The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017

GBD 2017 Childhood Cancer Collaborators*

Summary

Background Accurate childhood cancer burden data are crucial for resource planning and health policy prioritisation. Model-based estimates are necessary because cancer surveillance data are scarce or non-existent in many countries. Although global incidence and mortality estimates are available, there are no previous analyses of the global burden of childhood cancer represented in disability-adjusted life-years (DALYs).

Methods Using the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 methodology, childhood (ages 0–19 years) cancer mortality was estimated by use of vital registration system data, verbal autopsy data, and population-based cancer registry incidence data, which were transformed to mortality estimates through modelled mortality-to-incidence ratios (MIRs). Childhood cancer incidence was estimated using the mortality estimates and corresponding MIRs. Prevalence estimates were calculated using MIR to model survival and multiplied by disability weights to obtain years lived with disability (YLDs). Years of life lost (YLLs) were calculated by multiplying age-specific cancer deaths by the difference between the age of death and a reference life expectancy. DALYs were calculated as the sum of YLLs and YLDs. Final point estimates are reported with 95% uncertainty intervals.

Findings Globally, in 2017, there were 11·5 million (95% uncertainty interval 10·6–12·3) DALYs due to childhood cancer, 97·3% (97·3–97·3) of which were attributable to YLLs and 2·7% (2·7–2·7) of which were attributable to YLDs. Childhood cancer was the sixth leading cause of total cancer burden globally and the ninth leading cause of childhood disease burden globally. 82·2% (82·1–82·2) of global childhood cancer DALYs occurred in low, low-middle, or middle Socio-demographic Index locations, whereas 50·3% (50·3–50·3) of adult cancer DALYs occurred in these same locations. Cancers that are uncategorised in the current GBD framework comprised 26·5% (26·5–26·5) of global childhood cancer DALYs.

Interpretation The GBD 2017 results call attention to the substantial burden of childhood cancer globally, which disproportionately affects populations in resource-limited settings. The use of DALY-based estimates is crucial in demonstrating that childhood cancer burden represents an important global cancer and child health concern.

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Introduction Children with cancer who live in high-income countries (HICs) have good outcomes, with approximately 80% surviving 5 years after their diagnosis.1 However, more than 90% of children at risk of developing childhood cancer each year live in low-income and middle-income countries (LMICs).1,1 Considered by many as one of the major advances of modern science, the improvement in outcomes in children with cancer seen in HICs over the past several decades has not translated to most LMICs, where existing data suggest that far fewer children survive.1 An accurate appraisal of childhood cancer incidence and outcomes is non-existent in many LMICs, due in part to a lack of the cancer registry and vital registration systems necessary to record and report these data.1,4 Childhood cancers are often fatal without appropriate and timely diagnosis and treatment and, by contrast with adult cancers, there are no evidence-based population screening programmes or lifestyle risk-reduction strategies that are effective in improving outcomes.5,6 As a result, increasing survival will require considerable planning by policy makers to ensure adequate resource allocation and health system function. Information on the burden of childhood cancer is crucial to informing these efforts and thus, model-based estimates are necessary to determine cancer burden in settings without data until cancer data coverage improves.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 provides estimates for 359 diseases and injuries, including cancers, and is therefore uniquely positioned to fill the gap in health planning data as countries work to expand their cancer surveillance systems.8 Additionally, standard GBD outcomes include estimates of disability-adjusted life-years (DALYs), a useful composite metric that accounts for both the mortality and morbidity of a disease.9 DALYs allow for cross-disease and cross-geography comparisons that contextualise disease burden. So far, however, no...
The GBD cancer estimation process focuses first on the estimation of cancer burden against other diseases for priority setting. We identified that childhood cancer results in a substantial burden due to childhood cancers in 2017 is substantial, primarily because of fatal burden. This burden is disproportionately high in low, low-middle, and middle Socio-demographic Index (SDI) settings, which together contribute 82.2% of global childhood cancer DALYs. Childhood cancers are a major cause of global disease burden, even when compared with other diseases of childhood or with adult cancers.

### Implications of all the available evidence

By presenting the global burden of childhood cancer in DALYs, we identified that childhood cancer results in a substantial disease burden despite a relatively low absolute number of incident cases and deaths. This burden is particularly notable in resource-limited settings, where the ability to directly compare the burden of various diseases through DALYs is particularly relevant for policy makers, who must consider a myriad of health priorities in addition to childhood cancers and can use these data to make evidence-based resource allocation and cancer-control planning decisions. As countries implement, monitor, and evaluate capacity-building programmes as part of the WHO Global Initiative for Childhood Cancer, refining the methodology of childhood cancer burden estimation in future GBD iterations will be crucial to identify high-impact interventions and provide the most useful information for cancer control efforts by governments, stakeholders, and the global health community.

