

Supplementary Appendix: methods and results appendix to “Global burden of adverse effects of medical treatment from 1990 to 2021: a Global Burden of Disease Study 2021”

This appendix provides further methodological detail for “Global burden of adverse effects of medical treatment from 1990 to 2021: a Global Burden of Disease Study 2021.”

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Section 2: GBD OVERVIEW

Section 2.1: Geographic locations of the analysis

Global Burden of Disease (GBD) 2021 estimates incidence, prevalence, mortality, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life year (DALYs) for 371 diseases and injuries over 204 countries and territories, specified by age, sex, location and year. Age was stratified into 25 groups from early neonatal to 95 years and older. 204 countries and territories were further categorized into 21 regions and seven super-regions (Europe, eastern Europe, and central Asia; high income; Latin America and the Caribbean; north Africa and the Middle East; south Asia; southeast Asia, east Asia, and Oceania; and sub-Saharan Africa). Detailed subnational analyses were done for 21 countries and territories, for a total of 983 unique locations. Estimates were also provided based on grouping by socio-demographic index quintiles and World Bank Income Levels of each location. Numbers and rates for incidence, prevalence, YLDs, and DALYs were calculated from 1990 to 2021, while YLLs were calculated over the period from 1980 to 2021 annually.

Section 2.2: GBD cause list

A total 371 diseases of fatal and non-fatal causes and injuries were included. They were hierarchized in to Level 0 to 6, where Level 0 indicates an aggregate of all causes. Level 1 causes include three categories: communicable, maternal, neonatal, and nutritional diseases, non-communicable diseases, and injuries. Level 2 disaggregates Level 1 categories into 22 clusters of causes. Level 3 includes 175 causes, 132 of which were at Level 4. The remaining 43 Level 3 causes which were clusters of causes disaggregating into 170 specific Level 4 causes. Of the 371 diseases and injuries, 365 had non-fatal outcomes and 288 had fatal outcomes. Sequelae from

diseases and injuries are categorized within Levels 5 and 6. The most detailed assessments of all sequelae are conducted at Level 6 and these are then aggregated into broader summary categories at Level 5.

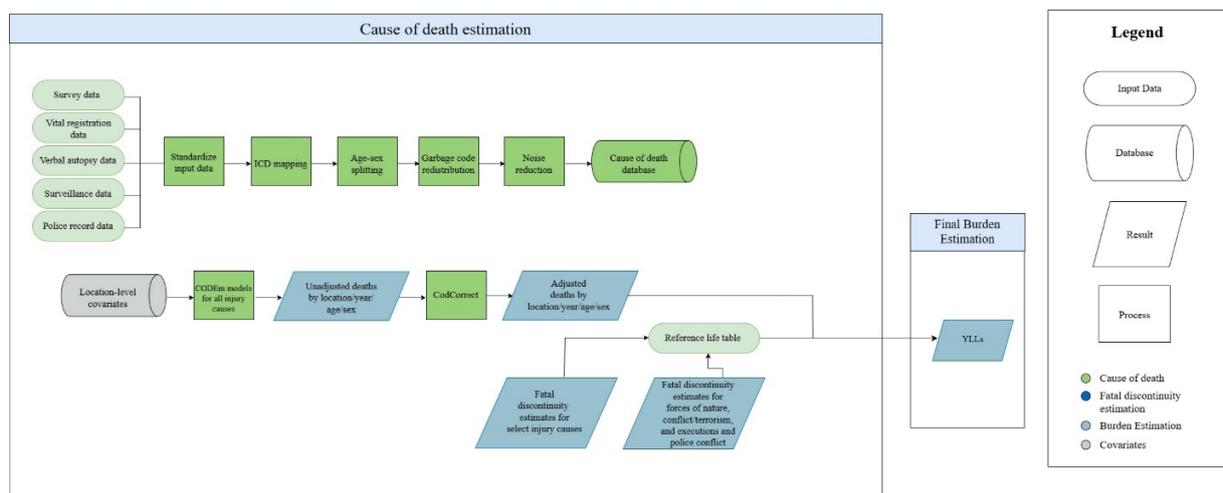
The GBD cause list continues to evolve to reflect the policy relevance, and public health and medical care importance of the causes of major losses of health. For GBD 2021, 12 new causes of death were reported, including COVID-19, other primary respiratory malignancies, pulmonary arterial hypertension, hepatoblastoma, Burkitt lymphoma, other non-Hodgkin lymphoma, eye cancer, retinoblastoma, other eye cancers, soft tissue and other extraosseous sarcomas, malignant neoplasm of bone and articular cartilage, and neuroblastoma and other peripheral nervous cell tumors. 4 age groups for ages younger than 5 years were added: 1–5 months, 6–11 months, 12–23 months, and 2–4 years. New sources of data were added, including 199 country-years of vital registration, 5 country-years of surveillance data, and 21 country-years of verbal autopsy data. GBD 2021 applied enhanced methods of data processing corrections to account for incomplete data, stochastic variation, and garbage codes.

