (10.4 per 100,000, 95% UI 3.56–26.14), with Australasia at the opposite end (prevalence: 76.86 per 100,000, 95% UI 18.74–304.96; DALYs: 0.44 per 100,000, 95% UI 0.07–1.86) (Fig. S3).

The Central African Republic exhibited the highest age-standardized prevalence of female infertility in 2021 at 3016.48 per 100,000 (95% UI 1877.54–4852.36), followed by Gabon, Djibouti, Comoros, Mozambique, and Eritrea. Similarly, the highest age-standardized DALYs were reported in the Central African Republic (16.48 per 100,000, 95% UI 6.06–37.78), with Gabon and Djibouti closely following. Australia displayed the lowest ASRs for prevalence cases and DALYs, succeeded by Colombia and New Zealand. In absolute terms, China and India observed the highest numbers of cases, with 29,317,000 (95% UI 14,569,167–52,098,692) and 29,075,289 (95% UI 16,070,794–49,483,699) respectively, followed by Indonesia and Pakistan. The smallest nations, such as Tokelau and Niue, reported the lowest counts, with zero DALYs recorded in both, followed by the Cook Islands, Greenland, and Monaco (Fig. S4).

| Characteristics | 1990 | | 2021 | | 1990–2021 |
	Number of prevalence cases (95% UI)	The age-standardized prevalence rate/100,000 (95% UI)	Number of prevalence cases (95% UI)	The age-standardized prevalence rate/100,000 (95% UI)	EAPC (95%CI)
Global	59,690,000 (32,625,584–104,614,493)	1118.29 (601.76–1958.53)	110,089,459 (58,608,815–195,025,585)	1367.36 (730.34–2405.83)	0.71 (0.55–0.88)
Sex			Pp′		
Female	59,690,000 (32,625,584–104,614,493)	2267.26 (1219.63–3969.94)	110,089,459 (58,608,815–195,025,585)	2764.62 (1476.33–4862.57)	0.7 (0.53–0.87)
Age					
15–19 years	791,658 (97,993–2,338,497)	152.41 (18.87–450.21)	1,014,989 (69,016–3,271,028)	162.66 (11.06–524.22)	−0.17 (−0.53 to 0.18)
20–24 years	7,957,251 (2,863,602–16,004,113)	1617.04 (581.93–3252.29)	13,082,608 (4,616,284–26,411,136)	2190.81 (773.04–4422.8)	1.04 (0.76–1.32)
25–29 years	10,618,578 (3,352,786–26,006,674)	2399.03 (757.49–5875.63)	19,170,379 (6,129,768–46,190,159)	3258.37 (1041.87–7850.89)	1.2 (0.92–1.48)
30–34 years	13,279,984 (3,429,389–30,328,858)	3445.57 (889.77–7868.99)	26,866,483 (6,932,324–64,075,582)	4444.56 (1146.82–10,600.11)	0.86 (0.65–1.06)
35–39 years	17,089,875 (5,157,052–38,349,601)	4851.71 (1464.05–10,887.21)	30,599,403 (8,491,888–69,339,499)	5455.74 (1514.07–12,362.93)	0.46 (0.31–0.62)
40–44 years	9,834,566 (2,599,136–22,294,902)	3432.88 (907.26–7782.31)	19,070,839 (4,763,496–43,742,361)	3812.26 (952.22–8744.09)	0.32 (0.24–0.4)
45–49 years	118,087 (23,532–620,857)	50.86 (10.13–267.39)	284,758 (48,245–1,686,995)	60.14 (10.19–356.28)	−0.16 (−0.55 to 0.23)
SDI regions					
Low SDI	10,739,460 (6,073,679–17,862,342)	1013.23 (566.62–1755.73)	30,053,933 (16,629,265–51,679,485)	1469.37 (811.58–2550.34)	1.28 (0.73–1.82)
Low-middle SDI	10,739,460 (6,073,679–17,862,342)	1013.23 (566.62–1755.73)	30,053,933 (16,629,265–51,679,485)	1469.37 (811.58–2550.34)	1.28 (0.73–1.82)
Middle SDI	22,576,313 (12,416,219–39,052,724)	1304.33 (698.69–2274.38)	39,038,802 (20,324,320–70,133,766)	1497.32 (782.01–2673.19)	0.63 (0.52–0.74)
High-middle SDI	16,546,621 (8,904,341–29,353,027)	1425.78 (763.92–2536.75)	21,200,266 (10,465,956–38,450,758)	1540.61 (792.65–2777.42)	0.23 (0.2–0.26)
High SDI	5,090,008 (2,095,085–10,270,333)	517.46 (213.94–1042.73)	7,476,943 (2,888,374–14,892,481)	684.26 (262.42–1379.74)	1.35 (1.21–1.5)

Table 1. The prevalence and age-standardized prevalence rates of female infertility in 1990 and 2021, with trends observed globally from 1990 to 2021. *ASPR* age-standardized prevalence rates.