### Methods

#### Overview

The GBD study was created to establish comprehensive and comparable global health metrics. Estimates of incidence, prevalence, mortality, years of life lost (YLLs), years lived with disability (YLDs), and DALYs are generated for each disease and injury, with each metric reported by year, location, age group, and sex. Each successive GBD iteration supersedes the results of previous GBD rounds for the entire newly estimated time series. GBD 2017 is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting (appendix p 4). Data sources used in GBD 2017 are available online.

#### Estimation of cancer burden

The GBD cancer estimation process focuses first on the estimation of cancer mortality (see appendix pp 7–8 for flow diagrams of the GBD 2017 cancer estimation process). Cancer mortality data sources include vital registration systems, cancer registration systems, and verbal autopsy data (a map of the site-years of childhood cancer data available in GBD 2017 is available on appendix p 10). Cancer registries are active in some locations that do not have reliable cancer mortality data, and many cancer registries only report incidence. Thus, mortality-to-incidence ratios (MIRs) were used to transform cancer registry incidence data to mortality estimates, maximising data availability in locations with scarce mortality information. MIRs for all age, sex, location, and year combinations were modelled using a spatiotemporal Gaussian process regression with incidence data from cancer registries and mortality data from cancer registries or high-quality vital registration systems. In brief, spatiotemporal Gaussian process regression has three steps: logit random effects models, spatiotemporal smoothing, and Gaussian process regression (appendix p 13; see also the supplementary materials for reference 15). The mortality estimates derived with this approach were pooled with the directly obtained mortality data from vital registration systems and verbal autopsies, and used in cancer-specific Cause of Death Ensemble models (CODEm), which are necessary because mortality data do not exist for every age, sex, location, and year combination estimated by GBD 2017. The CODEm approach uses all available
mortality data even if data quality varies, tests individual as well as ensemble models, and is capable of selecting the optimal model or set of models on the basis of the out-of-sample predictive validity. Each COODEm used covariates and age group restrictions specific to each cancer type (appendix pp 15–34). Cause-specific mortality estimates were subsequently scaled to independently modelled all-cause mortality.17,18

The mortality estimates for each cancer type were divided by the corresponding MIR to obtain incidence estimates. 10-year prevalence was modelled using estimated survival based on the MIR. Total prevalence was divided into sequelae (phases of cancer treatment) to estimate the cancer type-specific YLDs (appendix p 34). Two sequelae were estimated for cohorts that survive 10 years after diagnosis: (1) diagnosis or treatment and (2) remission, after which disability risk is returned to that of the general population. Four sequelae were estimated for cohorts that do not survive 10 years after diagnosis: (1) diagnosis or treatment, (2) remission, (3) metastatic or disseminated, and (4) terminal phases. To generate YLD estimates, each sequela prevalence was multiplied by a sequela-specific disability weight, representing the magnitude of health loss associated with a specific health outcome, measured on a scale from 0 (full health) to 1 (equivalent to death; appendix p 39).19 YLLs were estimated by multiplying the difference between a standard life expectancy at the age of death and the estimated number of deaths at that age.19 The YLD and YLL estimates were summed to provide

| SDI status                      | Absolute incidence (95% UI) | Age-standardised incidence rate (95% UI) | Absolute mortality (95% UI) | Age-standardised mortality rate (95% UI) | Absolute YLLs (95% UI) | Absolute YLDs (95% UI) | Absolute DALYs (95% UI) |
|--------------------------------|-----------------------------|----------------------------------------|----------------------------|----------------------------------------|------------------------|------------------------|------------------------|
| Low SDI countries              | 91700                       | (81,500–102,000)                       | 59100                      | (50,000–67,700)                       | 1.2                    | 0.7                    | 2.0                    |
| Low-middle SDI countries       | 67900                       | (61,400–74,100)                        | 105                        | (9,5–115)                             | 5900                   | 5900                   | 11800                  |
| Middle SDI countries           | 31700                       | (29,800–33,700)                        | 171                        | (15,7–18)                             | 31900                  | 31900                  | 63800                  |
| High-middle SDI countries      | 97600                       | (83,100–106,000)                       | 301                        | (25,5–32,7)                           | 16900                  | 16900                  | 33800                  |
| High SDI countries             | 49700                       | (46,200–53,800)                        | 208                        | (19,3–22,5)                           | 6700                   | 6700                   | 13400                  |
| Global other rare lymphomas    | 29500                       | (26,700–32,600)                        | 1.1                        | (1,0–1,3)                             | 14000                  | 14000                  | 28000                  |
| Global non-Hodgkin lymphomas   | 29500                       | (26,700–32,600)                        | 1.1                        | (1,0–1,3)                             | 14000                  | 14000                  | 28000                  |
| Global acute myeloid leukaemia | 22000                       | (18,700–24,400)                        | 0.9                        | (0,7–1,0)                             | 10400                  | 10400                  | 20800                  |
| Global leukaemias not otherwise specified* | 68400 | (56,900–77,700) | 2.7 | (2,2–3,1) | 19700 | 19700 | 39400 |
| Global brain and nervous system cancers | 67400 | (58,400–76,400) | 2.6 | (0,5–6,0) | 25800 | 25800 | 51600 |
| Global liver cancers           | 35000                       | (32,000–38,000)                        | 1.0                        | (0,1–0,1)                             | 26000                  | 26000                  | 52000                  |
| Global renal cancers           | 24400                       | (21,900–26,800)                        | 1.0                        | (0,9–1,1)                             | 31000                  | 31000                  | 62000                  |
| Global other rare cancers†     | 29400                       | (27,600–31,200)                        | 1.1                        | (1,0–1,1)                             | 7200                   | 7200                   | 14400                  |
| Global unspecified cancers†    | 98300                       | (89,200–106,400)                       | 3.8                        | (3,5–4,2)                             | 26200                  | 26200                  | 52400                  |