Section 3: GBD 2021 causes of death database

Section 3.1: Cause of death identification

The majority of cause of death (CoD) data is derived from vital registration records collected in the World Health Organization (WHO) Mortality Database, which compiles information submitted by individual countries. Each cause of death is coded directly to a three- or four-digit ICD code whenever feasible, while cause codes in data organized by the International Classification of Diseases (ICD) are categorized into aggregated groups.

eFigure 1. Cause of death estimation for injuries in GBD 2021



The CoD database encompasses detailed country-year data from 1980 to 2021, including underlying causes of death coded with three- to four-digit codes, categorized by country, year, sex, and age groups. These detailed causes are classified according to either the ICD-9 or ICD-10 coding systems. The WHO updates the ICD-detail coding biannually, either through the release of new versions or by incorporating additional data from collaborating countries. As the most current classification for cause of death, updates from the WHO increasingly feature ICD-10 data.

Section 3.2: Definition of adverse effects of medical treatment

Within the GBD 2021 hierarchy, injuries are categorized as a Level 1 condition. We estimated the burden of 36 distinct injuries, which are grouped into three categories: transport injuries, unintentional injuries, and self-harm and interpersonal violence. Adverse effects of medical treatment (AEMT) is classified as a level 3 cause under the level 1 category of 'injuries' and the Level 2 category of 'unintentional injuries'. AEMT is defined as deaths or long-term and short-term disabilities sustained as the result of undergoing a procedure, treatment, or other exposure to the health-care system. This exposure can occur in inpatient admission, outpatient facilities, emergency care, or during home treatments. The mapping of AEMT was conducted using the coding systems ICD-9 and ICD-10, with the exception of alcohol poisoning and drug overdoses, which were categorized separately from the injury framework. Specific ICD-9 and ICD-10 codes related to AEMTs are presented below, with detailed cause names for each code provided in **Table S1-2**.

eTable 1. ICD-9 and ICD-10 codes included in the GBD 2021 cause category of adverse effects of medical treatment for fatal estimates

	ICD10	ICD9
Fatal estimates	D52.1, D59.0, D59.2, D59.6, D69.5, D70.1–D70.2, D78–D78.8, E03.2, E06.4, E09 E09.9, E16.0, E23.1, E24.2, E27.3, E36–E36.8, E66.1, E88.3, E89–E89.9, G21.0 G21.1, G24.0, G25.1, G25.4, G25.6–G25.7, G72.0, G93.7, G97–G97.9, I95.2–I95.3, I97–I97.9, I98.9, J70.0–J70.5, J95–J95.9, K43–K43.9, K52.0, K62.7, K91–K91.9, K94, K95.8, M87.1, N14–N14.4, N30.4, N65–N65.1, N99–N99.9, P93–P93.8, P96.2, P96.5, R50.2, Y40–Y84.9, Y88–Y88.3	244.0–244.1, 244.3–244.8, 251.3, 253.7, 349.0–349.1, 357.6, 457.0, 518.7, 519.0, 536.4, 539–539.9, 551.2, 552.2, 553.2, 558.1, 564.2–564.4, 569.6, 579.3, 598.2, 779.4–779.5, E870–E876, E878–E879, E930–E949

Non-fatal estimates	D69.5–D69.59, D70.1–D70.2, D78–D78.89, D89.81–D89.813, E03.2, E06.4, E09–E09.9, E16.0, E23.1, E24.2, E27.3, E36–E36.8, E66.1, E87.0–E87.99, E89 E89.9, G21.0–G21.19, G24.0–G24.09, G25.1, G25.4, G25.6–G25.79, G62.0, G72.0, G93.7, G96.0, G96.11, G97–G97.9, H05.33–H05.339, H05.42–H05.53, H59–H59.89, H91.0–H91.09, H95–H95.9, I95.2–I95.81, I97–I97.9, J70–J70.4, J95–J95.9, K08.5–K08.59, K43–K43.9, K52.0, K62.7, K68.11, K91–K91.9, K94–K95.89, L23.3, L27.0–L27.1, L56.0–L56.1, L64.0, L76–L76.82, M10.2–M10.29, M87.1–M87.19, M96–M96.9, N14–N14.4, N30.4–N30.41, N46.021, N46.121, N52.2–N52.39, N65–N65.1, N99–N99.9, P93–P93.8, P96.2, P96.5, R50.2–R50.83, Y40, Y84.9, Y88–Y88.3, Z21.0, Z42–Z51.9, Z88–Z94.0, Z94.6–Z99.9	244.0–244.1, 244.3, 251.3, 253.7, 279.5–279.53, 331.81, 333.92, 349–349.9, 357.6, 359.24, 379.6–379.63, 440.3–440.32, 457.0, 458.2–458.29, 518.6–518.7, 519.0–519.1, 525.6–525.79, 526.62–526.63, 530.86–530.87, 536.4–536.49, 539–539.9, 551.2–551.29, 552.2–552.29, 553.2–553.29, 564.2–564.4, 569.6–569.8, 579.3, 595.82, 596.81–596.83, 598.2, 612–612.1, 779.4–779.5, 780.62–780.66, 995.89, E870–E876.9, E878–E879.9, E930–E949.9, V44–V45, V45.2–V45.4, V45.7, V45.77, V45.79–V45.8, V45.87–V45.89
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Section 3.3: Age-sex splitting