| Characteristics | 1990 | | 2021 | | 1990–2019 |
	Number of DALYs cases (95% UI)	The age-standardized DALYs rate/100,000 (95% UI)	Number of DALYs cases (95% UI)	The age-standardized DALYs rate/100,000 (95% UI)	EAPC (95%CI)
Global	325,937 (114,823–807,747)	6.08 (2.16–15.24)	601,134 (213,158–1,468,475)	7.48 (2.65–18.23)	0.73 (0.56–0.89)
Sex					
Female	325,937 (114,823–807,747)	12.32 (4.39–30.93)	601,134 (213,158–1,468,475)	15.12 (5.35–36.88)	0.71 (0.54–0.88)
Age					
15–19 years	5074 (469–17,952)	0.98 (0.09–3.46)	6162 (316–23,164)	0.99 (0.05–3.71)	−0.39 (−0.69 to 0.09)
20–24 years	48,663 (11,823–133,352)	9.89 (2.4–27.1)	78,482 (19,501–207,846)	13.14 (3.27–34.81)	0.92 (0.67–1.17)
25–29 years	60,406 (11,757–172,481)	13.65 (2.66–38.97)	109,615 (22,334–309,837)	18.63 (3.8–52.66)	1.19 (0.93–1.46)
30–34 years	70,119 (13,341–189,815)	18.19 (3.46–49.25)	142,815 (26,433–384,261)	23.63 (4.37–63.57)	0.88 (0.67–1.09)
35–39 years	89,176 (20,855–261,597)	25.32 (5.92–74.27)	160,995 (35,790–465,102)	28.7 (6.38–82.93)	0.49 (0.34–0.65)
40–44 years	51,868 (10,293–164,620)	18.11 (3.59–57.46)	101,535 (19,710–317,437)	20.3 (3.94–63.46)	0.36 (0.28–0.44)
45–49 years	630 (95–3355)	0.27 (0.04–1.44)	1530 (209–8644)	0.32 (0.04–1.83)	−0.14 (−0.52 to 0.25)
SDI regions					
Low SDI	25,922 (9533–58,929)	6.15 (2.3–13.99)	67,696 (24,767–161,485)	6.52 (2.41–15.87)	0.13 (−0.26 to 0.53)
Low-middle SDI	60,815 (21,169–143,024)	5.67 (1.99–13.47)	167,400 (58,563–403,460)	8.16 (2.85–19.77)	1.22 (0.69–1.75)
Middle SDI	121,994 (42,876–302,346)	7 (2.43–17.25)	211,708 (75,088–517,044)	8.14 (2.89–19.78)	0.67 (0.56–0.78)
High-middle SDI	88,611 (30,730–229,796)	7.62 (2.66–19.76)	112,846 (38,219–282,874)	8.25 (2.84–20.21)	0.23 (0.2–0.27)
High SDI	28,320 (8576–75,480)	2.88 (0.87–7.63)	41,101 (11,612–110,625)	3.78 (1.06–10.35)	1.33 (1.18–1.48)

Table 2. The number of disability-adjusted life years (DALYs) and the age-standardized DALY rates attributable to female infertility in 1990 and 2021, along with global trends from 1990 to 2021. *DALYs* disability-adjusted life years.
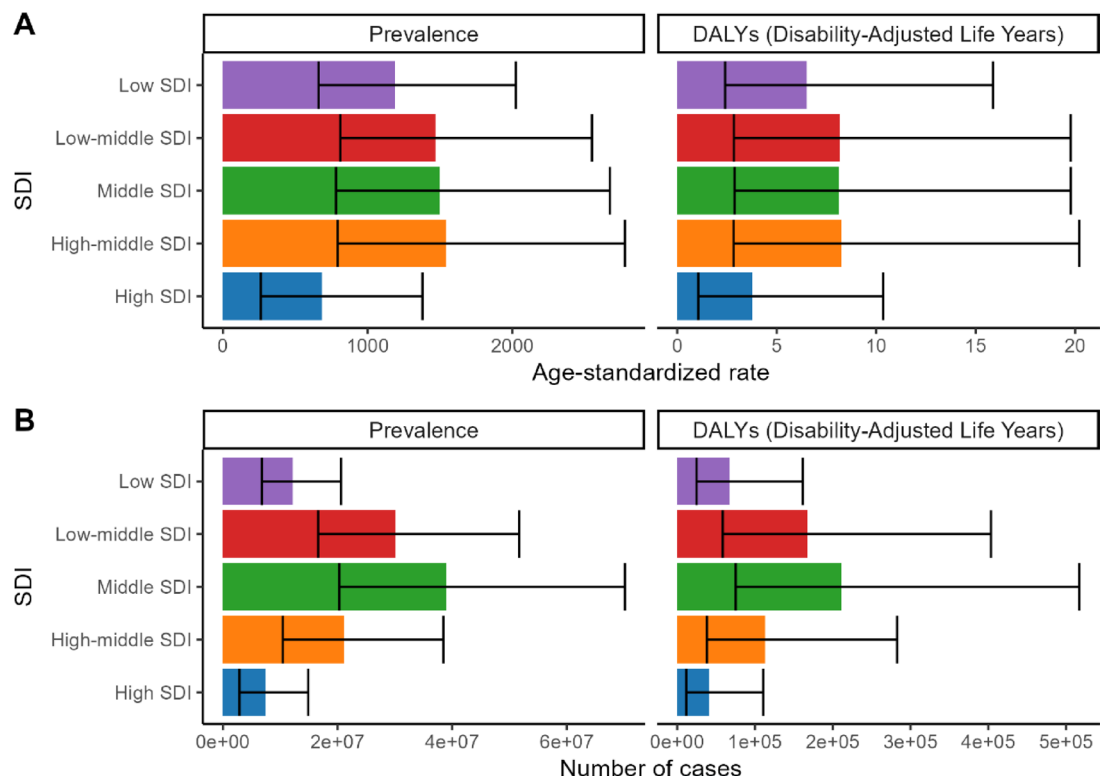
Fig. 1. Age-standardized prevalence rates (ASPR) and the number of cases of female infertility prevalence and DALYs across different socio-demographic index (SDI) regions in 2021. *DALYs* disability-adjusted life years; *SDI* socio-demographic index, *ASPR* age-standardized prevalence rates.

Temporal trends in the burden of female infertility disease from 1990 to 2021

Over the 31-year period, the global disease burden showed an upward trend in female infertility patients. The prevalence cases surged from 59,690,000 in 1990 to 110,089,459 in 2021, marking an increase of 84.44%. The corresponding ASPR experienced a 22.27% rise. A similar trend was observed in the disability-adjusted life years (DALYs), with an 84.43% increase in the number of DALYs cases and a 23.03% rise in the age-standardized DALY rate (Fig. 2, Tables 1 and 2).

Examining age-specific data, among women aged 35–39, the prevalence of infertility rose from 17,089,875 in 1990 to 30,599,403 in 2021—an increase of 79.05%. The corresponding age-standardized rate similarly increased by 12.45%. In the 30–34 age group, the number of infertility cases increased from 13,279,984 in 1990 to 26,866,483 in 2021, a significant rise of 102.31%, with the corresponding age-standardized rate also showing an increase of 28.99%. These data indicate that while the heaviest disease burden remains concentrated in women aged 35–39, the number of infertility cases in women aged 30–34 is rising rapidly (Fig. 3).

Regionally, different trends were observed across various sociodemographic index (SDI) levels. Except for the high SDI regions, which showed a slow increase followed by a decreasing trend, the ASPR and the age-standardized DALYs rate in other SDI regions exhibited an overall upward trend. Notably, the ASR in the low and low-middle SDI regions initially displayed a decrease, followed by a sharp increase starting around 2010. For the prevalence cases, the low-medium SDI area initially increased, then decreased, and subsequently experienced a rapid rise starting in 2010. Conversely, in China, the number of cases and DALYs continuously increased. Meanwhile, the prevalence and DALYs in high and high-middle SDI regions remained stable (Fig. S5, Tables 1 and 2).