Absolute incidence, mortality, YLLs, YLDs, and DALYs represent the total childhood cancer (0–19 years, both sexes combined) values, rounded to the nearest hundred. Rates are reported per 100 000 person-years. SDI categories do not sum to precisely the global total because GBD does not provide separate estimates for all locations globally and an adjustment factor is made between all estimated locations, which each have a corresponding estimated SDI value for 2017, and the global aggregate. Causes refer to overall childhood cancer unless a specific cancer type is stated. DALYs disability-adjusted life years. SDI Socio-demographic Index. UI uncertainty interval. YLDs=years of life lived with disability. YLLs=years of life lost. *Included leukaemias not otherwise specified, chronic lymphocytic leukaemias, and chronic myeloid leukaemias. †Cancers with less than 1000 total deaths globally in 2017. ‡Cancers without a detailed GBD cause.

Table: Childhood cancer burden, 2017
DALY estimates. More detailed descriptions of the methods for disease burden estimation can be found in the appendix for this paper and in the GBD 2017 capstone publications. Definitions

The childhood age group in this analysis encompasses children and adolescents, defined as ages 0–19 years. The 0–14-year age range is used to define pediatrics in some countries and global health organisations, and data for subsets of this age range are available online using the GBD Compare Tool and the GBD Results Tool. All cancers as defined in the 10th revision of the International Classification of Diseases, chapter II (neoplasms), are included in the GBD cancer estimation process (appendix p 10). Only malignant neoplasms were included in this analysis; non-melanoma skin cancers were excluded. In this analysis, we restructured the cancer diagnostic categories to depict the most relevant childhood cancer information, categorising any cancer with less than 1000 global deaths annually as other rare cancers, and any cancer without a specific GBD cause as uncategorised cancers. All rates in this paper are reported per 100 000 person-years, with the GBD 2017 world standard population used for calculation of age-standardised rates. See the appendix for definitions of GBD world super-regions (p 54) and GBD world regions (p 60).

GBD 2017 produced estimates at global, national, and select subnational levels; this analysis focuses on the global and regional estimates. Country and subnational estimates are available online using the GBD Compare and GBD Results tools. Results are presented by Socio-demographic Index (SDI) quintile in a subset of tables and figures given the usefulness of SDI as a summary measure of where countries are on the development spectrum (appendix p 47). SDI is a composite measure of income per capita, total fertility rate under 25 years of age, and average educational attainment, and has been shown to correlate well with health outcomes.

Uncertainty analysis

Final point estimates are reported with 95% uncertainty intervals (UIs). The UIs were calculated as the 2.5th and 97.5th percentile of the distribution of 1000 draws at each step in the cancer estimation process, with the uncertainty propagated through each step (UI estimation is described in further detail in the appendix p 39).

Role of the funding source

The funders of this research had no role in the design of the GBD cancer estimation process, collection or analysis of data, interpretation of results, or in the writing of this manuscript. The corresponding author had full access to all data used in this study and had final responsibility for the decision to submit for publication.

Results

Childhood cancer resulted in 11·5 million (95% UI 10·6–12·3) DALYs globally in 2017, of which 97·3% (97·3–97·3) came from YLLs and 2·7% (2·7–2·7) came from YLDs (table). A substantial portion of the global burden of childhood cancer exists in low, low-middle, and middle SDI countries (82·2% [82·1–82·2] of the global childhood cancer total DALYs; table), countries that are concentrated in Asia, Africa, and Central and South America (figure 1A). This geographical pattern of cancer burden distribution is noticeably different from that observed in adults (figure 1B), with only 50·3% (50·3–50·3) of the global adult cancer absolute DALY burden affecting low, low-middle, and middle SDI countries (appendix p 66).

