ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

Global, National, and Socioeconomic Disparities in Malignant Neoplasms of Bone and Articular Cartilage among Children, Adolescents, and Young Adults, 1990–2021: A Multilevel AAPC Analysis and Future Projection Based on the Global Burden of Disease Study 2021

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Abstract: *Malignant neoplasms of bone and articular cartilage (MNBAC) affect children, adolescents, and young adults (CAYA, 0–39 years), but global burden trends remain unclear due to insufficient age-stratified assessments. Using 1990–2021 Global Burden of Disease (GBD) data from 204 regions, we analyzed age-standardized prevalence (ASPR) and disability-adjusted life-year (ASDR) rates via Joinpoint regression, age-period-cohort (APC) models, ARIMA forecasting, and Socio-demographic Index (SDI) correlation analysis. Globally, ASPR increased (AAPC=0.49%) while ASDR remained stable (AAPC=0.09%), with widening gender disparities: male ASPR and ASDR rose (AAPC=0.77%, 0.31%), whereas female ASDR declined (AAPC=-0.27%). National trends were heterogeneous, with rising burden in Tokelau, Niue, and China, and declining burden in Estonia, Russia, and other Eastern European countries. ARIMA projections (2022–2027) show continued male burden increase and female decline. MNBAC burden in CAYA is rising globally with male predominance and cross-national variability, requiring targeted interventions for young males and tailored resource allocation.*

Keywords: *Malignant neoplasms of bone and articular cartilage; Global burden of disease; Annual average percent change; Children, adolescents, and young adults*

1. Introduction

Although malignant neoplasms of bone and articular cartilage (MNBAC) account for only 0.2% of all human malignancies, their substantial clinical burden in children, adolescents, and young adults (CAYA; 0–39 years) demands urgent attention [1]. MNBAC differs significantly between CAYA and the elderly: the latter mostly has metastatic bone lesions, while the former is primarily affected by primary osteosarcoma [2], a highly aggressive tumor peaking during rapid skeletal growth [3]. Even after peak bone mass is reached, sustained bone remodeling keeps CAYA susceptible to primary malignant bone tumors [4], and CAYA sarcoma patients often face long-term complications like bone mineral density loss and skeletal muscle loss, impairing mobility [5]. Thus, CAYA-centric MNBAC research is critical for developing targeted clinical guidelines and improving survivor outcomes.

Despite widespread use of the GBD database in MNBAC research, existing evidence is limited by fragmented, insufficiently refined age stratification, with overfocus on middle-aged and elderly populations leaving a gap in younger groups [6]. All-age analyses fail to capture CAYA subgroup features, while studies focusing solely on ≥65 years overlook age-specific MNBAC characteristics in CAYA, hindering elucidation of their epidemiological patterns.

To address this gap, we systematically evaluated MNBAC burden in CAYA across 204 countries/territories using 1990–2021 GBD 2021 data. We analyzed global, national, and regional trends, quantified annual changes via AAPC, mapped age/sex-stratified burden profiles, explored associations with SDI, and used ARIMA models to forecast future burden (2022–2027). This study aims to quantify CAYA MNBAC burden, clarify spatiotemporal patterns, and provide evidence for targeted healthcare

ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

allocation and long-term public health planning.

2. Material and methods

2.1 Study population and data collection

Data for this study were retrieved from the GBD 2021 dataset via GHDx (https://gbd2021.healthdata.org/gbd-results/), including MNBAC epidemiological data from 204 countries/territories, 21 global administrative regions, and 5 SDI-stratified regions (1990–2021). The study population was CAYA aged 0–39 years (subdivided into 8 age groups). Statistical analyses were conducted for the total population and by gender, evaluating key MNBAC epidemiological indicators (spatial distribution, prevalence rate, ASPR, crude DALYs, ASDR) with 95% UIs. We calculated each country's SDI (a GBD composite indicator integrating per capita income, average schooling ≥15 years, and female fertility rate ≤25 years [7]), ranging 0.005–1 (higher = better socioeconomic development) and categorized into 5 levels. SDI was used to analyze the association between socioeconomic development and MNBAC burden, serving as a benchmark for cross-regional/cross-temporal comparisons.

