

Supplementary materials

Methods

Study design and data sources

This study used a population-based approach leveraging data from the GBD Study 2021. The GBD, coordinated by the Institute for Health Metrics and Evaluation (IHME), systematically compiles data from diverse sources, including vital registration systems, cancer registries, hospital records, national health surveys, and scientific literature. The analysis included children 0–14 years of age across 204 countries and territories from 1990 to 2021. Data were stratified by gender, age, and SDI quintiles to facilitate nuanced comparisons across populations. To address potential biases arising from data sparsity in low-resource settings, the GBD estimation process integrates multiple layers of model-based adjustments (see “Modeling framework”), including statistical imputation for missing or sparse data, correction for diagnostic heterogeneity, and extensive uncertainty quantification.

Population and case definition

The target population included children 0–14 years of age diagnosed with neuroblastoma, defined according to International Classification of Diseases (ICD) codes (ICD-10: C74.1, C74.9). Age groups were categorized as infants (< 5 years), children (5–9 years), and pre-adolescents (10–14 years). Data inconsistencies were addressed with GBD’s standardized modeling techniques to ensure comparability across regions and time periods.

Outcomes measured

Primary outcomes included 1) ASIR: the number of new cases per 100,000 population, standardized for age; 2) age-standardized mortality rate (ASMR): the number of deaths per 100,000 population, standardized for age; and 3) DALYs: a composite measure of disease burden, calculated as the sum of YLLs due to premature mortality and YLDs. Results are reported with 95% UIs to account for variability in data quality and modeling assumptions.

Statistical analysis

Trends were analyzed with the estimated annual percentage change (EAPC) for ASIR, ASMR, and DALYs from 1990 to 2021. EAPC was calculated with a log-linear regression model: $EAPC = [\exp(\beta) - 1] \times 100\%$, where β represents the slope of the natural logarithm of rates regressed on calendar year. A positive EAPC indicates an increasing trend, whereas a negative EAPC denotes a decline. Statistical significance was assessed with 95% CIs, and trends were considered non-significant if the CI included zero.

Regional and gender disparities

Disparities were analyzed through data stratification by SDI quintile and gender. The SDI, a composite measure of income per capita, average education level, and fertility rate, was used to classify countries into low, low-middle, middle, high-middle, and high SDI groups. Gender-specific trends were assessed to identify potential biological or environmental contributors to the observed differences in disease burden.

Subgroup and interaction analyses

Subgroup analyses were performed to evaluate trends within geographic regions and SDI quintiles. Interaction terms were incorporated into regression models to test for significant differences between subgroups. Age-specific rates were calculated for infants (< 5 years), children (5–9 years), and pre-adolescents (10–14 years), to identify age groups with the highest burden.

Modeling framework

The GBD used the Cause of Death Ensemble Model (CODEm) to estimate mortality and an independent modeling process to estimate incidence and prevalence. CODEm integrates multiple predictive covariates, including healthcare access metrics, cancer treatment availability, and population demographics, to improve estimate accuracy. Incidence, prevalence, and YLDs were modeled with DisMod-MR 2.1, a Bayesian meta-regression tool.

Future projections

Projections of neuroblastoma burden to 2045 were estimated with the Norpred model. This model incorporates demographic changes, historical trends, and regional healthcare

improvements to predict incidence, mortality, and DALY rates. Scenario analyses were conducted to estimate the potential effects of interventions, such as improved healthcare funding or the implementation of early detection programs.