Of the childhood cancer age groups, the 0–4-year age group had the greatest contribution to global childhood cancer DALYs (4·3 million [95% UI 3·8–4·7]), or 37·0% [36·9–37·0] of the global 0–19 year childhood cancer absolute DALY burden; figure 2). Across all childhood cancer age groups, a consistently higher proportion of total DALYs was made up by YLLs (96·8% [96·8–96·8] to 98·1% [98·1–98·1] of the total age group-specific DALYs) than by YLDs (1·9% [1·9–1·9] to 3·2% [3·2–3·2] of the total age group-specific DALYs; appendix p 68). Leukaemias constituted the highest proportion of categorised childhood cancer DALY burden globally, followed by brain and nervous system cancers, with 34·1% (34·0–34·1) of all childhood cancer DALYs globally attributable to leukaemias and 18·1% (18·1–18·1) attributable to brain and nervous system cancers. These two cancer types contributed to the greatest proportional categorised DALY burden globally in all childhood age groups, except for adolescents (15–19 years). In adolescents, other rare cancers, which include cancers such as those of the testes, ovaries, and thyroid, contributed the second highest proportional DALY burden categorised (19·5% [19·4–19·5]). There was a substantial proportion of uncategorised cancers, those neoplasms without a specific cancer type noted in the current GBD data structure, throughout the childhood and adolescent age range, representing 26·5%
Age-standardised DALY rate quintiles for childhood cancers

- Quintile 1 (0–20%)
- Quintile 2 (21–40%)
- Quintile 3 (41–60%)
- Quintile 4 (61–80%)
- Quintile 5 (81–100%)

Age-standardised DALY rate quintiles for adult cancers

- Quintile 1 (0–20%)
- Quintile 2 (21–40%)
- Quintile 3 (41–60%)
- Quintile 4 (61–80%)
- Quintile 5 (81–100%)
Between world regions, with the greatest proportional DALY burden for the majority of childhood cancer types, and the low SDI quintile had the most childhood cancer types that ranked second in DALY burden. Although four of the five countries with the highest childhood cancer DALYS were in the GBD super-regions (1) south Asia and (2) southeast Asia, east Asia, and Oceania, sub-Saharan Africa had the greatest DALY burden for more childhood cancer types than any other super-region. The intra-category rankings highlight that for most countries, GBD super-regions, and SDI settings, uncategorised cancers had the highest estimated DALY burden of all the childhood cancer types.

Figure 2: Global DALY burden of childhood cancer types, both sexes combined, 2017, in absolute and proportional burden in the 0–19 years age group (A), and absolute and proportional burden by 5-year childhood age group (B, C).

DALY=disability-adjusted life-year. *Cancers without a detailed GBD cause. †Cancers with less than 1000 total deaths globally in 2017. ‡Included leukaemias not otherwise specified, chronic lymphoepithelial leukaemias, and chronic myeloid leukaemias.
ranked sixth in terms of DALY burden, with a DALY burden lower only than the burden attributable to cancers of the lung, liver, stomach, colon, and breast. This ranking pattern was different when childhood cancers were compared with other diseases of childhood (figure 6B), in which the highest childhood cancer DALY burden ranking was in high-middle and middle SDI settings—countries that generally have transitioning development status—rather than the lowest SDI settings. Compared with other diseases of childhood, childhood cancer ranked ninth globally in terms of DALY burden, lower than the global burden of lower respiratory infections, diarrhoeal diseases, malaria, and HIV or AIDS, but higher than the global burden of measles, typhoid, and tuberculosis.

**Discussion**

To our knowledge, this paper is the first analysis to quantify the global burden of childhood cancer using DALYs. A standard global health metric routinely applied in health policy decision making, DALYs provide a more comprehensive, lifelong perspective to quantifying...
### Inter-category (column) ranking

| Category                        | India                      | China                      | Pakistan                   | Nigeria                    | Indonesia                   | Ethiopia                    | Bangladesh                  | South Africa                  | Nigeria                      | South Africa                  | Pakistan                   | Bangladesh                  | South Africa                  | Nigeria                      |
|--------------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|
| Leukaemias not otherwise specified* | 1                         | 1                         | 1                         | 1                          | 2                          | 3                           | 3                           | 6                           | 6                           | 6                           | 10                        | 2                          | 1                          | 1                           |
| Non-Hodgkin lymphoma           | 6                         | 7                         | 7                         | 7                          | 7                          | 7                           | 7                           | 7                           | 7                           | 7                           | 7                         | 7                          | 7                           | 7                           |
| Hodgkin lymphoma               | 1                         | 6                         | 6                         | 6                          | 6                          | 6                           | 6                           | 6                           | 6                           | 6                           | 6                         | 6                          | 6                           | 6                           |
| Acute myeloid leukaemia        | 3                         | 9                         | 9                         | 9                          | 9                          | 9                           | 9                           | 9                           | 9                           | 9                           | 9                         | 9                          | 9                           | 9                           |
| Uncategorised cancers‡         | 4                         | 1                         | 1                         | 1                          | 1                          | 1                           | 1                           | 1                           | 1                           | 1                           | 1                         | 1                          | 1                           | 1                           |