In the process of constructing a consolidated demographic database, we identified that the aggregation of age groups represents a significant source of inconsistency. Conventionally, demographic data are reported in broad age categories, such as 0–4, 5–14, and 15–49, often combining both sexes. This issue of comparability among age-sex groups became apparent while compiling the GBD CoD database. To address this, we developed a tool termed 'age-sex splitting,' which disaggregates aggregated age groupings and the 'both sexes combined' category into their likely constituent age groups, based on respective cause-specific and country-specific age distributions.

The analytical framework for the GBD includes six age categories for infants and children under five years: early neonatal (0–6 days), late neonatal (7–27 days), 1–5 months, 6–11 months, 12–23 months, and 2–4 years. For individuals over five years, there are 19 age categories: 5–9 years, 10–14 years, and so forth, progressing in five-year increments up to the terminal age group of 95 years and older. We handle unknown ages and sexes in a manner consistent with our treatment of the 'all ages combined' age category and the 'both sexes combined' sex group. The primary assumption underlying this formula is that the relative risk of death by age group, in comparison to a reference age group, remains constant across different populations. While this assumption may not hold true in specific instances, a robust biologically based pattern of relative risk of death by age for most causes is generally observed. The basic formula is as follows:

$$D_a = R_a N_a \left(\frac{D_a^{a+x}}{\sum_a^{a+x} (R_a N_a)} \right)$$

Where:

D_a is the number of deaths from a cause in the age group a

R_a is the global cause-specific mortality rate of the age group a

N_a is the country-year-sex-specific population in the age group a

D_a^{a+x} is the number of deaths in the age group a to $a + x$

In the less common case that CoD sources report data with both sexes combined, the same principle of invariant relative risk can be applied to sex as well as age to split data across both age and sex. The relative risk of death for each cause-age group-sex was derived from the global distribution of mortality rates, mapped to GBD at the most detailed cause level for each CoD. Cause aggregation was performed to generate values at all Level 1, 2, and 3 causes. Estimated adult and child VR completeness were adjusted for separately. Cause-age-sex-location-year-specific deaths and populations were aggregated to produce cause-specific mortality rates by age-sex.

Section 4: Causes of death modelling methods

Section 4.1: CODEm

Mortality for AEMTs was estimated using the Cause of Death Ensemble model (CODEm) approach. First, all pertinent data are identified and gathered. Second, a variety of plausible models capturing well-documented associations are developed. Four families of statistical models are used: linear mixed effects regression (LMER) models and spatiotemporal Gaussian process regression (ST-GPR) of the natural log of the cause-specific death rate, and LMER and ST-GPR models of the logit of the cause fraction. Relationships between the response variable and covariates and combinations of covariates are identified and tested for statistical significance and plausibility. In the case of AEMTs, the covariates included were: education (years per capita; strong negative biological link), healthcare access and quality index (strong evidence of negative relationship), population-weighted mean temperature (strong positive biological link), Logarithm of Development Index (I\$ per capita; weak positive relationship), and socio-demographic index (weak negative relationship). Third, out-of-sample predictive validity testing was repeated 20 times for each model to create ranks. Testing included factors such as the coverage of the predicted 95% UI and the root mean square error for the log of the cause-specific death rate. Fourth, differently weighted combinations of models were created and assessed. Weight combinations determined the contribution of each rank to the combined models. The combined model with the highest out-of-sample predictive validity was chosen as the final model. The final model was used to produce 1000 draws, the mean of which was used as the final estimate, and 0.025 and 0.975 quantiles of which were used as the 95% UI.