2.2 Autoregressive integrated moving average

The ARIMA model integrates the Autoregressive (AR) and Moving Average (MA) models, with its core assumption that time series data are time-dependent random variables—their autocorrelation can be characterized by the model, enabling the prediction of future values using historical data. The model is mathematically expressed as

$$Yt=\phi 1Yt-1+\phi 2Yt-2+\cdots+\phi pYt-p+et-\theta 1et-1-\cdots-\theta qet-q \tag{1}$$

where ($\phi 1Yt-1+\cdots+\phi pYt-p+et$) represents the AR component and ($et-\theta 1et-1-\cdots-\theta qet-q$) denotes the MA component. Specifically, $Yt-p$ is the observed value at time ($t-p$), p and q are the orders of the AR and MA components respectively, and et is the random error term at time t [8]. A key requirement for ARIMA model input data is that the time series must be stationary and follow a zero-mean random sequence.

2.3 Age-period-cohort model

The APC model disentangles the independent effects of age, period, and birth cohort on health outcomes. Age effect reflects risk differences driven by intrinsic factors (e.g., physiological development). Period effect represents concurrent influences of external factors (e.g., medical advances) across all age groups. Cohort effect captures long-term trends shaped by unique socio-historical events experienced by the same birth cohort. Due to perfect multicollinearity among age, period, and cohort, conventional regression cannot directly estimate parameters. A log-linear framework with the Intrinsic Estimator (IE) method was adopted,

$$(Yi)=\mu+\alpha * agei+\beta * periodi+\gamma * cohorti+\varepsilon i \tag{2}$$

where Yi represents the disease burden (e.g., prevalence, DALYs), α, β, and γ are the effect coefficients, μ is the intercept, and ε is the random residual [9].

2.4 Statistical Analysis

Descriptive analyses characterized global CAYA MNBAC burden; new cases, ASPR, and ASDR were compared by sex, age group, region, and country. Age-standardized rates (with 95% CIs) were calculated using the 2017 GBD world standard population and the population-weighted formula:

$$\text{age-standardized rate}=\frac{\sum_{i=1}^{A}a_i w_i}{\sum_{i=1}^{A}w_i} \tag{3}$$

where a_i = age-specific MNBAC rate for the i-th stratum, w_i = 2017 GBD world standard population weight, and A = upper age boundary [7]. AAPC (1990–2021), derived from Joinpoint Regression Model slope coefficients, quantified annual indicator changes [10]; trends were defined by AAPC and 95% CI (>0 = increasing, <0 = decreasing). For ARIMA modeling, time series data were stabilized by differencing; the optimal model was selected via auto.arima() using AIC, AICc, and BIC. Model performance (ME, RMSE, MAE, MPE, MAPE, MASE) was assessed, and residuals were confirmed as

ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

white noise via ACF1 test [11]. All analyses and visualizations used Joinpoint Regression Program 5.1.0 and R 4.4.0..

3. Result

3.1 Global trends

From 1990 to 2021, the disease burden of MNBAC in the CAYA population exhibited evolving trends with notable gender disparities (Table. 1). For both sexes, the absolute number of prevalent cases and DALYs increased: prevalent cases rose from 168,213 to 247,849, and DALYs increased from 972,405 to 1,256,569. In terms of ASRs, ASPR increased from 4.29 to 4.97 (AAPC = 0.49%), while ASDR experienced a minimal increase from 24.68 to 25.20 (AAPC = 0.09%). Gender disparities were pronounced. In males, both the absolute numbers and ASRs increased substantially: prevalent cases surged from 93,687 to 152,171, ASPR climbed from 4.73 to 5.97 (AAPC = 0.77%), and ASDR increased from 27.47 to 30.26 (AAPC = 0.31%). In females, prevalent cases increased moderately (from 74,526 to 95,678). However, the ASRs showed a distinct pattern: ASPR remained largely stable, with a minimal increase from 3.84 to 3.93 (AAPC = 0.07%), while ASDR declined from 21.84 to 19.94 (AAPC = -0.27%).