### Inter-category (row) ranking

| Category                        | India                      | China                      | Pakistan                   | Nigeria                    | Indonesia                   | Ethiopia                    | Bangladesh                  | South Africa                  | Nigeria                      | South Africa                  | Pakistan                   | Bangladesh                  | South Africa                  | Nigeria                      |
|--------------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|
| Leukaemias not otherwise specified* | 6                         | 5                         | 3                         | 2                          | 2                          | 1                           | 1                           | 2                           | 2                           | 3                           | 3                         | 2                          | 2                           | 2                           |
| Non-Hodgkin lymphoma           | 4                         | 4                         | 4                         | 4                          | 4                          | 4                           | 4                           | 4                           | 4                           | 4                           | 4                         | 4                           | 4                           | 4                           |
| Hodgkin lymphoma               | 3                         | 3                         | 3                         | 3                          | 3                          | 3                           | 3                           | 3                           | 3                           | 3                           | 3                         | 3                           | 3                           | 3                           |
| Acute myeloid leukaemia        | 2                         | 2                         | 2                         | 2                          | 2                          | 2                           | 2                           | 2                           | 2                           | 2                           | 2                         | 2                           | 2                           | 2                           |
| Uncategorised cancers‡         | 1                         | 1                         | 1                         | 1                          | 1                          | 1                           | 1                           | 1                           | 1                           | 1                           | 1                         | 1                           | 1                           | 1                           |

### Global

| Category                        | India                      | China                      | Pakistan                   | Nigeria                    | Indonesia                   | Ethiopia                    | Bangladesh                  | South Africa                  | Nigeria                      | South Africa                  | Pakistan                   | Bangladesh                  | South Africa                  | Nigeria                      |
|--------------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|
| Leukaemias not otherwise specified* | 3                         | 4                         | 5                         | 6                          | 10                         | 10                          | 9                           | 10                          | 9                           | 10                          | 9                         | 10                          | 9                           | 10                          |
| Non-Hodgkin lymphoma           | 5                         | 4                         | 6                         | 5                          | 6                          | 6                           | 6                           | 6                           | 6                           | 6                           | 6                         | 6                           | 6                           | 6                           |
| Hodgkin lymphoma               | 3                         | 3                         | 3                         | 3                          | 3                          | 3                           | 3                           | 3                           | 3                           | 3                           | 3                         | 3                           | 3                           | 3                           |
| Acute myeloid leukaemia        | 2                         | 2                         | 2                         | 2                          | 2                          | 2                           | 2                           | 2                           | 2                           | 2                           | 2                         | 2                           | 2                           | 2                           |
| Uncategorised cancers‡         | 1                         | 1                         | 1                         | 1                          | 1                          | 1                           | 1                           | 1                           | 1                           | 1                           | 1                         | 1                           | 1                           | 1                           |

### 2017 Inter-category ranking refers

| Region                          | India                      | China                      | Pakistan                   | Nigeria                    | Indonesia                   | Ethiopia                    | Bangladesh                  | South Africa                  | Nigeria                      | South Africa                  | Pakistan                   | Bangladesh                  | South Africa                  | Nigeria                      |
|--------------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|
| Western Europe                  | 3                         | 3                         | 3                         | 3                          | 3                          | 3                           | 3                           | 3                           | 3                           | 3                           | 3                         | 3                           | 3                           | 3                           |
| Latin America and Caribbean     | 4                         | 4                         | 4                         | 4                          | 4                          | 4                           | 4                           | 4                           | 4                           | 4                           | 4                         | 4                           | 4                           | 4                           |
| North Africa and Middle East    | 5                         | 5                         | 5                         | 5                          | 5                           | 5                           | 5                           | 5                           | 5                           | 5                           | 5                         | 5                           | 5                           | 5                           |
| South Asia                      | 6                         | 6                         | 6                         | 6                          | 6                           | 6                           | 6                           | 6                           | 6                           | 6                           | 6                         | 6                           | 6                           | 6                           |
| Southeast Asia, East Asia, and Oceania | 7                         | 7                         | 7                         | 7                           | 7                           | 7                           | 7                           | 7                           | 7                           | 7                           | 7                         | 7                           | 7                           | 7                           |
| Fifty most populous countries   |                           |                           |                           |                            |                            |                            |                            |                            |                            |                            |                            |                           |                            |                            |                            |
childhood cancer burden than has been reported in the past. Previous approaches to reporting the global burden of childhood cancers have focused on incidence, mortality, and survival; each of these metrics, although essential, provide a limited assessment when reviewed individually. DALYs can provide a useful summary measure of early mortality and treatment-related morbidity, especially for the childhood cancer population, in which early deaths contribute many YLLs to DALYs and in which children surviving cancer treatment often live for many years with chronic disability. In our analysis of GBD 2017, we report that although the absolute numbers of global childhood cancer incident cases and deaths were relatively small, the global burden of childhood cancer as represented in DALYs was substantial. The majority of these childhood cancer DALYs affected countries with a lower SDI, probably due to both the younger population structure observed in lower-income settings as well as a disproportionately large YLL burden, reflective of the lower survival rates observed in countries with frail health systems.