Section 4.2: CoDCorrect

The CoDCorrect process is used to ensure that the sum of cause-specific models will equal the results of the all-cause mortality estimates, maintaining internal consistency. The CoDCorrect process starts by rescaling Level 1 causes to all-cause mortality estimates, and then continues for all subsequent levels. The core algorithm for CoDCorrect is as follows:

$$CD_{lyasjd} = D_{lyasjd} \left(\frac{PD_{lyasjd}}{\sum_{j=1}^k D_{lyasjd}} \right)$$

Where:

CD_{lyasjd} is the corrected number of deaths for a location l , year y , age a , sex s , cause j , and draw d

D_{lyasjd} is the uncorrected number of deaths estimated from a cause-specific model for a location l , year y , age a , sex s , cause j , and draw d

PD_{lyasjd} is the parent CoD for a location l , year y , age a , sex s , cause j , and draw d

Section 4.3: Calculation of Years of life lost (YLLs)

YLLs were calculated by multiplying the number of deaths for each cause-age-sex-location-year by the standard life expectancy at each age-sex-location-year. The standard life-expectancy was calculated using a global, sex-agnostic, all-time theoretical “best” life expectancy and the average age of death from with-shock life tables for each age-sex-location-year.

Section 4.4: Age-standardization

A non-weighted mean of 2021 age-specific proportional distributions from the GBD 2021 population estimates for all national locations with a population greater than 5 million people were

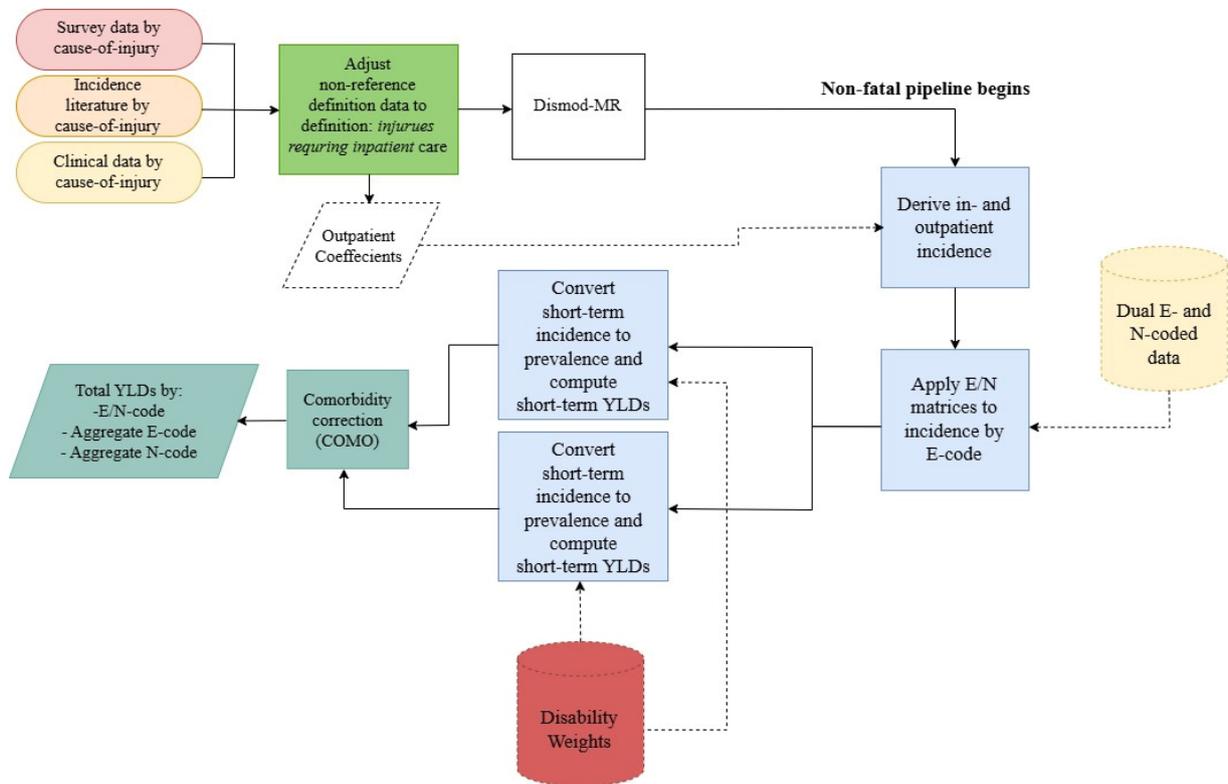
used to generate a standard population age structure. This standard population was used to calculate age-standardized estimates.

Section 5: Non-fatal outcome estimation

Section 5.1: Survey data preparation

Non-fatal estimates include incidence, prevalence, and years of healthy life lost due to disability (YLDs). DALYs were calculated as the sum of YLLs and YLDs. Injuries can result in a number of physical injury sequelae, hereinafter referred to as "nature-of-injury". Nature-of-injury was matched to cause-of-injury, and both categories were retained in the data collection process.

eFigure 2. Non-fatal outcome estimation flow



Section 5.2: Data sources

Data from hospital and emergency department records, insurance claims, and surveys was used for non-fatal estimates. In the case of injuries, many hospital records used a mix of cause-of-injury and nature-of-injury codes. Datasets that had at least 15% of cases coded to cause-of-injury were

included. Sources with less than the 15% threshold had more disproportionate cause-of-injury coding.