The burden of female infertility displays considerable variability across GBD regions. Hierarchical cluster analysis was conducted to identify regions with similar patterns of change in disease burden. According to Fig. 4, Andean Latin America exhibited a significant increase in both ASPR and age-standardized DALYs rate, whereas regions like Oceania, Eastern Sub-Saharan Africa, Southern Sub-Saharan Africa, and Southern Africa showed significant decreases, alongside regions with minimal health systems.

Among the 204 evaluated countries, from 1990 to 2021, the changes in the number of prevalence cases and DALYs followed similar patterns, with Peru experiencing the most significant increases in both metrics. Conversely, Armenia witnessed substantial declines (prevalence: −76.36%; DALYs: −76.57%), followed by Malawi, Albania, and Rugia, which also saw decreases in both case numbers and DALYs (Fig. 5C,D).

Regarding ASR, Ecuador registered the largest increase in ASPR and age-standardized DALYs rate burden over the period from 1990 to 2021, with an Estimated Annual Percent Change (EAPC) in prevalence of 9.32, 95% confidence interval (CI) from 7.26 to 11.41; and DALYs EAPC of 9.13, 95% CI from 7.12 to 11.18. This trend was followed by Peru and Bolivia (Plurinational State). The most significant decrease was observed in
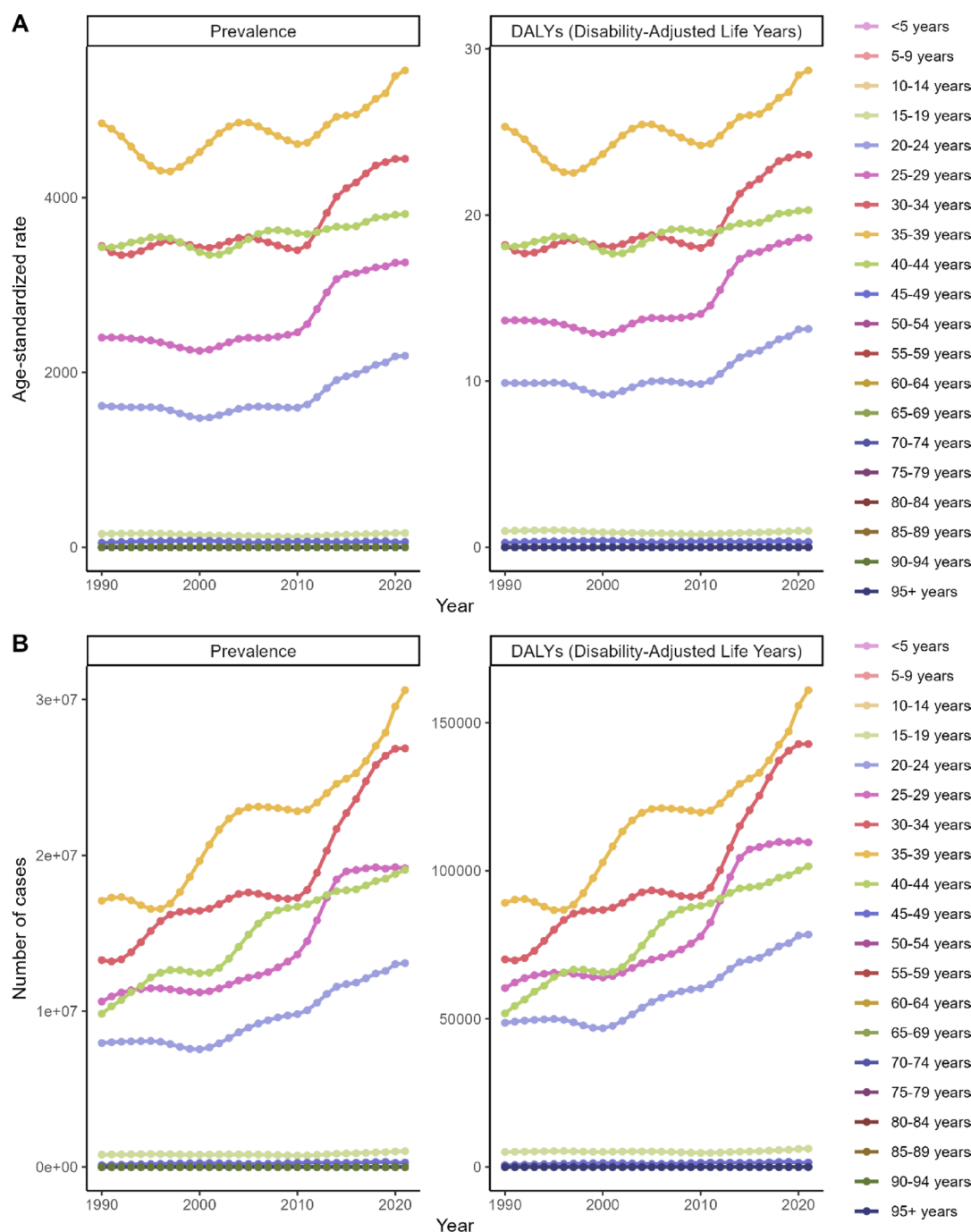
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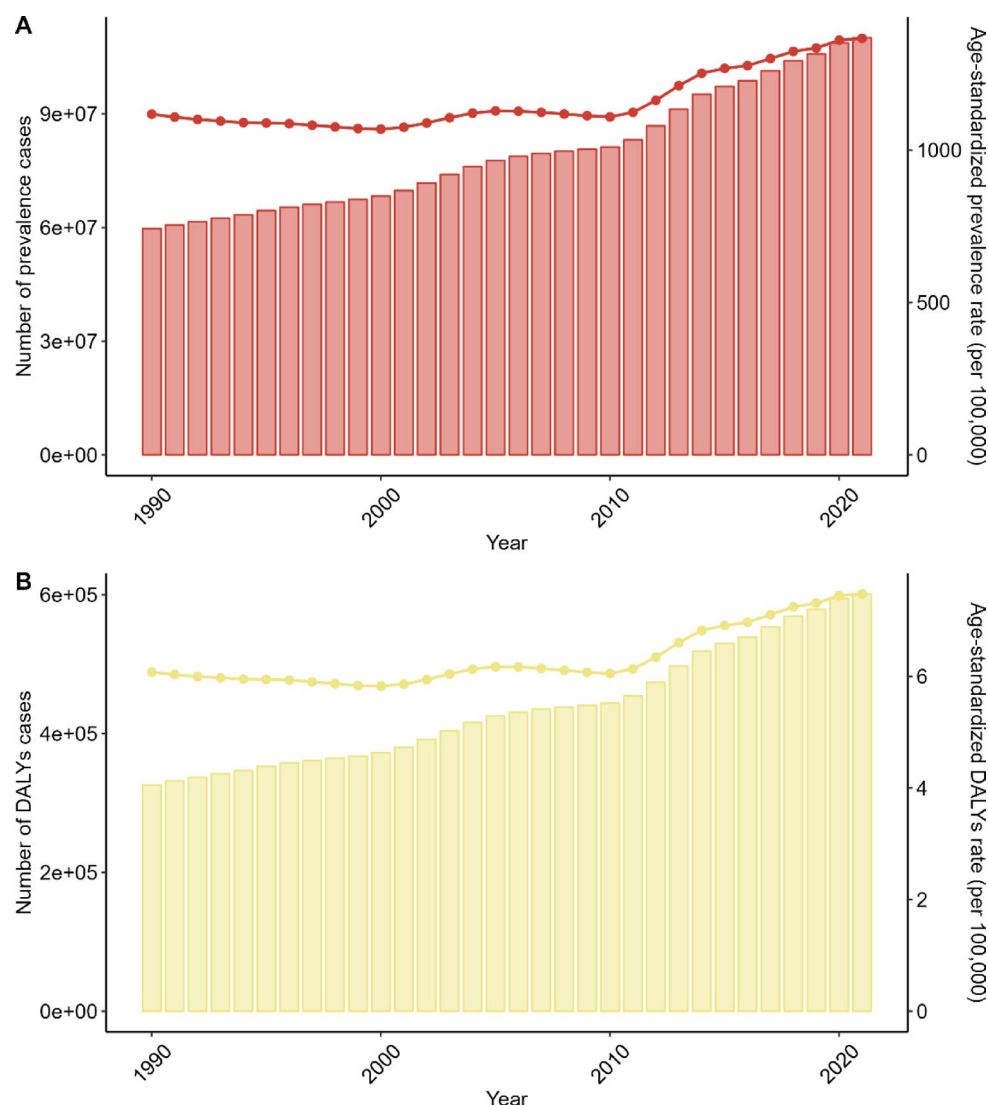
Fig. 2. Age-standardized prevalence rates and the number of cases of female infertility prevalence and DALYs from 1990 to 2021, highlighting global trends over this period. *DALYs* disability-adjusted life years, *ASPR* age-standardized prevalence rates.