As expected, lower SDI settings were noted to have the highest age-standardised overall childhood cancer mortality rates. However, the association between childhood cancer incidence rates and SDI represented in figure 5A is unexpected, given that there are few established environmental risk factors for the majority of childhood cancers and current evidence suggests that pathological germline cancer predisposition mutations affect less than 10% of the childhood cancer population. The cause of the trend between incidence and SDI is unknown but probably multifactorial. Although there is heterogeneity in environmental exposures between world regions and much to learn regarding potential genetic variability between populations, these factors alone are unlikely to explain the estimated variation in childhood cancer incidence by SDI. Limitations in access to health care and diagnostic capacity for children with cancer have been suggested to contribute to artificially low case ascertainment in resource-limited settings. Missed diagnoses caused by poor access to health facilities, misdiagnoses as non-oncological diseases, and under-registration due to overburdened cancer registration systems all probably contribute to this phenomenon. The GBD 2017 results highlight that improving the accuracy of global childhood cancer burden assessment will require not only expanding the quantity and quality of population-based cancer registration systems, but also increasing access to health care with the capacity to identify children with cancer regardless of where they live.

Treatment of childhood cancer in LMIC settings has been shown to be very cost-effective according to WHO—Choosing Interventions that are Cost-Effective criteria, but because of finite resources and competing health priorities in many LMIC settings, an accurate appraisal of childhood cancer disease burden using comparable metrics is essential for health policy decision making.

As low SDI countries develop, the burden of infectious diseases tends to decline and thus the relative burden of non-communicable diseases, including cancers, tends to rise—a phenomenon known as epidemiological transition. The use of DALYs provides a unique ability to contextualise the burden of childhood cancers in comparison with general diseases of childhood, and we found that childhood cancer ranks among the top five causes of DALY burden in middle and high-middle SDI settings, with a lower ranking on either end of the SDI spectrum, particularly in low SDI settings. This pattern is consistent with the epidemiological transition, with the highest childhood cancer burden relative to the burden of general diseases of childhood occurring in countries transitioning from lower to higher development status.