Section 5.3: Data processing

Input data was processed prior to using DisMod-MR 2.1 to estimate incidence and prevalence. All input data was mapped to GBD causes via ICD mapping, specifically ICD-9 and ICD-10. The non-fatal estimate mapping for AEMT was conducted using a methodology analogous to that employed for fatal estimate mapping. The relevant ICD codes are provided in the table below.

eTable 2. ICD-9 and ICD-10 codes included in the GBD 2021 cause category of adverse effects of medical treatment for non-fatal estimates

	ICD10	ICD9
Fatal estimates	D52.1, D59.0, D59.2, D59.6, D69.5, D70.1–D70.2, D78–D78.8, E03.2, E06.4, E09 E09.9, E16.0, E23.1, E24.2, E27.3, E36–E36.8, E66.1, E88.3, E89–E89.9, G21.0 G21.1, G24.0, G25.1, G25.4, G25.6–G25.7, G72.0, G93.7, G97–G97.9, I95.2–I95.3, I97–I97.9, I98.9, J70.0–J70.5, J95–J95.9, K43–K43.9, K52.0, K62.7, K91–K91.9, K94, K95.8, M87.1, N14–N14.4, N30.4, N65–N65.1, N99–N99.9, P93–P93.8, P96.2, P96.5, R50.2, Y40–Y84.9, Y88–Y88.3	244.0–244.1, 244.3–244.8, 251.3, 253.7, 349.0–349.1, 357.6, 457.0, 518.7, 519.0, 536.4, 539–539.9, 551.2, 552.2, 553.2, 558.1, 564.2–564.4, 569.6, 579.3, 598.2, 779.4–779.5, E870–E876, E878–E879, E930–E949
Non-fatal estimates	D69.5–D69.59, D70.1–D70.2, D78–D78.89, D89.81–D89.813, E03.2, E06.4, E09–E09.9, E16.0, E23.1, E24.2, E27.3, E36–E36.8, E66.1, E87.0–E87.99, E89 E89.9, G21.0–G21.19, G24.0–G24.09, G25.1, G25.4, G25.6–G25.79, G62.0, G72.0, G93.7, G96.0, G96.11, G97–G97.9, H05.33–H05.339, H05.42–H05.53, H59–H59.89, H91.0–H91.09, H95–H95.9, I95.2–I95.81, I97–I97.9, J70–J70.4, J95–J95.9, K08.5–K08.59, K43–K43.9, K52.0, K62.7, K68.11, K91–K91.9, K94–K95.89, L23.3, L27.0–L27.1,	244.0–244.1, 244.3, 251.3, 253.7, 279.5–279.53, 331.81, 333.92, 349–349.9, 357.6, 359.24, 379.6–379.63, 440.3–440.32, 457.0, 458.2–458.29, 518.6–518.7, 519.0–519.1, 525.6–525.79, 526.62–526.63, 530.86–530.87, 536.4–536.49, 539–539.9, 551.2–551.29, 552.2–552.29, 553.2–553.29, 564.2–564.4, 569.6–569.8, 579.3, 595.82, 596.81–596.83, 598.2, 612–612.1, 779.4–779.5, 780.62–780.66, 995.89,

L56.0–L56.1, L64.0, L76–L76.82, M10.2–M10.29, M87.1–M87.19, M96–M96.9, N14–N14.4, N30.4–N30.41, N46.021, N46.121, N52.2–N52.39, N65–N65.1, N99–N99.9, P93–P93.8, P96.2, P96.5, R50.2–R50.83, Y40,Y84.9, Y88–Y88.3, Z21.0, Z42–Z51.9, Z88–Z94.0, Z94.6–Z99.9	E870–E876.9, E878–E879.9, E930–E949.9, V44–V45, V45.2 V45.4, V45.7, V45.77, V45.79–V45.8, V45.87–V45.89
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In the case of injuries, both cause-of-injury and nature-of-injury codes were extracted. For GBD 2021, injuries were restricted to cases in which some form of health care was warranted in a system with full access to health care, excluding trivial injuries. Cases in which healthcare was warranted but not received due to restricted access to health care were included. Injuries were subdivided into three categories: type of care needed, care-seeking behavior, and duration of disability. Injuries that require overnight hospitalization were defined as "inpatient injuries", while injuries warranting other healthcare such as outpatient or emergency care were defined as "outpatient injuries". Cases that received warranted care were defined as "treated injuries", while those that did not were labeled "untreated injuries". Injuries which cause disability for less than one year were defined as short-term injuries. Cases in which there more disability one-year post-injury compared to pre-injury were assumed to have lifelong disability and are defined as long-term injuries, and the difference in disability level pre- and one year post-injury was assumed to be the permanent disability level.

