Global, regional, and national incidence, mortality, DALY, and prevalence rates of orofacial clefts in children and adolescents from 1990 to 2021, with predictions to 2050

Bowen Dai[1,2], Yuqi Song[3], Xiaoyu Yu[2], Dongxu Li[4*], Xiaoming Li[5,6*]

[1]School of Mental Health and Psychological Science, Anhui Medical University, Hefei, China
[2]Southwest Medical University, Luzhou, China
[3]Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[4]Department of Orthopedics, Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[5]Department of Psychiatry, Chaohu Hospital of Anhui Medical University, Hefei, Anhui, China
[6]Department of Medical Psychology, School of Mental Health and Psychological Science, Anhui Medical University, Hefei, China

*Corresponding authors:
Xiaoming Li
Department of Psychiatry
Chaohu Hospital of
Anhui Medical University
Hefei, Anhui, China
Phone/mobile:
+8613485606912
mail: lixiaoming@ahmu.edu.cn

Dongxu Li
Department of Orthopedics
Wuhan Union Hospital
Tongji Medical College
Huazhong University of
Science and Technology
Wuhan 430022, China
Phone/mobile: 19235608674
E-mail: 19235608674@163.com

Orofacial clefts (OC) are among the most common congenital facial anomalies globally, categorized into cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO) [1]. Approximately one in 700 live births is affected by OC [2], and the incidence is notably higher in Asian populations compared to White and African populations [3]. The risk of OC can be attributed to a combination of genetic susceptibility and environmental factors, including maternal alcohol consumption and smoking [1, 4, 5].

OC not only affects the physical health of affected children – such as feeding difficulties in infancy potentially leading to malnutrition – but also imposes long-term negative impacts on their psychological and social functioning, including psychiatric disorders and intellectual disability [6, 7]. While family support and social resources can help mitigate these issues, their effectiveness is often constrained by regional disparities in available resources [8].

OC, as congenital disorders, concentrate their greatest burden early in life, with children and adolescents being the most directly and complexly affected group. Existing burden-of-disease studies based on all-age populations, such as those by Wang *et al.*, are susceptible to the confounding effects of widespread comorbidities, cumulative social factors, and long-term sequelae in adult and elderly populations [9]. These factors may obscure the distinct burden characteristics specific to the child and adolescent population. Therefore, this study explicitly focuses on individuals aged 0–19 years, conducting a multidimensional assessment of the OC burden for the first time within this specific age group, with particular attention paid to more granular age-sex stratification to accurately capture trends in burden across different age groups and sexes. Furthermore, we project OC burden trends up to 2050, providing forward-looking evidence for medium- to long-term prevention and intervention strategies. Overall,

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this work aims to offer more population-specific, timely, and targeted evidence to support precise prevention, early intervention, and optimized resource allocation for different subgroups and developmental stages of children and adolescents.

Methods. *Overview and data analysis.* Data on OC burden were obtained from the GBD 2021 database (https://vizhub. healthdata.org/gbd-results/). The data freeze date and download date for this study are May 16, 2024 and November 23, 2024 respectively. The extraction was restricted to data between 1990 and 2021. We standardized disease definitions for children and adolescents (ages 0–19) with OC. The analysis classified participants into seven age groups: less than 28 days, 1–5 months, 6–11 months, 2–4 years, 5–9 years, 10–14 years, and 15–19 years. Numbers of incident cases, deaths, disability-adjusted life years (DALYs), and prevalent cases, along with the corresponding incidence, mortality, DALY, and prevalence rates, were the main indicators used to describe the burden of OC at global, national, regional, and age and sex levels.

Definitions. The SDI reflects a region's socio-economic status based on per capita income, average years of schooling, and fertility rate among females under 25. It categorizes regions into five levels – low, low-middle, middle, high-middle, and high SDI – reflecting the association between socioeconomic development and the burden of OC among children and adolescents [10, 11].