A different DALY pattern was observed when childhood cancers were compared with individual adult cancers—a suitable comparison for guidance of resource allocation.
| Age group | Population size | DALYs (95% UIs) in 2017 | Global rank | High SDI rank | High-middle SDI rank | Middle SDI rank | Low-middle SDI rank | Low SDI rank |
|-----------|-----------------|--------------------------|-------------|---------------|----------------------|----------------|---------------------|-------------|
| Childhood cancer | 11 549 600 (10 649 000–12 334 700) | 6 | 22 | 10 | 7 | 1 | 1 | |
| Oesophageal cancer | 9 762 300 (9 517 700–10 015 700) | 7 | 10 | 6 | 6 | 10 | 9 | |
| Pancreatic cancer | 6 065 200 (5 883 200–6 245 300) | 8 | 4 | 7 | 11 | 15 | 16 | |
| Other malignant neoplasms | 8 805 300 (8 541 100–9 137 700) | 9 | 8 | 8 | 9 | 8 | | |
| Cervical cancer | 8 046 300 (7 531 100–8 385 100) | 10 | 19 | 12 | 8 | 7 | 5 | |
| Prostate cancer | 7 052 600 (6 048 700–8 347 200) | 11 | 7 | 11 | 12 | 11 | 13 | |
| Brain and nervous system cancer | 6 656 500 (5 827 800–7 170 100) | 12 | 11 | 9 | 10 | 14 | 14 | |
| Non-Hodgkin lymphoma | 5 896 600 (5 759 100–6 018 400) | 13 | 9 | 13 | 13 | 12 | 12 | |
| Lip and oral cavity cancer | 5 204 800 (4 933 700–5 447 800) | 14 | 20 | 18 | 14 | 18 | 10 | |
| Ovarian cancer | 4 630 300 (4 488 000–4 786 900) | 15 | 33 | 14 | 15 | 16 | 17 | |
| Bladder cancer | 3 590 300 (3 468 600–3 759 800) | 16 | 12 | 15 | 21 | 20 | 20 | |
| Gynaecological tract cancer | 3 476 400 (3 036 000–3 700 400) | 17 | 15 | 19 | 17 | 18 | 18 | |
| Larynx cancer | 3 379 500 (3 182 300–3 563 900) | 18 | 25 | 20 | 18 | 17 | 15 | |
| Other pharynx cancer | 2 844 700 (2 635 200–3 054 400) | 19 | 24 | 26 | 20 | 13 | 11 | |
| Other leukaemia | 3 121 400 (2 733 700–3 167 800) | 20 | 23 | 17 | 16 | 19 | 21 | |
| Kidney cancer | 3 012 400 (2 838 400–3 122 600) | 21 | 14 | 16 | 22 | 26 | 28 | |
| Acute myeloid leukaemia | 2 389 400 (2 182 900–2 585 600) | 22 | 18 | 24 | 24 | 21 | 19 | |
| Multiple myeloma | 2 211 400 (2 162 200–2 254 400) | 23 | 16 | 23 | 25 | 25 | 24 | |
| Uterine cancer | 2 136 800 (2 052 500–2 219 500) | 24 | 21 | 22 | 23 | 22 | 25 | |
| Nasopharynx cancer | 2 013 900 (1 942 300–2 105 600) | 25 | 29 | 21 | 19 | 23 | 22 | |
| Malignant skin melanoma | 1 671 100 (1 519 200–1 912 800) | 26 | 17 | 25 | 28 | 30 | 30 | |
| Acute lymphoid leukaemia | 1 599 600 (1 446 400–1 828 800) | 27 | 30 | 27 | 26 | 28 | 29 | |
| Thyroid cancer | 1 093 200 (943 200–1 185 300) | 28 | 28 | 28 | 27 | 27 | 27 | |
| Hodgkin lymphoma | 1 027 700 (887 000–1 209 800) | 29 | 21 | 30 | 29 | 24 | 23 | |
| Chronic lymphoid leukaemia | 686 600 (582 000–741 100) | 30 | 27 | 29 | 31 | 33 | 32 | |
| Mesothelioma | 665 100 (543 000–686 200) | 31 | 26 | 31 | 32 | 31 | | |
| Chronic myeloid leukaemia | 631 200 (574 900–688 500) | 32 | 32 | 32 | 30 | 29 | 26 | |
| Testicular cancer | 351 300 (313 400–3 715 000) | 33 | 33 | 33 | 33 | 33 | | |

A

Figure 6: Contribution of childhood cancer to global cancer (A) and child health (B) DALY burden, both sexes combined, 2017

Disease rank assigned by total absolute DALYs globally in 2017. Childhood cancer burden is represented by the total DALYs for population aged 0–19 years. Adult cancer burden is represented by the total DALYs for each cancer subtype for the population aged 20 years and older. Total DALYs are rounded to the nearest hundred. Colour intensity is proportional to rank number. (A) All cancer causes are included. (B) Top 20 global causes of absolute DALY burden in children aged 0–19 years; childhood diseases excluded injuries and perinatal diseases. DALY=disability-adjusted life-year. SDI=Socio-demographic Index. UI=uncertainty interval.

decisions given that childhood cancers are typically treated under one clinical service, whereas adult cancers are often treated under various cancer-specialised services. Specifically, childhood cancers are the top cause of cancer burden, as expressed in DALYs, in low and low-middle SDI settings. This is a markedly different concentration of burden than occurs in adult cancers, in which DALY burden is heavily weighted towards countries
with high and middle SDI status, and is probably due in part to the older population structure in higher SDI settings, as well as to lifestyle risk factors that are more prevalent in higher-resourced settings.\(^4\) This variation in the epidemiological patterns of cancer burden distribution in children and adults supports the view that the mechanisms of addressing cancer burden in adults, which focus on risk-reduction strategies and screening interventions, are not as relevant in the paediatric and adolescent age groups at this time. Childhood cancers generally progress rapidly, are not amenable to screening, and are fatal without swift diagnosis and treatment.\(^8\) Thus, improving childhood cancer outcomes will require well functioning health systems capable of early diagnosis and effective treatment.