Section 5.4: Spatiotemporal Gaussian process regression (ST-GPR) modelling

Input data was adjusted to match the same definition and account for undocumented or untreated cases. Correction factors were applied to account for double-counting due to repeat hospital visits within a three-month window. Data were adjusted to account for cases in which the cause of interest was a non-primary diagnosis. ST-GPR was used to estimate the proportion of treated

injuries, thus allowing for data to be corrected to represent both treated and untreated cases. Healthcare Access and Quality (HAQ) Index was used to correct for cases in which injuries warranting care were sustained, but were untreated due to restricted access to healthcare. Finally, MR-BRT (Meta-regression—Bayesian, regularised, trimmed) was used to adjust data to represent both inpatient and outpatient cases.

Section 5.5: MR-BRT meta-regression modelling

The MR-BRT modeling tool was used to estimate the ratio of female to male admissions using sex-specific data. The results of this model were used to disaggregate the both-sex data points into sex-specific data. Hospital administrative records were used as the reference data type, and other data types were crosswalked to administrative records via adjustment factors. derived from MR-BRT meta-regressions, with a spline on age and covariates (hospital beds per 1000 and lag-distributed income) to account for non-systematic differences between the data types. The linear mixed-effects meta-regression in MR-BRT can be described as:

$$y_{ij} = \beta_0 + \beta_1 x_1 + \dots + \beta_n x_n + u_j + \epsilon_{ij}$$

Where:

y_{ij} is the value of observation i in study j

$\beta_0 + \beta_1 x_1 + \dots + \beta_n x_n$ are the linear predictors, including the intercept and the effects of covariates

u_j is a random intercept corresponding to study j

ϵ_{ij} is the stochastic error for observation i in study j

Key features of MR-BRT include:

- Bayesian priors: Incorporate external information with uniform or Gaussian priors.
- LASSO and ridge regression: Implement L1 (Laplace priors) and L2 (Gaussian priors) regularization.
- Trimming: Identifies and removes outliers during the model fitting process.
- Spline terms: Uses B-splines to model nonlinear effects of covariates, with control over flexibility.
- Ratio model: Handles pairs of exposure intervals, often used with a spline to capture nonlinear exposure effects.

MR-BRT has several features that expand upon the classical mixed effects meta-regression model. Bayesian priors can be applied to any estimated coefficient, allowing external data to be incorporated. Uniform priors set hard boundaries for estimated coefficients. Gaussian priors act as suggestions for the value of an estimated coefficient, with the strength of the prior determined by the standard deviation of the Gaussian distribution. LASSO variable selection and ridge regression can be implemented by specifying Laplace priors or Gaussian priors, respectively, with mean 0 on the β coefficients. The integrated trimming algorithm identifies and removes the effects of outliers. A B-spline, or basis spline, can be used to describe the nonlinear effect of a covariate, with fine-tuned control over flexibility. Finally, "ratio models" allow pairs of exposure intervals to be used as an independent variable, often working in conjunction with splines to capture nonlinear exposure effects.

In addition to the new sources of data, GBD 2021 implemented several changes compared to GBD 2019. Crosswalk analysis was done using MR-BRT, instead of the previously used penalized spline regressions. The MAD outliering technique was newly incorporated, allowing

implausible utilization estimates in the input data to be systematically identified prior to modeling. Finally, the all-cause mortality covariate was excluded from the ST-GPR model. These changes collectively resulted in more robust estimates of inpatient utilization across GBD demographics. The source code for MR-BRT is publicly available on GitHub as the Python package `mrtool` (ihmeuw-msca, 2023). The `mrtool` package builds upon the open source mixed effects package `LimeTr` (<https://github.com/zhengp0/limetr>).

Section 5.6: DisMod-MR 2.1

Incidence for cause-of-injury categories was modelled using the Bayesian meta-regression method DisMod-MR 2.1. Separate DisMod-MR 2.1 were used to meta-analyse the data for the proportions of cases with different severity levels or sequelae. This computational engine has been developed since GBD 2010, and substantial improvements have refined it since. The DisMod-MR 2.1 runs a sequence of estimation at five levels: global, super-region, region, country, and, where applicable, subnational location. Each subsequent level is informed by the upper level with mixed-effects, non-linear regression by using all available data. The country-level covariate for injuries was Socio-demographic Index (SDI). In data-sparse locations, the coefficients of parent location levels were used to utilize the predictive power of the covariates.