DALYs represent the total healthy life years lost due to disease, including years of life lost (YLLs) and years lived with disability (YLDs). This metric is used to quantify the burden of OC at global, national, and regional levels among children and adolescents.

Annual percentage change (APC) and average annual percentage change (AAPC) were calculated using linear regression.

Statistical analysis. Joinpoint regression models, as a collection of linear statistical models, are commonly used to assess temporal trends in disease burden by estimating changes in disease rates through least squares and identifying turning points based on the residual sum of squares. This study employed the Joinpoint model (version 4.9.1.0; National Cancer Institute, Rockville, Maryland, USA).

The Autoregressive Integrated Moving Average (ARIMA) model was applied to forecast trends in the OC burden for the period 2021-2050. This model assumes that data series are time-dependent random variables and uses parameters for autoregression (p), differencing (d), and moving averages (q) to account for autocorrelation and forecast trends. To fit the optimal ARIMA model, the process involved three steps: (a) conducting a stationarity test, (b) identifying the model and determining its order, and (c) performing model diagnostics. These predictions aim to provide insights into the potential future impact of OC on children and adolescents.

All analytical calculations in this study were performed using R Studio (version 4.1.2), and all $c$values were two-sided, with $p < 0.05$ considered statistically significant.

Results. From 1990 to 2021, the global incidence, mortality, DALY, and prevalence rates of OC showed an overall declining trend (–35.56%, –88.08%, –81.46%, and –0.06%) (Table I, Supplementary Tables SI–SIII). However, incidence (APC = 0.28) and prevalence (APC = 0.14) increased between 2004 and 2008 (Figure 1).

In 2021, the incidence, mortality, DALY, and prevalence rates of OC were higher in males than in females. From 1990, both sexes showed a downward trend in incidence rate (–34.77% in males, –36.39% in females), mortality rate (–87.98% in males, –88.19% in females), DALY rate (–81.26% in males, –81.68% in females), and prevalence rate (–0.05 in males, –0.06 in females) (Table I, Supplementary Tables SI–SIII). The neonatal period represents the peak stage for mortality, DALYs, and prevalence rates of OC (Table I, Supplementary Tables SI, SII). Before the age of 5 months, males exhibited higher mortality and DALY rates compared to females, with a reversal observed between 5 months and 4 years of age (Supplementary Figure S1).

In 2021, the highest incidence, mortality, and DALY rates were observed in the low SDI region (Supplementary Figure S2). The highest prevalence rate was observed in the low-middle SDI region (Supplementary Figure S2). From 1990, the incidence, mortality, DALY, and prevalence rates declined across all SDI regions, with high middle SDI regions showing the steepest reductions (–48.77%, –97.52%, –93.84%, and –15.26%) (Table I, Supplementary Tables SI–SIII). Although overall declines were observed, the reduction in high SDI regions was relatively gradual, whereas the low SDI regions experienced transient fluctuations, including a temporary rise around 2001, before returning to a gradual decline (Supplementary Figure S2).

In 2021, Central Asia recorded the highest incidence rate (14.52 per 100,000, 95% UI: 10.08 to 19.65), while Oceania exhibited the highest mortality (0.55 per 100,000, 95% UI: 0.1 to 1.42) and DALY rates (51.73 per 100,000, 95% UI: 11.55 to 129.42) (Supplementary Figure S3). From 1990, Oceania experienced the largest increase in incidence rate (13.89%), while East Asia experienced the greatest decrease in incidence rate and prevalence rate (–60.89% and –23.97%, respectively)