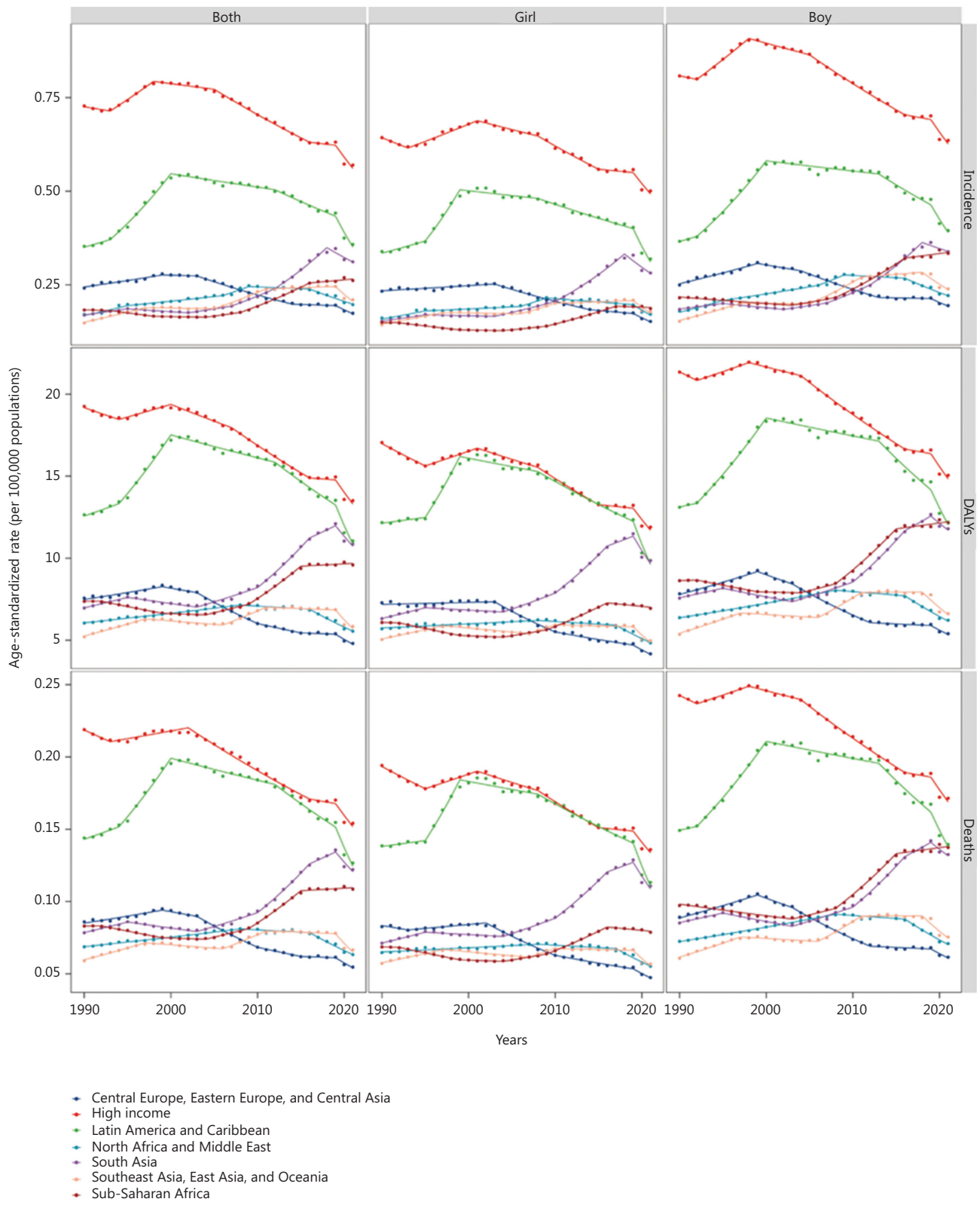


Figure S1 Trends in the annual percentage change (APC) and average annual percentage change (AAPC) in incidence rates, disability-adjusted life years (DALYs), and mortality rates for childhood neuroblastoma by GBD region and gender, from 1990 to 2021.