DisMod-MR 2.1 can be run using Gaussian, log-Gaussian, Laplace, or Log-Laplace likelihood functions. The default log-Gaussian equation is as follows:

$$-\log[p(y_j|\Phi)] = \log(\sqrt{2\pi}) + \log(\delta_j + s_j) + \frac{1}{2} \left(\frac{\log(a_j + \eta_j) - \log(m_j + \eta_j)}{\delta_j + s_j} \right)^2$$

Where:

y_j is a measurement value (ie. datapoint)

Φ denotes all model random variables

η_j is the offset value for a particular "integrand" (prevalence, incidence, remission, excess mortality rate, with-condition mortality rate, cause-specific mortality rate, relative risk, or standardized mortality ratio)

a_j is the adjusted measurement for datapoint j , and is defined by:

$$a_j = e^{(-u_j - c_j)} y_j$$

Where:

u_j is the total area effect (ie. the sum of the random effects at three levels of the cascade: super-region, region, and country)

c_j is the total covariate effect (ie. the mean combined fixed effects for sex, study-level, and country-level covariates), and is defined by:

$$c_j = \sum_{k=0}^{K[I(j)]-1} \beta_{I(j),k} \hat{X}_{k,j}$$

with standard deviation:

$$s_j = \sum_{l=0}^{L[I(j)]-1} \zeta_{I(j),l} \hat{Z}_{l,j}$$

Where:

k denotes the mean value of each datapoint in relation to a covariate (also called x-covariate)

$I(j)$ denotes a datapoint for a particular integrand, j

$\beta_{I(j),k}$ is the multiplier of the k^{th} x-covariate for the l^{th} integrand

$\hat{X}_{k,j}$ is the covariate value corresponding to the datapoint j for covariate k

l denotes the SD of each datapoint in relation to a covariate (also called z-covariate)

$\zeta_{I(j),l}$ is the multiplier of the l^{th} z-covariate for the l^{th} integrand

δ_j is the SD for adjusted measurement j , and is defined by

$$\delta_j = \log[y_j + e^{(-u_j - c_j)} \eta_j + c_j] - \log[y_j + e^{(-u_j - c_j)} \eta_j]$$

Where m_j denotes the model for the j^{th} measurement, not counting effects or measurement noise and is defined by:

$$m_j = \frac{1}{B(j) - A(j)} \int_{A(j)}^{B(j)} I_j(a) da$$

Where:

$A(j)$ is the lower bound of the age range for a datapoint j

$B(j)$ is the upper bound of the age range for a datapoint j

$I(j)$ denotes the function of age corresponding to the integrand for datapoint j

For age-splitting, DisMod-MR 2.1 estimated countries' age-pattern using all data disaggregated by age. This procedure was done by calculating the constant, k , as follows:

$$k = \frac{\mu_{all\ age}}{\hat{\mu}}$$

Where:

$\mu_{all\ age}$ is the aggregated all-age data point

$\hat{\mu}$ is the all-age estimated utilization rate

The constant, k , was multiplied by age-specific utilization rates from the DisMod-MR 2.1 to split aggregated age data into granular age groups. Datapoints that did not follow the expected age or time pattern or plausibility as expected based on subject-matter or in-country expert opinion were marked as outliers. Points that were three median absolute deviation points above the age-

standardized mean utilization for each sex-location-year-source combination were also marked as outliers.

In addition to causes, the age-sex-location-year prevalence of nine impairments was modeled. Impairments are conditions or specific areas of functional health loss that span across numerous GBD causes as sequelae, and for which there are better data available to estimate the occurrence of the impairment rather than estimating each sequelae based on the underlying cause. The nine impairments are: anaemia, epilepsy, hearing loss, heart failure, intellectual disability, infertility, vision loss, Guillain-Barré syndrome, and pelvic inflammatory disease. The individual sequelae prevalence values were squeezed or inflated so that their sums fit the appropriate impairment envelope.

Prior to incidence modeling using DisMod-MR 2.1, ST-GPR was used to smooth input data over age-location-year to produce estimates for every age-sex-location-year combination. The following three covariates were used for every location: the natural log of hospital beds per 1000, the natural log of health expenditure per capita, and the HAQ Index. ST-GPR assumes that the trend of interest follows a Gaussian process, defined by a mean function and a covariance function. Random draws of 1000 samples were obtained, the final estimated mean of which was the mean of the draws. 95% UIs were calculated by taking the 2.5 and 97.5 percentile of the sample distribution.

Section 5.7: Severity distribution and disability weights

YLDs were calculated by multiplying the number of people living with a particular health outcome by a disability weight (DW) and by the duration of the outcome. DWs represent the degree of health loss associated with the particular health outcome on a scale from 0 to 1; with 0 implying full

health and 1 equivalent to death. For injuries, the health outcome was linked to nature-of-injury rather than cause-of-injury, as the physical injury sequelae were more closely linked to actual health loss. As multiple sequelae can occur due to a single cause-of-injury, a nature-of-injury category hierarchy was constructed. This hierarchy was created using a pooled dataset of six follow-up studies from China, the Netherlands, and the US, as well as the Medical Expenditure Panel Survey (MEPS). All patient-reported outcome measures were standardized, then mapped to corresponding disability weights. A regression of logit-transformed disability weight on nature-of-injury category, age group, and never-injured status was run to calculate the mean long-term disability attributable to each nature-of-injury category. For each case, the nature-of-injury category with the largest burden was selected so that a one-to-one relationship between cause and nature-of-injury was formed. Hierarchies for inpatient and outpatient injuries were developed separately.