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Table I. Incidence for children and adolescents with OC between 1990 and 2021 at the global and regional level

| Parameter | Rate per 100,000 (95% UI) | | | | | |
| | 1990 | | 2021 | | 1990–2021 | |
Location	Incident cases	Incidence rate	Incident cases	Incidence rate	Cases change	Rate change
Global	243735.52 (179582.34, 309986.17)	10.79 (7.95, 13.72)	183302.41 (135255.43, 241690.82)	6.95 (5.13, 9.17)	–24.79 (–30.45, –18.69)	–35.56 (–40.4, –30.33)
Sex						
Male	124247.98 (91825.49, 157756.84)	10.74 (7.93, 13.63)	95136.89 (70804.09, 125665.85)	7 (5.21, 9.25)	–23.43 (–29.16, –17.42)	–34.77 (–39.64, –29.64)
Female	119487.54 (87826.82, 152719.92)	10.85 (7.98, 13.87)	88165.52 (64450.13, 115817.02)	6.9 (5.05, 9.07)	–26.21 (–31.73, –19.54)	–36.39 (–41.15, –30.64)
SDI						
High	19184.17 (14943.54, 23686.01)	7.63 (5.95, 9.42)	12250.69 (8958.26, 15793.47)	5.26 (3.85, 6.79)	–36.14 (–42.89, –30.5)	–31.04 (–38.33, –24.95)
High-middle	35467.68 (27356.63, 44190.28)	9.58 (7.39, 11.94)	14891.05 (10856.42, 19103.22)	4.91 (3.58, 6.3)	–58.02 (–63.13, –52.83)	–48.77 (–55.01, –42.44)
Middle	70155.05 (52194.59, 89621.54)	9.18 (6.83, 11.72)	41628.6 (30595.38, 54118.79)	5.56 (4.08, 7.22)	–40.66 (–46.34, –34.35)	–39.45 (–45.24, –33.01)
Low-middle	77840.54 (55680.33, 103242.81)	13.17 (9.42, 17.47)	61922.27 (45962.81, 82936.3)	8.1 (6.01, 10.85)	–20.45 (–27.53, –12.31)	–38.49 (–43.96, –32.2)
	40949.91 (28498.52, 53784.88)	14.65 (10.19, 19.24)	52492.49 (37730.85, 70030.42)	8.99 (6.46, 12.04)	28.19 (16.67, 41.63)	–38.66 (–44.17, –32.22)
Regions						
Andean Latin America	2389.09 (1779.89, 3030.16)	12.6 (9.39, 15.99)	2073 (1528.44, 2708.14)	8.76 (6.46, 11.44)	–13.23 (–28.43, 1.86)	–30.52 (–42.69, –18.44)
Australasia	523.94 (476.49, 581.77)	8.35 (7.6, 9.27)	446.01 (310.35, 596.5)	5.91 (4.12, 7.91)	–14.87 (–36.09, 6.93)	–29.19 (–46.84, –11.06)
Caribbean	930.21 (637.85, 1240.05)	6.16 (4.22, 8.21)	836.26 (589.84, 1178.51)	5.48 (3.86, 7.72)	–10.1 (–26.37, 7.62)	–11.06 (–27.16, 6.47)
Central Asia	7838.79 (5676.28, 9950.71)	24.82 (17.97, 31.51)	5026.86 (3489.66, 6802.15)	14.52 (10.08, 19.65)	–35.87 (–48.93, –22.53)	–41.51 (–53.42, –29.34)
Central Europe	2950.68 (2260.74, 3684.57)	7.51 (5.76, 9.38)	1199.29 (846.88, 1582.11)	5.09 (3.6, 6.72)	–59.36 (–66.3, –53.25)	–32.25 (–43.83, –22.07)
Central Latin America	9706.58 (7405.57, 12225.27)	11.75 (8.96, 14.79)	4740.34 (3408.77, 6221.52)	5.56 (4, 7.29)	–51.16 (–57.21, –45.42)	–52.68 (–58.55, –47.12)

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Table I. Cont.