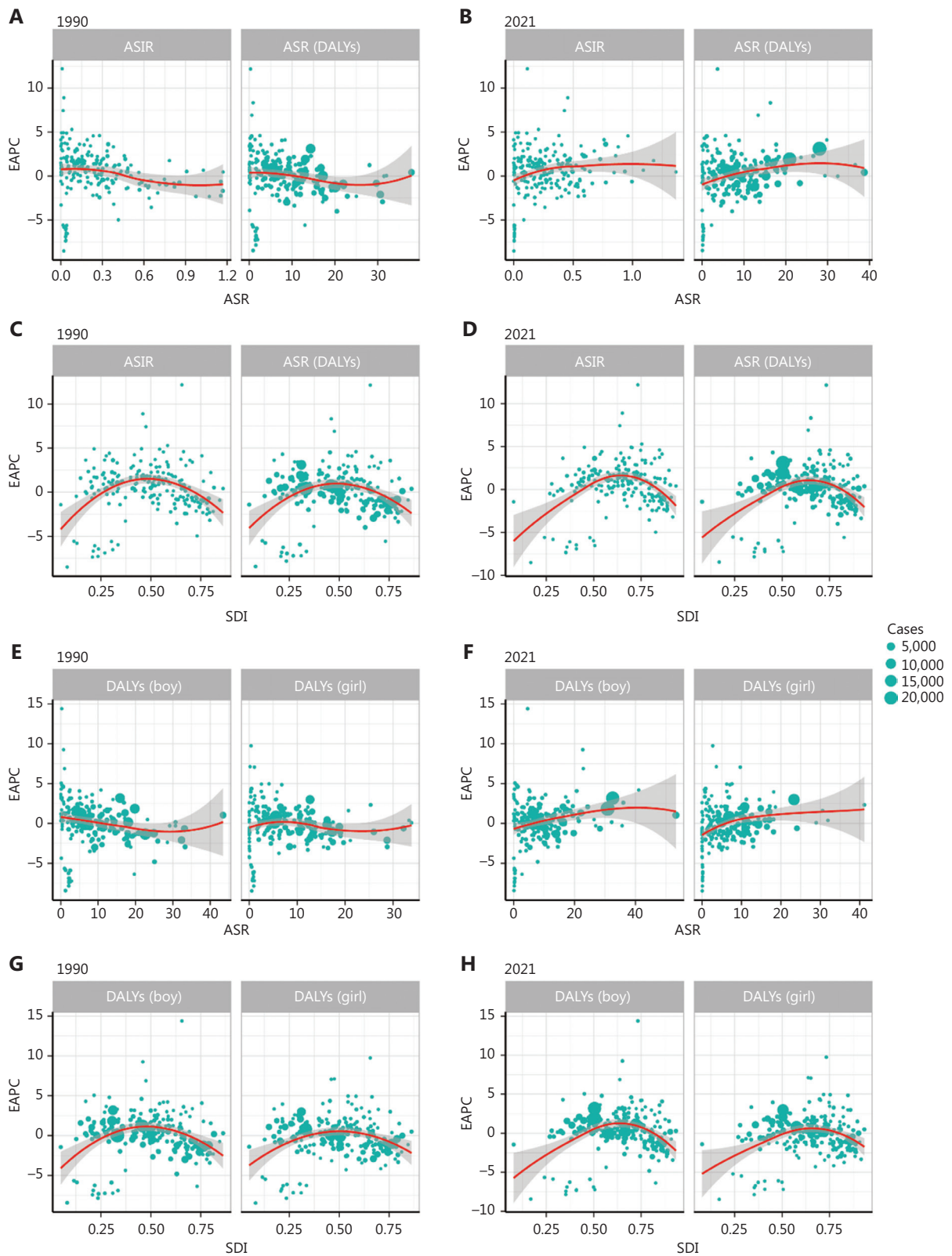


Figure S2 Correlation analysis between estimated annual percentage change (EAPC) and the socio-demographic index (SDI) or age-standardized rate (ASR) for childhood neuroblastoma and other peripheral nervous system tumors in 1990 and 2021. Each circle represents a country, and circle size is proportional to the disability-adjusted life years (DALYs) for the condition.