Table 1: Total number of cases, ASR and AAPC of MNBAC in CAYA at global level, 1990-2021.

		Prevalence	DALYs	
Both	1990 Number (95% UI)	168,213 (140,875, 203,122)	972,405 (813,895, 1,184,421)	Global
	2021 Number (95% UI)	247,849 (204,357, 295,413)	1,256,569 (1,048,292, 1,517,025)	
	1990 ASRs per 100000 (95% UI)	4.29 (3.62, 5.16)	24.68 (20.76, 29.97)	
	2021 ASRs per 100000 (95% UI)	4.97 (4.10, 5.92)	25.20 (21.02, 30.42)	
	AAPC (95% CI)	0.49 (0.38, 0.60)	0.09 (-0.01, 0.18)	
Male	1990 Number (95% UI)	93,687 (74,159, 113,384)	547,217 (424,780, 665,168)	
	2021 Number (95% UI)	152,171 (113,908, 190,998)	770,343 (580,871, 982,129)	
	1990 ASRs per 100000 (95% UI)	4.73 (3.76, 5.71)	27.47 (21.41, 33.35)	
	2021 ASRs per 100000 (95% UI)	5.97 (4.47, 7.50)	30.26 (22.81, 38.56)	
	AAPC (95% CI)	0.77 (0.69, 0.85)	0.31 (0.21, 0.42)	
Female	1990 Number (95% UI)	74,526 (56,999, 106,999)	425,188 (320,068, 614,779)	
	2021 Number (95% UI)	95,678 (77,754, 121,671)	486,227 (394,704, 636,209)	
	1990 ASRs per 100000 (95% UI)	3.84 (2.97, 5.46)	21.84 (16.56, 31.36)	
	2021 ASRs per 100000 (95% UI)	3.93 (3.19, 4.99)	19.94 (16.18, 26.09)	
	AAPC (95% CI)	0.07 (-0.09, 0.22)	-0.27 (-0.41, -0.13)	

Abbreviations: AAPC=average annual percentage change; CI=confidence interval; UI=uncertainty interval; ASRs=age-standardized rates; MNBAC=malignant neoplasms of bone and articular cartilage; CAYA=children, adolescents, and young adults; DALYs=disability adjusted life years.

3.2 National-Level Trends in AAPC of ASPRs and ASDR

Significant national/regional and gender disparities existed in the AAPC of ASDR for MNBAC (Figure. 1A-C). Tokelau exhibited prominent positive AAPCs for ASDR across all gender subgroups. Saint Vincent and the Grenadines also had positive AAPCs for ASDR in all genders, with the strongest upward trend observed in females. Niue recorded positive AAPCs for ASDR across genders, with female subgroups showing among the highest positive trends. Panama, Puerto Rico, and American Samoa ranked among the top 10 regions with positive AAPCs for ASDR. In China, the overall ASDR AAPC was positive, and the male ASDR AAPC exceeded the overall value. In contrast, Estonia had the most notable downward trends for ASDR across all genders. The Republic of Moldova showed negative AAPCs for ASDR in all subgroups, with the steepest decline in females. Lithuania also exhibited prominent negative AAPCs for ASDR across genders. Additionally, several European countries, including Latvia, Slovenia, the Russian Federation, and Poland, ranked among the top 10 regions with the most negative AAPCs for ASDR across all gender stratifications. The results of ASPR were roughly consistent with those of ASDR.

ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

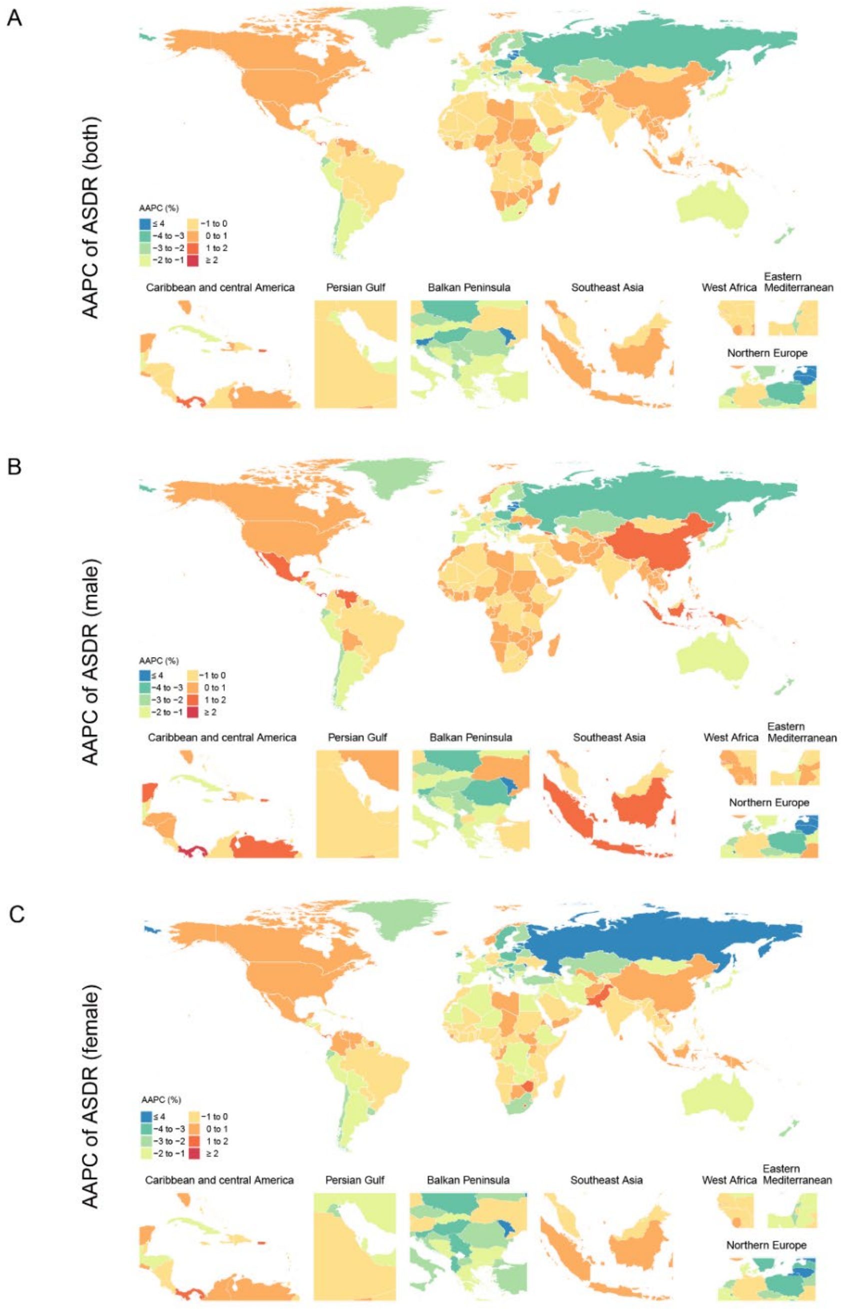

Figure 1: Global maps showing the average AAPCs in ASPR and ASDR for MNBAC among the CAYA population, 1990–2021. (A) AAPC of ASDR (both sexes, %); (B) AAPC of ASDR (male, %); (C) AAPC of ASDR (female, %)