Parameter	1990		2021		1990–2021	
	Rate per 100,000 (95% UI)					
Central Sub-Saharan Africa	3733.29 (2516.07, 4946.6)	12.05 (8.12, 15.96)	4471.89 (3198.55, 6112.86)	6.08 (4.35, 8.31)	19.78 (–1.24, 43.63)	–49.54 (–58.39, –39.5)
East Asia	43150.13 (32544.48, 53678.51)	9.38 (7.07, 11.67)	12651.02 (9475.07, 16014.85)	3.67 (2.75, 4.64)	–70.68 (–74.67, –66.23)	–60.89 (–66.21, –54.96)
Eastern Europe	3774.26 (2719.42, 4815.61)	5.61 (4.04, 7.16)	1586.56 (1121.19, 2126.92)	3.44 (2.43, 4.61)	–57.96 (–63.33, –53.21)	–38.73 (–46.55, –31.81)
Eastern Sub-Saharan Africa	15197.82 (10377.71, 20426.96)	13.7 (9.36, 18.42)	18546.18 (13042.18, 25246.99)	8.15 (5.73, 11.09)	22.03 (8.25, 37)	–40.54 (–47.25, –33.24)
High-income Asia Pacific	5042.62 (3779.54, 6350.14)	10.02 (7.51, 12.62)	2180.6 (1421.83, 2947.33)	7.08 (4.62, 9.57)	–56.76 (–65.59, –48.3)	–29.32 (–43.75, –15.5)
High-income North America	3937.74 (2830.49, 5155.43)	4.82 (3.46, 6.31)	3367.65 (2357.8, 4455.78)	3.76 (2.63, 4.98)	–14.48 (–23.04, –6.48)	–21.95 (–29.77, –14.65)
High-middle SDI	35467.68 (27356.63, 44190.28)	9.58 (7.39, 11.94)	14891.05 (10856.42, 19103.22)	4.91 (3.58, 6.3)	–58.02 (–63.13, –52.83)	–48.77 (–55.01, –42.44)
North Africa and Middle East	25886.22 (18883.23, 33252.78)	14.64 (10.68, 18.81)	18033.88 (13630.87, 23855.23)	7.63 (5.76, 10.09)	–30.33 (–38.82, –19.17)	–47.93 (–54.27, –39.58)
Oceania	138.37 (93.43, 197.17)	4.11 (2.78, 5.86)	298.96 (211.22, 431.23)	4.68 (3.31, 6.75)	116.06 (79.22, 147.23)	13.89 (–5.53, 30.32)
South Asia	74558.2 (53276.13, 102626.66)	13.75 (9.82, 18.92)	57043.12 (41548.63, 77685.2)	8.35 (6.08, 11.37)	–23.49 (–31.67, –15)	–39.28 (–45.78, –32.54)
Southeast Asia	13065.72 (9327.03, 17114.88)	5.94 (4.24, 7.78)	14629.69 (10515.7, 19032.53)	6.38 (4.59, 8.3)	11.97 (–0.04, 25.25)	7.39 (–4.13, 20.13)
Southern Latin America	1444.89 (1080.22, 1872.51)	7.46 (5.57, 9.66)	764.38 (519.38, 1013.91)	3.92 (2.66, 5.2)	–47.1 (–59.05, –36.79)	–47.45 (–59.32, –37.21)
Southern Sub-Saharan Africa	2960.59 (2068.88, 4010.98)	11.19 (7.82, 15.16)	2587.43 (1853.86, 3470.34)	8.28 (5.93, 11.1)	–12.6 (–22.88, –2.42)	–26.03 (–34.73, –17.41)
Tropical Latin America	3782.85 (2986.23, 4683.23)	5.46 (4.31, 6.76)	3344.16 (2530.02, 4235.15)	5.02 (3.8, 6.36)	–11.6 (–18.4, –4.02)	–8.05 (–15.12, –0.17)
Western Europe	7394.39 (6172.44, 8535.24)	7.52 (6.28, 8.68)	4963.49 (3699.78, 6228.77)	5.41 (4.03, 6.79)	–32.87 (–42.34, –24.68)	–28.02 (–38.17, –19.23)
Western Sub-Saharan Africa	15329.15 (10349.32, 20589.19)	14.26 (9.63, 19.15)	24511.63 (17346.37, 33092.84)	9.13 (6.46, 12.32)	59.9 (43.31, 79.42)	–36 (–42.64, –28.19)