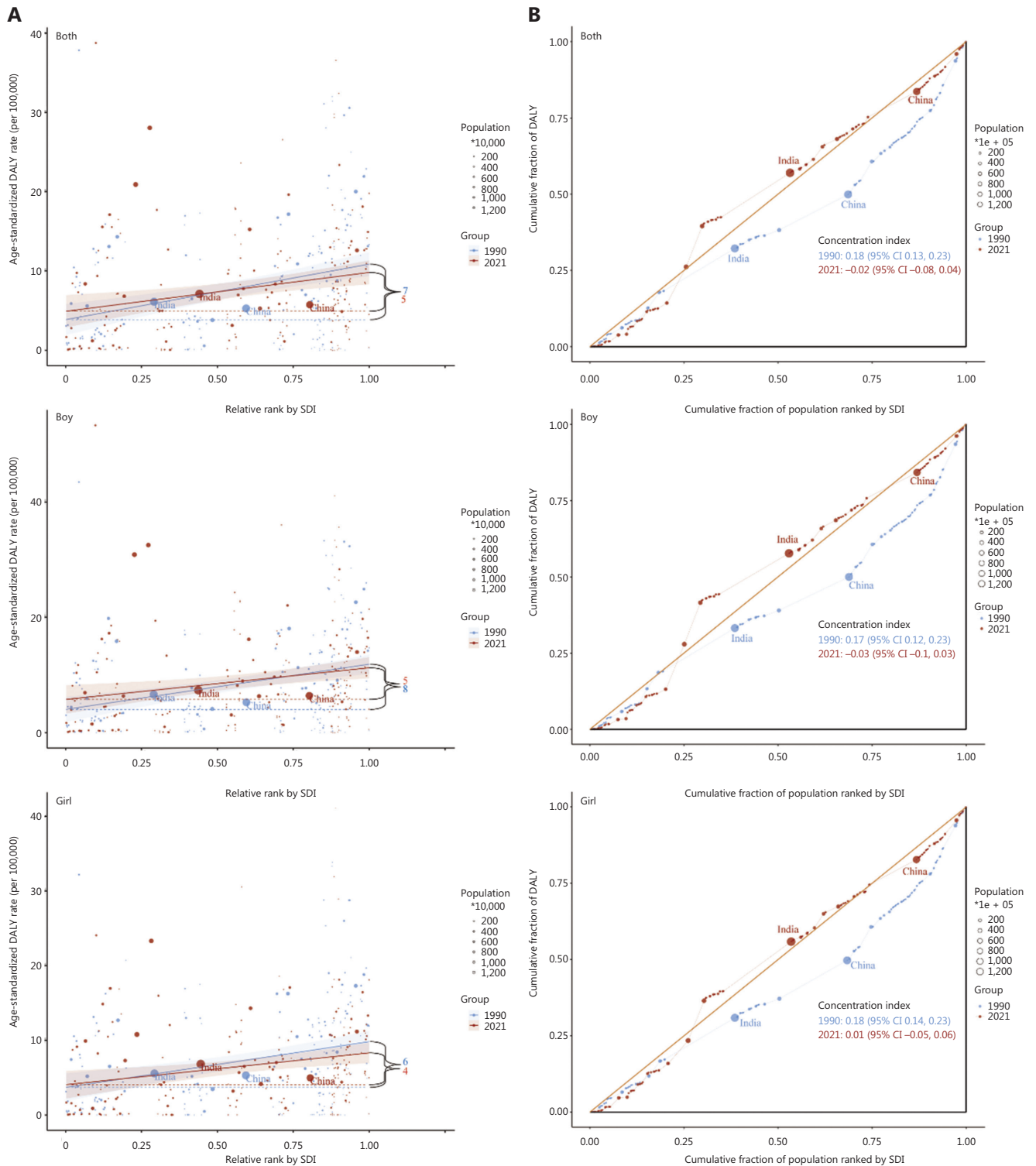


Figure S3 Health inequality analysis for childhood neuroblastoma and other peripheral nervous system tumors. Regression curves and concentration curves display trends in disability-adjusted life years (DALYs) by gender from 1990 to 2021, indicating the distribution of disease burden among socioeconomic groups.