3.3 Association with the SDI

Across SDI quintiles, prominent gender disparities were observed in both ASPR and ASDR, with males consistently having higher rates than females. Reverse or heterogeneous gender-specific trends shaped overall estimates (Figure. 2A, B). For males, ASPR generally increased, though high-middle SDI peaked and then slightly declined; male ASDR trends varied by SDI group, with some rising, some remaining stable, and others declining or rebounding. For females, ASPR fluctuated divergently, with some trends opposing males; female ASDR mostly trended downward, with only low-middle and middle SDI showing fluctuations, differing from male trends. Overall, ASPR converged by 2020 due to male increases and female fluctuations, while ASDR reflected gender disparities and varied by SDI group.

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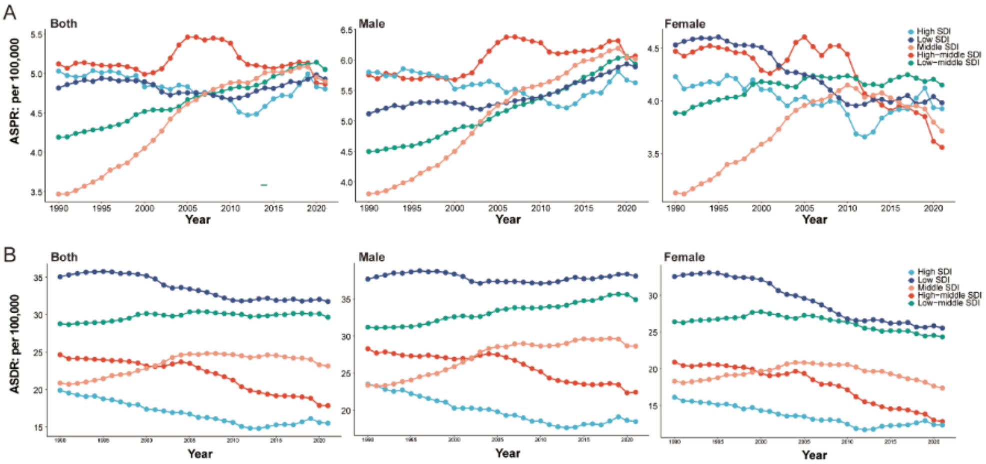

Figure 2. Global burden of MNBAC in CAYA: Trends and Socioeconomic Associations. (A–B). Trends in ASPR and ASDR by sex, across the SDI quintiles, 1990–2021. The five SDI groups are: high, high-middle, middle, low-middle, and low.

3.4 Age Trends

Based on the APC demographic model, analysis of the CAYA population with MNBAC (1992–2021) revealed consistent age distribution and temporal trends in disease burden. Across genders, the age-specific crude DALY rate showed an inverted U-shape, peaking at 15–20 years, low at birth, and moderating after 30 years. The 15–30 years high-incidence group saw a temporal decline in burden peaks, while post-30 burden converged across periods (Figure. 3A). By birth cohort, the age-specific crude DALY rate increased (1960–1980), peaked (1980–2000), then declined or fluctuated downward. ASDR was highest in 10–14 years and lowest in <5 years; most age groups declined, except for gender differences in <5 and 15–19 years. Crude burden decreased with cohort progression in females and the overall population, while males showed stable <5 years burden and increased 15–19 years burden in later periods (Figure. 3B). Time series analysis (1996–2021) confirmed the 15–19 years group had the highest DALY rate and the <5 years group the lowest (with the largest decline). Most groups declined stably, but males had upward trends in 15–19 (from 2006), 20–24 (from 2011), and 25–29 (from 2016) years (Figure. 3C). Prevalence and DALY results were consistent.