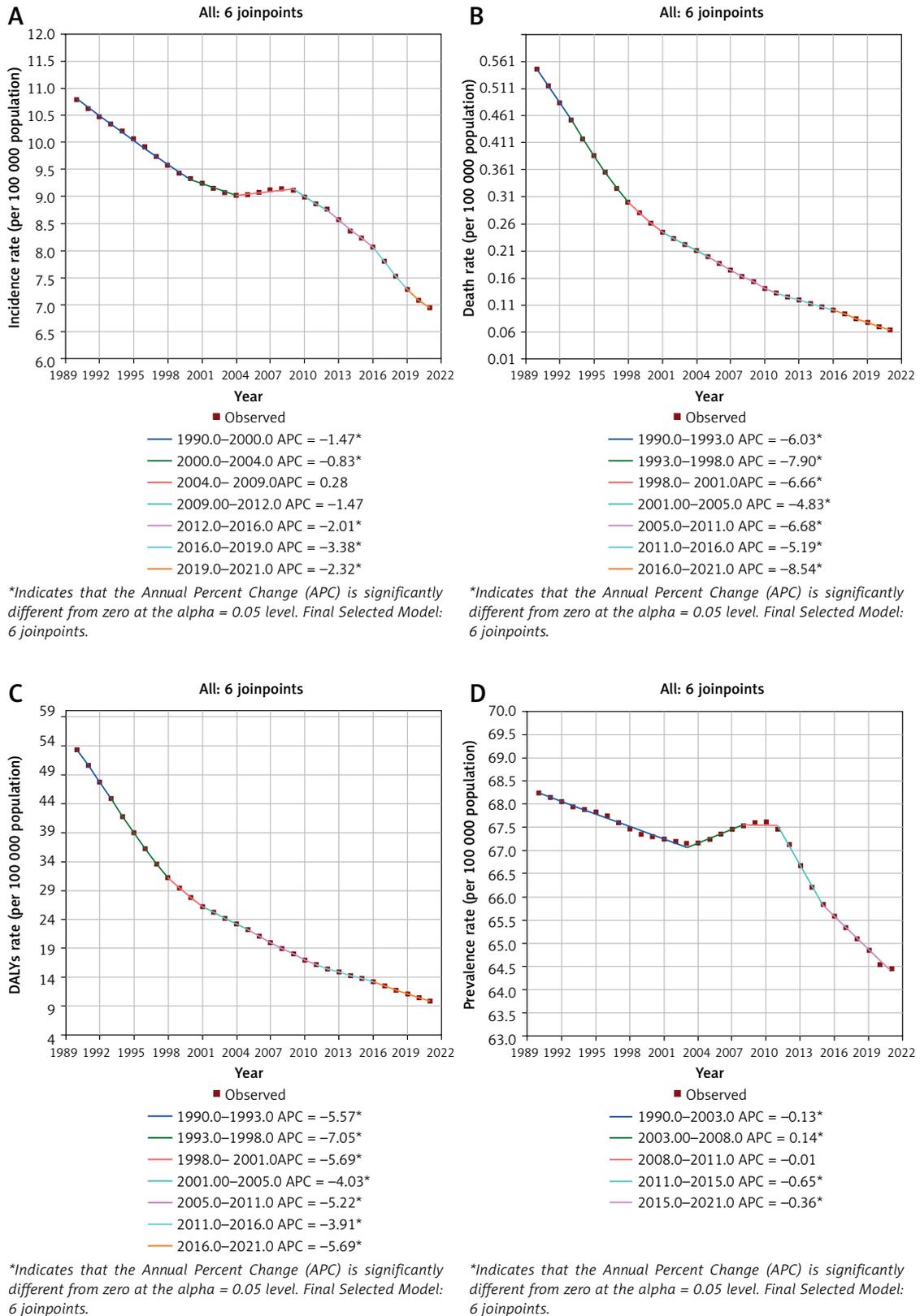*SDI – socio-demographic index, UI – uncertainty interval.*