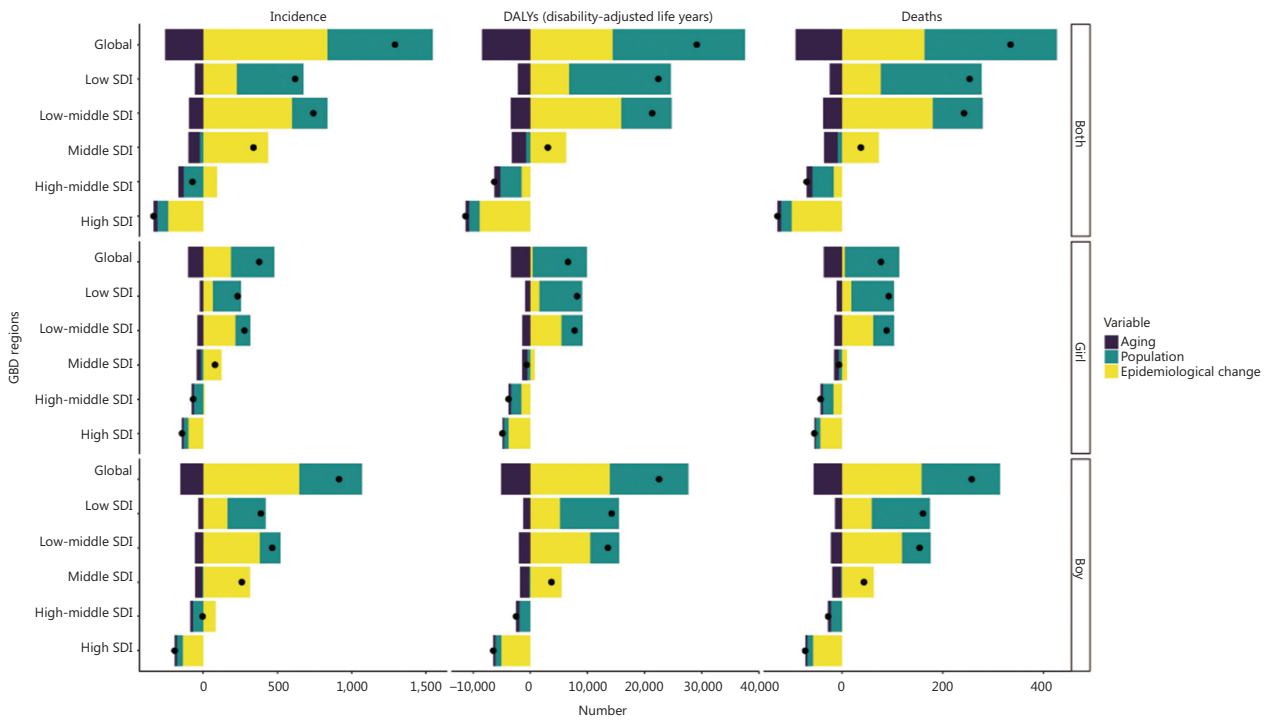


Figure S4 Relative contributions of age structure, population growth, and epidemiological changes to the global burden of neuroblastoma and other peripheral nervous system tumors. This figure highlights variations by region and gender, highlighting the factors driving disease burden changes.