Malawi (number of cases: EAPC = − 6.06, 95% CI from − 6.53 to − 5.6; DALYs: EAPC = − 6.04, 95% CI from − 6.50 to − 5.57), followed by Pakistan and Uganda (Fig. 5A,B).

Factors influencing EAPC and predicted results from 2022 to 2050

An analysis was conducted to assess the relationship between EAPC and age-standardized rates (ASR), EAPC and Human Development Index (HDI) in 2021 (Fig. 6). The 2021 ASR for female infertility serves as a baseline measure of the disease reservoir, while the 2021 HDI acts as a surrogate indicator of healthcare availability at the country level. We observed a correlation between EAPC and ASR; at relatively low ASR levels, a negative association emerged between EAPC and ASR in the number of affected individuals (ASPR: $\rho = -0.007$, $p = 0.92$) and a positive correlation with ASR in DALY ($\rho = 0.004$, $p = 0.95$), although these correlations were not statistically significant (Fig. 6A). Conversely, a statistically significant positive association was found between EAPC and HDI (ASPR: $\rho = 0.26$, $p < 0.01$; Age-Standardized DALYs rates: $\rho = 0.26$, $p < 0.01$) (Fig. 6B), indicating that in countries with high HDI, the incidence of female infertility increased in 2021 but showed a slowing trend when HDI exceeded 0.8.

Projections based on the autoregressive integrated moving average (ARIMA) model suggest that from 2022 to 2050, the global prevalence of female infertility is expected to gradually decline. However, the corresponding ASR is projected to continue rising. Similarly, DALYs are anticipated to slowly decrease during the period, yet the corresponding ASR is expected to persistently increase (Fig. S6).

Fig. 3. Age-standardized prevalence rates and the number of cases of female infertility prevalence and DALYs across different age groups from 1990 to 2021, with global trends depicted for the same period. *DALYs* disability-adjusted life years, *ASPR* age-standardized prevalence rates.

Discussion

Infertility represents a significant global health issue, affecting over 9% of women of childbearing age worldwide. In 2021, female infertility contributed to a substantial disease burden, with notable variations across different ages, sociodemographic index (SDI) regions, territories and countries. The World Health Organization (WHO) recognizes infertility as a global public health concern with profound implications for individuals and societies[15]. To our knowledge, this study is the first to comprehensively assess and quantify the burden of female infertility across 204 countries and territories from 1990 to 2021, also projecting future disease burden trends. This research aims to enhance understanding of the current and future dynamics of female infertility.