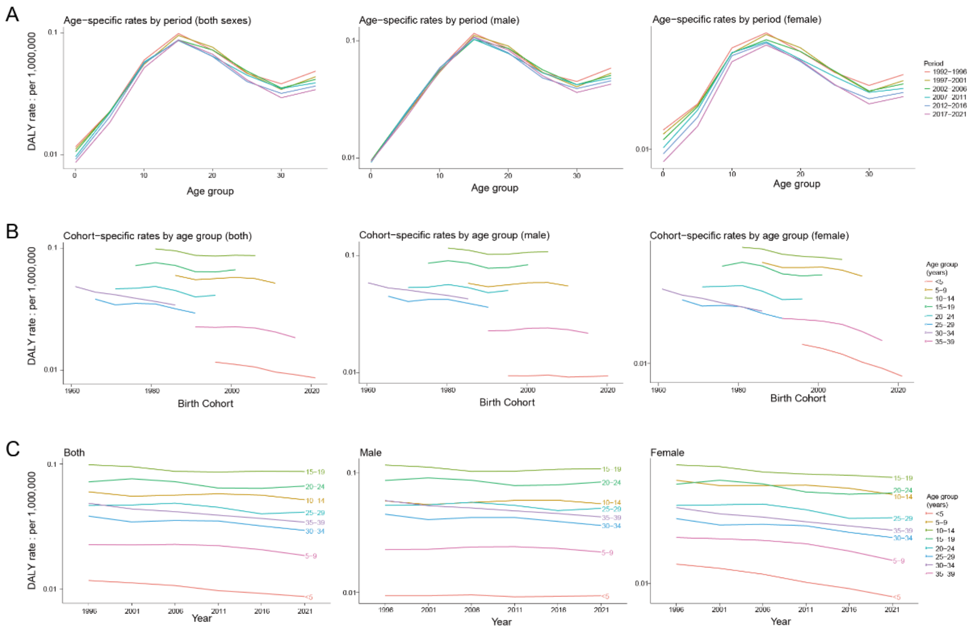

Figure 3. Trends of age-specific, period-based and cohort-based variation of MNBAC crude DALY rate in global in CAYA. (A) age-specific MNBAC crude DALY rate (per 100,000); (B) period-based MNBAC crude DALY rate (per 100,000); (C) cohort-based MNBAC crude DALY rate (per 100,000);

ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

3.5 Global Future Projections

ARIMA modeling forecasts distinct trends in the global burden of MNBAC among CAYA from 2022 to 2027 (Table 2). For the total population, prevalent cases are projected to increase from 249,724 in 2022 to 259,798 in 2027, while ASPR is expected to decline slightly from 4.93 to 4.86. The ASDR is predicted to decrease from 25.00 to 24.22, with a corresponding AAPC of -0.80%. Gender-stratified projections reveal a persistent disparity. In males, both prevalent cases and DALYs are projected to rise substantially—from 153,623 to 161,062 and from 772,984 to 794,943, respectively. The male ASPR is forecasted to increase from 5.96 to 6.04 (AAPC = 0.33%), and the ASDR from 30.31 to 30.65 (AAPC = 0.28%). Conversely, the female burden is predicted to remain stable or decline. Prevalent cases are projected to decrease from 94,855 to 91,561, and DALYs from 484,806 to 479,121. The female ASPR is expected to decline from 3.92 to 3.86 (AAPC = -0.36%), and the ASDR from 19.81 to 19.21 (AAPC = -0.75%).

Table 2: Total number of cases, ASR and AAPC of MNBAC in CAYA at global level, 2022-2027 (forecast).