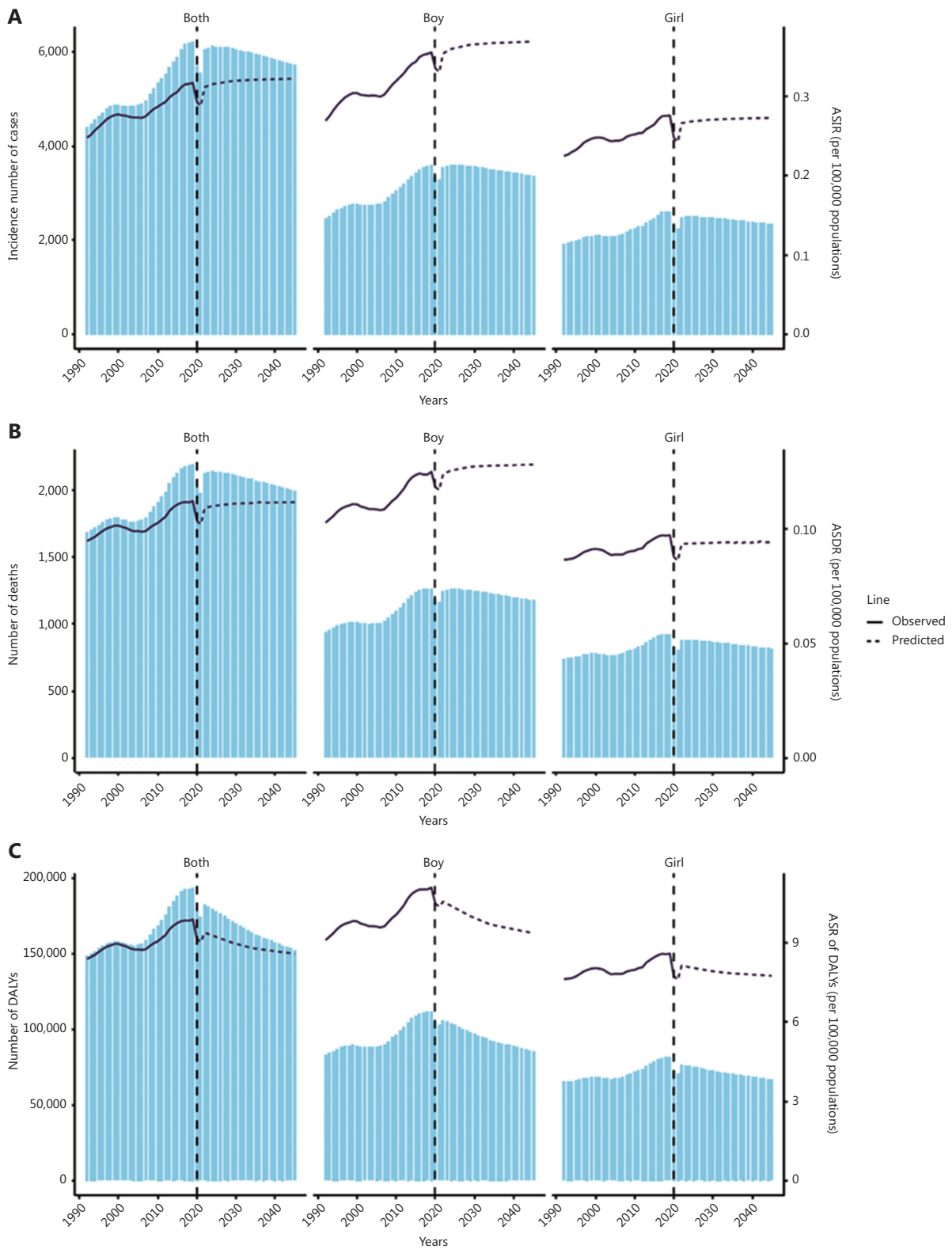


Figure S5 Projected global burden of childhood neuroblastoma and other peripheral nervous system tumors. (A) Predicted number of new cases and age-standardized incidence rate (ASIR). (B) Predicted number of deaths and age-standardized death rate (ASDR). (C) Predicted number and age-standardized rate (ASR) of disability-adjusted life years (DALYs). The age-standardized rates provide a standardized view of future trends in incidence, mortality, and disease burden.