Few studies have provided a global perspective, utilizing data from the GBD 2017 study, Sun et al. explored the global prevalence of infertility and its DALYs from 1990 to 2017, revealing an increasing global burden of infertility disease, with a notably higher prevalence among women than men[16]. However, these analyses
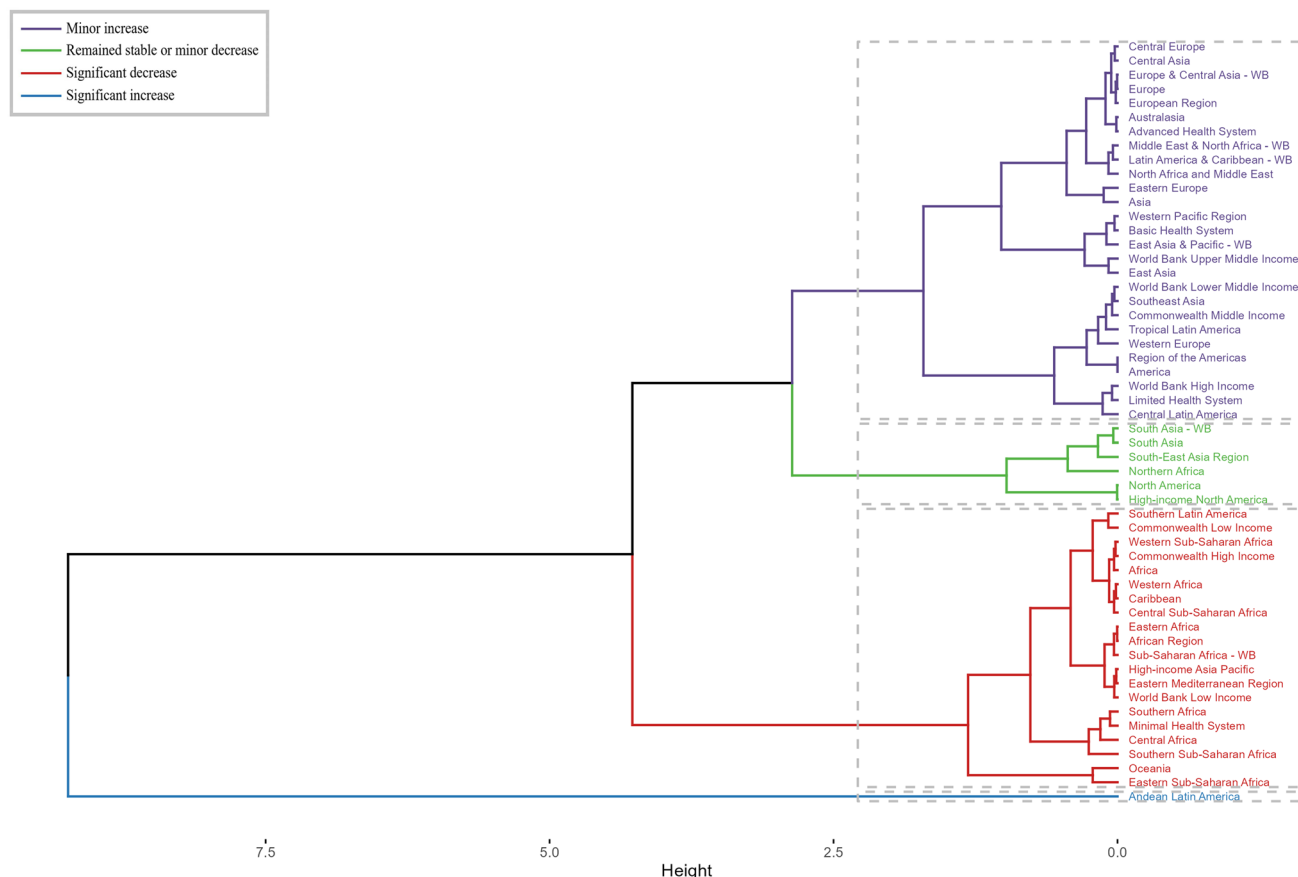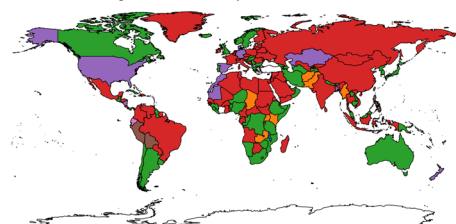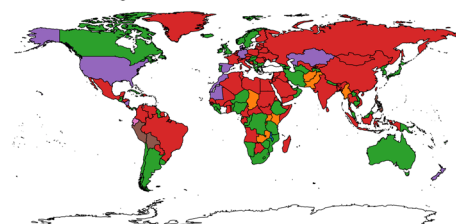
Fig. 4. Results of cluster analysis based on the EAPC in age-standardized rates for prevalence and DALYs attributable to female infertility from 1990 to 2021. *DALYs* disability-adjusted life years, *EAPC* estimated annual percentage change.
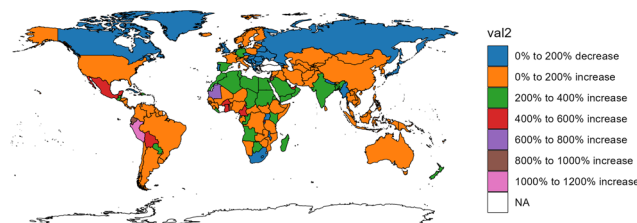