		Prevalence	DALYs	
Both	2022 Number (95% UI)	249,724 (248,193, 261,330)	1,254,791 (1,205,284, 1,297,184)	Global
	2027 Number (95% UI)	259,798 (247,239, 257,247)	1,247,676 (1,225,552, 1,280,473)	
	2022 ASRs per 100000 (95% UI)	4.93 (4.72, 5.05)	25.00 (23.61, 25.61)	
	2027 ASRs per 100000 (95% UI)	4.86 (4.79, 5.01)	24.22 (24.21, 25.40)	
	AAPC (95% CI)	-0.36 (-0.50, -0.23)	-0.80 (-0.80, -0.79)	
Male	2022 Number (95% UI)	153,623 (153,310, 161,376)	772,984 (761,756, 803,691)	
	2027 Number (95% UI)	161,062 (152,392, 158,575)	794,943 (762,696, 792,014)	
	2022 ASRs per 100000 (95% UI)	5.96 (5.79, 6.17)	30.31 (29.75, 31.21)	
	2027 ASRs per 100000 (95% UI)	6.04 (5.83, 6.09)	30.65 (29.83, 30.96)	
	AAPC (95% CI)	0.33 (0.20, 0.47)	0.28 (0.28, 0.28)	
Female	2022 Number (95% UI)	94,855 (87,951, 98,465)	484,806 (457,650, 506,276)	
	2027 Number (95% UI)	91,561 (90,890, 97,173)	479,121 (468,855, 497,914)	
	2022 ASRs per 100000 (95% UI)	3.92 (3.72, 4.06)	19.81 (18.75, 20.27)	
	2027 ASRs per 100000 (95% UI)	3.86 (3.78, 4.02)	19.21 (19.12, 20.19)	
	AAPC (95% CI)	-0.36 (-0.37, -0.36)	-0.75 (-0.76, -0.75)	

Abbreviations: AAPC=average annual percentage change; CI=confidence interval; UI=uncertainty interval; ASRs=age-standardized rates; MNBAC=malignant neoplasms of bone and articular cartilage; CAYA=children, adolescents, and young adults; DALYs=disability adjusted life years.

4. Discussion

This study, based on GBD 2021 data, provides the first systematic assessment of MNBAC burden This study, based on GBD 2021 data, provides the first systematic assessment of MNBAC burden among CAYA (0–39 years) across 204 countries/territories from 1990 to 2021. Our analysis reveals three key patterns: rising prevalence with stable disability rates, a widening male-predominant gender disparity, and extreme national heterogeneity.

From 1990 to 2021, global ASPR increased (AAPC = 0.49%), while ASDR remained stable (AAPC = 0.09%). This "rising prevalence with stable DALY" pattern likely reflects improved diagnostic technologies [11] and better treatment outcomes [12]. The decoupling of prevalence from disability-adjusted life years suggests that although more CAYA individuals are being diagnosed with MNBAC, their overall survival and quality of life have not deteriorated—possibly due to earlier detection and more effective multimodal therapies, including limb-sparing surgeries and targeted agents. The post-2019 decline in most indicators coincided with the COVID-19 pandemic, which disrupted screening, diagnostic workups, and routine healthcare access [13]. This interruption may have temporarily reduced case detection, but the long-term impact on delayed diagnoses and stage migration remains to be quantified.

The most striking finding is the growing gender disparity. Male ASPR and ASDR increased significantly (AAPC = 0.77% and 0.31%, respectively), while female ASDR declined (AAPC = –0.27%). This divergence is clinically meaningful and points to a combination of biological susceptibility [14], sex hormone effects [15], behavioral exposures [16], and potential diagnostic biases [17]. For instance, androgenic signaling may promote certain bone tumor phenotypes, whereas estrogen could have a protective modulatory effect on tumor microenvironments. Additionally, males in the CAYA age group are more likely to engage in high-impact physical activities or occupational exposures that could accelerate symptomatic presentation or tumor progression. The widening gap also raises concern about

ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

gender-specific healthcare-seeking behaviors—males may present later or receive different diagnostic workups. Future studies should integrate sex as a biological variable in basic and translational research on bone sarcomas.