Addressing the global burden of childhood cancer has gained greater relevance during the past 2 years since the World Health Assembly Cancer Resolution in May, 2017, and the WHO Global Initiative for Childhood Cancer announced during the High Level Meeting on non-communicable diseases at the UN General Assembly in September, 2018.\(^2\)\(^5\) The World Health Assembly Cancer Resolution requested resource-stratified guidance for the development of cancer-control programmes, specifically calling for children and adolescents to be included in the design of these programmes. The WHO Global Initiative for Childhood Cancer is the first programme designed to address this resolution with a focus on childhood cancer and aims to increase the overall survival for six key childhood cancers (acute lymphoblastic leukaemia, Burkitt’s lymphoma, Hodgkin lymphoma, low-grade glioma, retinoblastoma, and Wilms tumour) to 60% globally by 2030 through integration of childhood cancer into national cancer control policies and capacity-building interventions including the development of national centres of excellence and regional satellites.\(^6\) As initiatives such as these recommend countries develop and implement paediatric-specific cancer control plans over the next decade, country-specific and region-specific variations in disease burden and identification of high-yield opportunities for improvement in outcomes will be essential. In particular, evaluating the progress made in childhood cancer survival as part of the WHO Global Initiative for Childhood Cancer will be imperative to its success. The GBD study provides valuable estimates of childhood cancer epidemiology in areas where direct disease burden data are scarce or non-existent, provides the most comprehensive and contextualised global burden estimates to date through the use of DALYs, and is updated annually. Moreover, the GBD framework is already monitoring progress of the health-related UN Sustainable Development Goals.\(^7\)\(^8\) As the WHO Global Initiative for Childhood Cancer will develop indicators similar in structure to those used for tracking of Sustainable Development Goal targets, the GBD study provides an ideal platform for monitoring global progress in childhood cancer by quantifying changes in burden and tracking proposed indicators over time.

The deeper analyses of the GBD cancer estimation process described here highlight opportunities to improve the currently applied methodology with regard to childhood cancers in particular. Inclusion of data from paediatric-specific cancer registries would add key existing information for childhood cancer incidence not currently included in the GBD data sources.\(^7\) However, additional data sources alone will not resolve key structural limitations in the existing GBD approach. The present anatomical site-based system of reporting cancer types functions well for adult cancers, which are primarily carcinomas, but leaves 26·5% of childhood cancer DALYs globally with a label of uncategorised cancers. Morphology is crucial to appropriate diagnosis and treatment of childhood cancers, and thus the current GBD classification system inadequately communicates the burden of childhood cancers and represents a missed opportunity for actionable burden estimates. Using the International Classification of Childhood Cancer system as a framework for reporting childhood cancers would decrease the notable proportion that are uncategorised and should be prioritised in future GBD iterations.\(^2\)\(^9\)

A separate limitation in the reporting is that although GBD 2017 provided estimates for benign tumour burden in aggregate, it did not specify the portion attributable to CNS tumours. Thus, the estimates reported here do not include these tumours, which are important contributors to childhood cancer morbidity and include one of the six indicator cancers (low-grade gliomas) proposed by the WHO Global Initiative for Childhood Cancer.\(^2\)

Furthermore, the current GBD approach to modelling the treatment and survivorship phases of childhood cancer care might lead to a systematic underestimation of YLDs and DALYs. First, the estimation of YLDs relies on data for prevalence sequelae duration from HICs. However, superimposing HIC data in this manner might not accurately represent the duration of disability seen in LMICs. This consideration is important because children in LMIC settings tend to present to care later in their disease course, potentially leading to different distributions of cancer stage at diagnosis than are observed in HICs.\(^7\) Addressing this issue was not historically possible because of a paucity of childhood cancer staging information in population-based cancer registries.\(^7\) If the recently published Toronto guidelines providing concrete staging recommendations are adopted by registries in the coming years, however, opportunities to use staging data to improve the estimation of YLDs might be possible in the near future.\(^6\) Second, the current GBD estimation of YLDs assumes that all children receive and complete treatment. Unfortunately, many children with cancer in LMIC settings have notable risk of therapy abandonment.\(^6\) Although global data on childhood cancer abandonment are limited, creating a method to account for the proportion of children who
abandon therapy upfront is imperative given that untreated childhood cancer is generally fatal. Finally, the current GBD models do not incorporate the well established increased lifelong risk of multimorbidity and early death observed in childhood cancer survivors compared with the general population. The existing models of disability in childhood cancer survivors is limited to 10 years after cancer diagnosis, with children surviving past 10 years presumed to have the same risk of morbidity and mortality as the general population. Substantial data have shown this assumption to be inaccurate, and incorporation of survivorship cohort data would improve the GBD estimation of childhood cancer survivor burden.

These limitations suggest that the GBD 2017 estimates probably underestimate the DALYs associated with childhood cancer. Addressing these limitations in future GBD iterations would improve childhood cancer burden estimates and provide a better evidence base for policy, financial, and clinical decision making. Opportunities to improve on the current GBD methodology are both feasible and necessary to provide the most useful information to global health stakeholders interested in reducing disparities in global childhood cancer outcomes.

In summary, this analysis of the global burden of childhood cancer produced by the GBD 2017 study demonstrates substantial DALY burden, even when compared with cancers in adults and general diseases of childhood. Childhood cancer DALYs disproportionately affect countries with the fewest resources, underscoring the need for effective strategies to address the burden in these settings. These findings provide a global childhood cancer burden baseline from which to evaluate future progress and highlight that childhood cancer has a role in prioritisation frameworks that address global oncology and global child health.

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