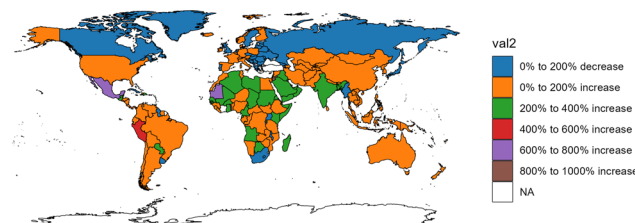**Fig. 5**. Changes in prevalence and DALYs attributable to female infertility across countries and territories from 1990 to 2021, along with the EAPC for the corresponding ASR. The map was generated utilizing R programming software (version 4.2.2), incorporating the "dplyr" package, as well as the "maps" "ggplot2" and "ggmap" packages. *DALYs* disability-adjusted life years, *EAPC* estimated annual percentage change, *ASR* age-standardized rate.
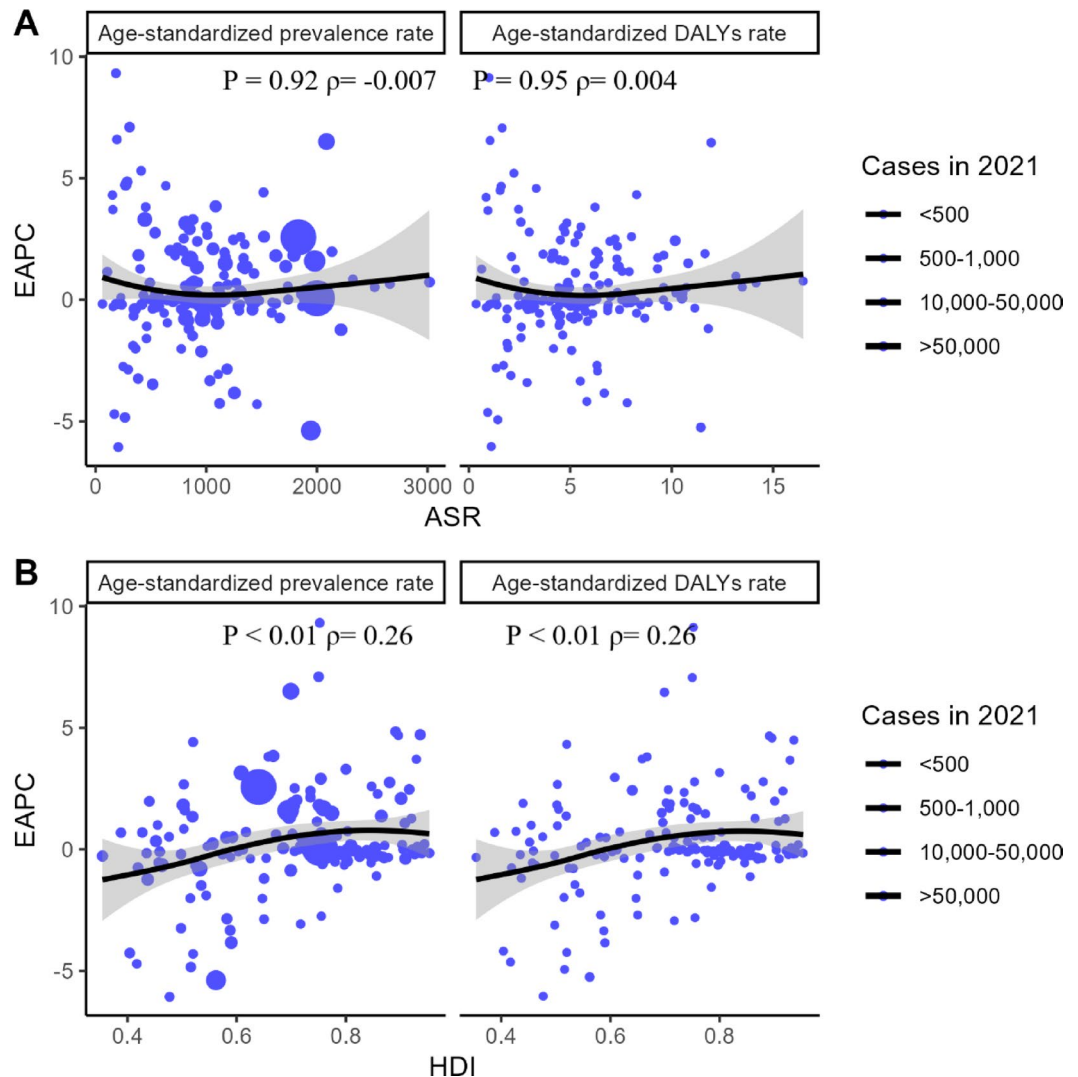
Fig. 6. Relationships between EAPC and age-standardized rates (ASR), and EAPC and the human development index (HDI) in 2021. *DALYs* disability-adjusted life years, *EAPC* estimated annual percentage change, *ASR* age-standardized rate, *HDI* human development index.

lacked depth in trend projection and further exploration. Leveraging data from GBD 2021, our study offers a comprehensive assessment of the global burden of female infertility. We found that in 2021, the number of prevalence female infertility cases predominantly concentrated in the medium SDI region, with the largest numbers reported in Asia. When examining ASPR and age-standardized DALYs rate, these were primarily found in the medium-high SDI region, with the East Asian region bearing the heaviest burden. This distribution may be attributed to factors such as demographics, lifestyle, dietary patterns, environmental exposures, and enhanced access to healthcare. In conjunction with previous scholarly estimates, our findings underscore that female infertility imposes a significant disease burden.

From 1990 to 2021, we noted a marked increase in the global number of female infertility prevalence, along with rises in disability-adjusted life years (DALYs) and their corresponding ASRs. Female age remains a crucial determinant of natural conception and the success of treatment-related conceptions, with fertility notably declining with advancing age, particularly after 35 years[17–19].

Upon analyzing the global burden of female infertility across all age groups, it becomes apparent that the highest concentration of cases is within the 35–39 age group. However, the most significant increases were observed in the 30–34 and 25–29 age groups, both in terms of prevalence and DALYs, as well as their corresponding ASRs. For instance, the prevalence of infertility in the 30–34 age group rose by 103.68%, with the ASR increasing by 29.91%. These changes may be attributed to factors such as delayed childbearing, urbanization, and increased emissions from industry and vehicles[20], as well as advancements in infertility detection and diagnostic methods.

This trend aligns with current understandings of women's fertility levels. Based on a survey involving 7172 women, researchers have found that women over the age of 35 are twice as likely to suffer from unexplained infertility compared to younger women[21]. Additionally, studies indicate a significant increase in chromosomal degeneration and aneuploidy in infertile patients over the age of 35[22,23]. It has also been documented that older

eggs exhibit considerably greater mitochondrial damage, and mitochondrial DNA (mtDNA) mutations in ovarian tissue significantly increase after the age of 45[24,25]. Given these findings, proactive measures and policies are essential for the diagnosis and treatment of female infertility, aiming to reduce the associated disease burden. Enhanced awareness and improved healthcare interventions could play pivotal roles in addressing this growing challenge.

Our regional analysis over the period from 1990 to 2021 reveals a slow increase followed by a decreasing trend in the number of female infertility prevalence, disability-adjusted life years (DALYs), and their corresponding age-standardized rates (ASR) in high sociodemographic index (SDI) areas. Further regression adaptation analysis indicated a nonlinear relationship between SDI and the prevalence of female infertility, DALYs, and corresponding ASR. Notably, a negative correlation emerged when SDI was greater than 0.75, suggesting that higher SDI values are associated with decreased trends in the prevalence and burden of female infertility. This finding aligns with the association analysis of Estimated Annual Percent Change (EAPC) and Human Development Index (HDI) in female infertility for the year 2021, where EAPC demonstrated a decreasing trend with HDI values over 0.8.

SDI and HDI are critical indicators for assessing the impact of socio-economic development on health and disease burden. Regions with high SDI and HDI typically exhibit superior health, economic, and social development, potentially correlating with lower disease burdens and higher quality of life[26]. This association likely reflects advantages such as better medical facilities, more equitable access to fertility treatments, higher socio-economic conditions, and enhanced overall health, well-being, and advocacy in high SDI regions[27]. These factors contribute to fewer reported fertility issues.