National trends varied markedly. Small island states (e.g., Tokelau, Niue) and China showed rising burden, attributed to limited healthcare infrastructure, under-resourced cancer registries, or improving case registration [18]. In China, the rising ASPR but stable-to-rising ASDR highlights regional disparities in resource allocation and referral delays [19]. While large urban centers may have access to advanced diagnostics and multidisciplinary care, rural areas still face shortages of pathologists, imaging equipment, and pediatric oncology expertise. Eastern European countries (e.g., Estonia, Russia) exhibited declining trends, reflecting healthcare system reforms [20] and the gradual adoption of standardized treatment protocols [21]. These contrasting patterns underscore the importance of context-specific health system strengthening—what works in a high-income European setting may not be directly transferable to a small island developing state or a rapidly industrializing nation.

Burden changes showed a non-linear association with SDI. After SDI exceeds 0.6, ASPR growth declines [22]. This inverted U-shaped curve may reflect the epidemiological transition: in low-SDI regions, underdiagnosis masks true burden; in middle-SDI regions, expanding healthcare access drives detection increases; in high-SDI regions, early detection and effective treatment lead to controlled prevalence. However, male ASPR correlated weakly positively with SDI, while female ASDR showed strong negative correlation, indicating gender-specific survival benefits [23]. In high-SDI settings, females may experience greater absolute gains from advanced surgical techniques, rehabilitation, and supportive care—possibly due to better treatment adherence or lower comorbidity burdens.

APC modeling showed peak burden at ages 15–19 years [24], with slightly higher female burden at 0–10 years [25]. The adolescent peak corresponds to rapid skeletal growth and hormonal changes, which may influence tumor biology. The early childhood female predominance could reflect sex-linked genetic or epigenetic factors operating in very young age groups. Period effects confirmed widening gender gaps over calendar time. Younger male cohorts (post-1990) show increasing risk—a serious public health signal suggesting that contemporary environmental, lifestyle, or reproductive factors may disproportionately affect young males. This cohort pattern warrants prospective surveillance and etiological research focusing on gene-environment interactions.

ARIMA projections (2022–2027) forecast continued male burden increase (ASPR AAPC = 0.33%, ASDR AAPC = 0.28%) and female decline [26]. This rising trend challenges healthcare system capacity [27], particularly in low- and middle-income countries where pediatric oncology services are already stretched. Without proactive investment in surgical oncology, radiotherapy, rehabilitation, and psychosocial support, the widening gap will translate into preventable disability and premature death among young males. Projections also call for gender-stratified resource planning—for example, increasing the number of male-focused adolescent and young adult (AYA) oncology units.

Limitations include variable data quality across regions, inability to separate primary vs. secondary neoplasms, lack of individual-level data (e.g., genetic markers, treatment regimens, socioeconomic status), and ARIMA's short-term nature [28]. Additionally, GBD estimates may be influenced by modeling assumptions in regions with sparse primary data.

5. Conclusion

In summary, this study maps the global burden of MNBAC in CAYA from 1990 to 2021, revealing a rising male-predominant burden, complex SDI associations, and an adolescent peak. Wide national disparities and projected continued increases—especially among males—call for urgent public health attention. Evidence-based interventions and targeted resource allocation are needed to curb this inequitable burden and improve long-term outcomes for young patients.

Acknowledgments

The authors would like to thank the Global Burden of Disease (GBD) 2021 database for providing the data support essential for this study. This work was conducted without external funding. The authors also thank the anonymous reviewers for their constructive comments, which greatly improved the quality of this manuscript.

ISSN 2618-1584 Vol. 8, Issue 3: 32-40, DOI: 10.25236/FMSR.2026.080305

Conflict of Interest Statement

The authors declare no conflict of interest, and no funding was received for this study.

Data availability statement

The data supporting the findings of this study are publicly available from the Global Burden of Disease (GBD) 2021 database at https://gbd2021.healthdata.org/gbd-results/. No new or additional datasets were generated in this research.

Author contributions

X.-F.K. conceptualization, data curation, formal analysis and validation, methodology, software, visualization, writing – original draft, writing – review & editing. S.-Q.P. conceptualization, resources, supervision, writing – review & editing.

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