Figure 1. Temporal trends in the incidence rate, mortality rate, and DALYs rate of OC in children and adolescents from 1990 to 2021. **A** – Temporal trends in the incidence rate. **B** – Temporal trends in the mortality rate. **C** – Temporal trends in the DALYs rate, **D** – Temporal trends in the prevalence rate

APC – annual percentage changes, AAPC – average annual percent changes.

(Supplementary Figures S3, S4). Mortality and DALY rates decreased across all regions, with the smallest reductions observed in Australia (–43.5% and –16.33%, respectively) (Table I, Supplementary Tables SI–SIII).

In 2021, Pakistan had the highest incident cases of OC (14,168.16, 95% UI: 10,768.41 to 18,969.92), while India had the highest number of deaths (164.59, 95% UI: 23.05 to 626.68) and DALYs (41,416.98, 95% UI: 23,442.45 to 83,240.59) (Supplementary Figure S5). Canada had the lowest incidence rate (1.79 per 100,000, 95% UI: 1.26 to 2.44), mortality rate (0 per 100,000, 95% UI: 0 to 0), and DALY rate (0.73 per 100,000, 95% UI: 0.46 to 1.12) (Supplementary Figure S6). From 1990, the greatest declines in incidence, mortality, DALY, and prevalence rates were observed in Libya (–67%), the United Kingdom (–100%), China (–96%), and Finland (–38.81%), respectively (Supplementary Tables SIV–SVII). In 2021, Myanmar had both the highest disease prevalence and the largest increase in prevalence from 1990 to 2021.

Projections indicate that from 2021 to 2050, the incidence rate and DALY rate of OC in children and adolescents will steadily decline, while the prevalence rate is expected to rise steadily. In contrast, the mortality rate is expected to exhibit periodic fluctuations before stabilizing around 2040 (Supplementary Figure S7).

Discussion. This study found that the burden of OC in children and adolescents was significantly negatively correlated with the SDI, with the most severe burden observed in low SDI regions. This finding not only reflects regional disparities in overall healthcare resources and health inequities but, more critically, is closely linked to the unique clinical management pathway required for OC as congenital anomalies. Effective management of this condition necessitates integrated care spanning prevention, diagnosis, surgical intervention, and rehabilitation. However, middle- and low-income countries exhibit substantial gaps across this continuum: low coverage of primary preventive measures such as preconception and perinatal nutritional interventions, limited public awareness, poor accessibility to specialized oral healthcare, and constraining household socioeconomic factors, all of which compromise the continuity of care [12, 13]. Therefore, reducing the burden of OC requires strengthening healthcare systems and specialized service capacity, enhancing public awareness through health education, improving treatment accessibility via economic and transportation support mechanisms, and integrating preventive measures such as peri-conception nutritional interventions into prioritized public health initiatives.

The analysis of OC burden among children and adolescents revealed distinct patterns by age and gender. Neonates (< 28 days) experienced the highest burden, likely due to the complexity of surgical interventions and perioperative care at this stage. Before 5 months of age, male infants exhibited higher rates of both mortality and DALYs compared to females. This may be associated with a greater susceptibility among male neonates to co-occurring severe congenital malformations or systemic diseases, which increases the difficulty and risks of early intervention [14, 15]. Notably, this trend reversed between 5 months and 4 years of age, with the relative burden shifting to female infants. Research indicates that the isolated cleft palate phenotype occurs more frequently in female infants. This subtype is less easily detectable in the early postnatal period, potentially leading to delays in diagnosis and treatment [16]. Furthermore, in some developing regions, socio-structural factors such as gender inequality may further impede timely and adequate healthcare access for female infants [16–18]. The interplay of these biological and social factors likely constitutes a significant reason for the increased disease burden among female infants in this age group.