Significant regional and country-specific disparities in the burden of female infertility were noted. For instance, between 1990 and 2021, the number of female infertility prevalence, DALYs, and corresponding ASR significantly increased in Latin American countries such as Peru and Ecuador. Conversely, a notable decrease in the corresponding ASR was observed in Armenia, likely due to varying environmental conditions, cultural factors, preventive healthcare programs, and economic development levels. For example, data from the Peruvian Institute of Statistics indicate that the interval between pregnancies among Peruvian women has lengthened, with an average gap of 4 years in 2009[28]. This extended interval may increase the age at second pregnancy, consequently elevating infertility rates.

Overall, while female infertility remains a significant public health issue in developed countries, its impact is more pronounced in developing regions where rapid population growth and widespread industrialization contribute to environmental and noise pollution, posing serious health threats[29]. We hypothesize that the trajectory of industrialized nations, marked by accelerated economic growth, may be associated with a postponement in reproductive age, particularly beyond 35 years in women, leading to an increased incidence of reported infertility. Furthermore, environmental exposures prevalent during industrialization may contribute to this phenomenon through epigenetic mechanisms that adversely impact fertility[30]. This observation is corroborated by the presence of the highest disease burdens in this study occurring in areas with medium and medium-high SDI.

To 2050, the projected results indicate a diverging trend in the disease burden of female infertility from 2022 onwards: while the number of affected individuals is expected to decrease, and the number of disability-adjusted life years (DALYs) is anticipated to follow a downward trend, the corresponding age-standardized rate (ASR) is projected to exhibit a continuous upward trend. These opposing trends can be attributed to several interrelated factors. First, the global population continues to age, and a significant increase in the proportion of women over 30 within the childbearing population may elevate the risk of infertility. This structural aging is likely to result in an upward trend in the ASPR, despite an actual decline in the number of affected individuals due to overall population decrease. Second, the impact of lifestyle and environmental risk factors such as delayed childbearing age, occupational stress, and environmental pollution is expected to heighten the relative risk of infertility among women of childbearing age. This increase could drive up the ASPR. Third, as diagnostic capabilities improve and awareness of fertility issues heightens, more cases of infertility are likely to be diagnosed. This could lead to an increase in the age-standardized prevalence, even in regions experiencing population declines. In summary, the contrasting trends in the actual number of people with infertility and the ASR are likely a reflection of demographic shifts, escalating high-risk behaviors, and socioeconomic developments expected in the coming years.

Socioeconomic development plays a pivotal role in comprehending fertility trends. The demographic transition model posits that societies transition from high to low birth and death rates as they undergo modernization. Enhanced female education is frequently associated with delayed marriage. Empirical evidence suggests that educated women are more inclined to utilize contraception, thereby contributing to reduced fertility rates[31]. High-risk fertility behaviors are more prevalent in low-income countries, often linked to unmet family planning needs and child marriage. For example, research conducted in East Africa indicates that such behaviors are correlated with child stunting and anemia, highlighting their health implications[32]. In the short term, these behaviors may lead to elevated fertility rates, but they can also increase child mortality, thereby influencing net population growth. Additionally, other high-risk activities, such as smoking, excessive alcohol consumption, and drug abuse, may result in infertility. The American Society for Reproductive Medicine, for instance, emphasizes take the adoption of a preventive approach to infertility by discouraging tobacco use and minimizing exposure to cigarette smoke both men and women[33]. These relationships are intricately interconnected. Socioeconomic development has the potential to mitigate high-risk behaviors and reduce fertility rates, thereby influencing demographic structural changes. For example, reduced fertility rates contribute to population aging, which can decelerate economic growth and potentially reverse socioeconomic advancements. Conversely, in less developed regions, persistent high-risk behaviors may maintain elevated fertility rates, often accompanied by substantial health challenges.

Consequently, female infertility is anticipated to persist as a substantial public health challenge in the future. A reduction in absolute numbers does not inherently signify a decrease in the disease burden, as a thorough evaluation of various contributing factors is essential. It is imperative to prioritize early screening and preventive measures for women experiencing infertility, in conjunction with interventions targeting lifestyle modifications and psychosocial support. Furthermore, advancing research into precision medicine and assisted reproductive technologies (ART) remains crucial.

Strength and limitations

Compared to GBD 2019, GBD 2021 incorporated 43 additional data sources for the estimation of infertility impairment[34]. Thus, GBD studies provide robust estimates of disease burden. While previous research has estimated the burden of female infertility, most such studies were confined to single regions or countries[35] or focused solely on specific factors related to female infertility[14].

This study is subject to certain limitations stemming from its reliance on the Global Burden of Disease (GBD) database data. A significant challenge is the absence of detailed data from smaller administrative divisions such as counties, provinces, and states[36]. While the GBD database encompasses numerous countries and regions worldwide, the accuracy and completeness of the data can vary substantially, particularly in low- and middle-income countries where data may be less detailed or more susceptible to bias. Additionally, the availability of raw data within this database presents another considerable limitation[37,38]. Although burden of disease data were estimated using standardized Bayesian regression tools, the limited data scope introduces uncertainties, notably the global outbreak of the COVID-19 pandemic may further complicate our results. Lastly, the GBD database provides population-level data, which does not include detailed personal patient information, thus limiting the depth of analysis possible regarding the epidemiological characteristics of specific subtypes or patient populations of female infertility.

Conclusion

Overall, female infertility imposes a significant disease burden and critically impacts global fertility, particularly in regions with high-medium levels of economic development. This study reaffirms the significant influence of age on female fertility, highlighting an emerging trend where the onset of female infertility is occurring at progressively younger ages. We also observe that while the absolute number of cases may decline over the next 25 years, the ASPR and age-standardized DALYs are projected to continue showing an upward trend. This underscores that female infertility remains a pressing public health issue that demands sustained research attention. Our findings should guide policymakers in prioritizing women's infertility healthcare and underscore the necessity for effective prevention and management interventions to mitigate the escalating burden of infertility. However, further research is needed to explore the risk factors for female infertility and prevalence trend to devise and implement effective strategies to reduce this disease's burden.