In 2021, Central Asia recorded the highest incidence of OC, while Oceania reported the highest mortality. In Central Asia, the high incidence may be primarily attributed to environmental exposure risks during embryonic development. Factors such as nutritional imbalances due to low vegetable intake, large temperature variations, and intense solar radiation may interact with genetic susceptibility during embryonic development, affecting fetal facial development and thereby leading to a significant incidence [19, 20]. In contrast, the damage associated with OC is closely related to maternal conditions, timing of treatment, and postoperative rehabilitation. Consequently, the high mortality in Oceania reflects more systemic issues related to healthcare accessibility and societal health. For instance, Papua New Guinea, a typical country in the region, faces severe shortages in the healthcare workforce, coupled with social challenges such as high adolescent pregnancy rates and significant disparities in causes of death across different population groups [21, 22]. These factors may hinder timely diagnosis, appropriate surgical intervention, and systematic postoperative rehabilitation for children with OC, making it even more difficult to establish a multidisciplinary collaborative care model, thereby significantly increasing the risk of adverse outcomes and mortality. By contrast, Eastern Europe had the lowest incidence rate, while Central Europe, high-income Asia-Pacific, high-income North America, and Western Europe reported zero mortality rates, reflecting their advanced healthcare systems and targeted preventive measures [23].

Projections suggest that by 2050, the incidence and DALY rates of cleft lip and palate among children and adolescents will continue to decline. However, its prevalence is expected to rise due to improved survival, leading to an accumulation of cases into older ages. Consequently, future resources must increasingly focus on the long-term follow-up, sequential treatment, and rehabilitation management of these growing pediatric and adolescent populations.

The primary treatments for OC include lip reconstruction, palatal closure, bone grafting, and other surgeries aimed at improving long-term quality of life [24]. Multidisciplinary care, encompassing both surgical and non-surgical treatments, is crucial for addressing the physical and psychological well-being of affected children and adolescents [5]. As adolescents with OC become more aware of their appearance, they may face discrimination, impacting self-confidence and increasing the risk of psychological disorders. Future OC treatments should focus on both facial reconstruction and the prevention and management of psychological challenges.

This study has several limitations. First, the GBD data do not include epidemiological information on OC in some countries, which may result in an underestimation of the disease burden. Second, the GBD methodology does not provide detailed categorization of OC types, limiting the granularity of the findings. Finally, and importantly, as this study was initiated prior to the release of GBD 2023, the analysis is based on data only up to 2021. This temporal limitation may result in the omission of critical structural changes occurring between 2022 and 2023, such as a transient rebound in neonatal incidence potentially linked to maternal hyperthermia from COVID-19 infection, the deferral of elective surgery due to post-pandemic fiscal constraints and health workforce attrition, and the impact of socioeconomic downturns on maternal nutrition and mental health. These unaccounted factors could significantly bias long-term projections to 2050, underscoring the need for updated research with more recent data to refine and complement the current findings.

In conclusion, this study demonstrated an overall decline in the burden of OC among children and adolescents from 1990 to 2021, a trend projected to continue until 2050. However, significant health challenges persist in low-SDI regions and among female children aged 5 months to 4 years. To address these disparities, it is recommended to actively promote the implementation of early screening and referral systems for OC in resource-limited settings. Concurrently, strengthening health education for women of childbearing age and enhancing the availability of specialized physicians and rehabilitation therapists in high-burden regions are crucial. Future research should prioritize gender-sensitive studies to thoroughly investigate the sociocultural and healthcare accessibility factors contributing to the differential health outcomes among female infants and young children, particularly in the 5-month to 4-year age group. Such efforts are essential to advance prevention and control strategies toward greater precision and equity.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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