Methods
Overview

Data specific to female infertility, including prevalence, disability-adjusted life years (DALYs), and corresponding age-standardized rates, were obtained from the Global Health Data Exchange (GHDx) website (https://vizhub.healthdata.org/gbd-results/). The Global Burden of Disease (GBD) 2021 study represents the most extensive and scientifically rigorous effort to assess epidemiological burdens globally, encompassing 371 diseases and injuries along with 84 risk factors. Counts and age-standardized rates were calculated globally, for seven super-regions, 21 regions, 204 countries and territories (including 21 countries with subnational locations), and 811 subnational locations, from 1990 to 2021[34]. These countries and territories were further segmented into five groups based on the sociodemographic index (SDI)[39]. The data sources for the 2021 GBD study included household surveys, demographic statistics, and other pertinent sources[34].

The DALY is a broad metric that captures the total health loss due to a disease, calculating the years of healthy life lost from when the disease begins until death. It is utilized in the GBD study to assess disease burden[40]. DALYs are computed by combining the years lost to premature death (YLL) with the years of life affected by disability from illness or injury (YLD). Female infertility does not lead to death, so the DALYs for female infertility are the same as the YLDs.

For all final estimates, 95% uncertainty intervals (UI) were created using the 2.5th and 97.5th percentile values from 500 samples. Uncertainty was accounted for at each stage of the estimation process. Statistical significance is defined as a 95% UI, excluding 0. Results such as prevalence, DALYs, ASPR, and age-standardized DALYs rate have their uncertainty quantified and represented with point estimates and 95% UI[41].

In this study, we used DisMod-MR, a Bayesian meta-regression tool, to model the non-fatal burden of female infertility[42]. The Mr-BRT (meta-regression—Bayesian, regularized, trimmed) tool, a sophisticated statistical instrument, is utilized in Global Burden of Disease (GBD) studies to estimate adjustment factors. This tool enhances the precision of estimates by accounting for biases and variations across diverse data sources. The Mr-BRT tool is particularly valuable in the context of disability-adjusted life years (DALYs) and other health metrics. By applying adjustment factors estimated through Mr-BRT, we can harmonize disparate datasets, thereby facilitating more accurate cross-study comparisons and strengthening the robustness of overall GBD estimates. In estimating the burden of ischemic heart disease in Isfahan, Iran, the researcher employed adjusted models to address issues of data incompleteness and misclassification, thereby underscoring the critical importance of precise data adjustment in burden estimation[43]. The GBD 2019 study on drug use disorders further exemplified the application of Bayesian meta-regression to analyze prevalence and incidence, illustrating the utility of advanced statistical techniques in global health research[44].

Additionally, this study involved the collection of background information such as the SDI, for subsequent correlation analyses. The SDI values, which range from 0 to 1, reflect a country's level of social development. According to the GBD 2021 study, countries are globally classified into five quintiles based on SDI—high, medium-high, medium, medium-low, and low—and 21 geographic regions[42,43]. Furthermore, this research utilized the Human Development Index (HDI), introduced by the United Nations Development Programme (UNDP) in 1990, which comprises educational attainment, life expectancy, and gross national income components. The HDI serves as a comprehensive measure employed by the United Nations to evaluate the economic and social development levels of its Member States. Since its inception, the HDI has been instrumental in guiding the development strategies of developing countries. The UNDP annually publishes HDI values for nations worldwide, employing them in the Human Development Report to assess countries' human development levels[45,46].

Case definition

In GBD2021, Primary Female infertility is characterized by the failure to conceive a child after 5 years of unprotected intercourse, not attributed to any other infertility cause. Secondary infertility was identified in couples who desired a child and had been together for over 5 years without using contraception since their last live birth. The incidence of female infertility was assessed using the International Classification of Diseases, Ninth Revision (ICD-9): 628-628.9, V26-V26.49, V26.51, V26.8-V26.9, V59.7-V59.74 and Tenth Revision (ICD-10): N97-98.9[47]. Based on the physiological characteristics of women, it was presumed that there was no burden of infertility in women under the age of 15. Consequently, the study population was segmented into seven age groups: 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45–49 years.

Statistics

Initially, the global prevalence of female infertility, along with disability-adjusted life years (DALYs) and corresponding age-standardized rates (ASRs), were reported for 2021. These were further delineated by different subtypes, including age, sociodemographic index (SDI), region, and country. The ASR was computed per 100,000 individuals using the following formula:

$$ASR = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i} \times 100,000$$

A: the number of age groups; a_i: the age-specific rate in ith the age group. w_i: the number of people in the corresponding ith age group among the standard population.

Temporal trends in disease burden from 1990 to 2021 were subsequently explored both globally and by subtype. Estimated Annual Percent Change (EAPC) values were calculated using linear regression models[48]. The EAPC was calculated using the formula: $EAPC = 100 \times (e^\beta - 1)$. A 95% confidence interval (CI) was calculated using the linear regression model. Where β is calculated from the formula $Y = \alpha + \beta X + \varepsilon$, with $Y = \ln(ASR)$, X denoting the calendar year, and ε as the error term. Based on these EAPC values, hierarchical cluster analysis was employed to identify patterns of change in the disease burden across the Global Burden of Disease (GBD) regions. These regions were classified into four categories: significant increase, small increase, stable or small decrease, and significant decrease.

Furthermore, the relationships among EAPC, ASR, and the Human Development Index (HDI) in 2021 were evaluated. Given the normal distribution of these three variables, Spearman correlation analysis was utilized to examine the associations. Projections of the future burden of disease from 2022 to 2050 were made using an autoregressive composite moving average (ARIMA) model under a maximum likelihood framework. The ARIMA model integrates autoregression, moving average, and moving weighted average, and is frequently employed in epidemiological studies to predict future variations using historical temporal patterns[49]. Statistical significance was established at a *p* value of less than 0.05. All data organization, management, and analysis were conducted using R software (version 4.2.2).

Data availability

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Author contributions

Jie Liu, Yi Qin: Study design, conceptualization, formal analysis, methodology, software, visualization, and writing-original draft; Hui Liu, Yonglin Liu, Yi Yang: Formal analysis, software and visualization; Yumei Ning, Huijun Ye: Investigation, project administration, supervision, and writing-review and editing. All the authors have reviewed and approved the manuscript for publication.

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Declarations

Competing interests

The authors declare no competing interests.

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