Cause-nature matrices were generated to map the proportion of nature-of injury categories that occur as a result of each cause-of-injury, and were developed from dual-coded hospital and emergency department datasets. Dirichlet models were used to estimate the proportion of nature-of-injury categories for one cause of injury simultaneously, allowing for consistent borrowing of information across age-sex, inpatient/outpatient, and high/low-income countries, and asserting that the nature-of-injury proportions for each cause add up to one. By applying these matrices to the cause-of-injury incidence from DisMod-MR 2.1., cases were disaggregated into injuries warranting hospital admission (inpatient injuries) and injuries warranting other health care (outpatient injuries), thus allowing disabilities weights to be applied separately.

The pooled dataset of six follow-up studies and MEPS, used to generate the nature-of-injury category hierarchies, were also used to assess the probability of developing permanent

health loss. Health loss due to injury was assumed to affect all cases in the short-term, with a proportion of these cases developing long-term (permanent) outcomes. The probability of developing long-term health loss was calculated using a logit-linear mixed effects regression, including dummies for all nature-of-injury categories, $injuries_{im}$, as well as the reference category, never injured_{*i*}:

$$\begin{aligned} \text{Logit}(DW)_{im} = & \alpha + \beta(injuries_{im}) + \beta(\text{never injured}_i) + \beta(\text{never injured}_i * age_i) \\ & + \beta(\text{fracture of pelvis}_i) + \beta(\text{fracture of pelvis}_i * age_i) + \beta(\text{poisoning}_i \\ & * age_i) + \beta(\text{moderate to severe TBI}_i * age_i) + RE_c + RE_i \end{aligned}$$

Where:

m refers to patient-reported outcome measure

i refers to individual

c refers to country

RE refers to random effects, controlling for variation

The difference between our counterfactual of no injury and predicted disability with injury at one-year post-injury was assumed to be the disability attributable to the nature of injury at one year. The ratio of this attributable disability relative to the long-term disability weight for that injury was calculated as the probability of long-term outcomes. These probabilities for inpatient and outpatient injuries were developed separately, each stratified by nature-of-injury and age. For cases in which disability persisted after one-year, disability was assumed to be permanent until death. The durations of short-term outcomes were determined by analyzing patient responses from two Dutch Injury Surveillance System follow-up studies and expert-driven estimates. The durations of short-term injuries were calculated separately for inpatient and outpatient injuries.

For many nature-of-injuries, a separate disability weight was estimated for treated and untreated cases. The percent of treated injuries, for a given location-year, was calculated using the HAQ Index. A cut-off of 75 was chosen as the threshold at and above which 100% of injuries were treated. The percent of treated injuries for all remaining location-years were scaled between 10% and 100% treated based on their respective HAQ Index score. For short-term injury outcomes, lasting less than one year, the prevalence for each cause-of-injury/nature-of-injury/severity-level grouping was approximated by multiplying the incidence by the specific duration associated with the nature of the injury and severity level. For long-term health loss, it was assumed that there was no remission and incidence was integrated over time to estimate prevalence. This integration was carried out using DisMod-MR code for each combination of cause and nature-of-injury by sex-location-year.

Section 5.8: Comorbidity Correction (COMO)

Comorbidity, the co-occurrence of different diseases, was adjusted for using a micro-simulation process as "COMO". Comorbidity was computed by simulating 20,000 individuals in each age-sex-location-year combination, exposed to the independent probabilities of having each of the sequelae included in GBD based on prevalence. Independent comorbidity was found to be the dominant factor, despite well-known examples of dependent comorbidity. Each individual was determined to have or not have the disease sequelae based on a draw from a binomial distribution, and ended up with 0 to the theoretical maximum of acquired disease sequelae. The DWs of each simulated individual was estimated based on the acquired disease sequelae, apportioning the overall DWs to each condition in proportion to the DWs of each condition in isolation.

Section 5.9: YLD computation

YLDs for each age-sex-location-year were estimated by taking the sum of the attributable DWs for a disease sequela across simulated individuals. The uncertainty in the prevalence of each disease sequela and uncertainty in the associated disability weights were incorporated into the comorbidity-corrected YLD results. This simulation process for each age-sex-location-year was repeated 500 times, producing 500 sample of comorbidity-corrected YLDs and 500 samples of DWs. It was assumed that there was no correlation in the uncertainty in prevalence and DWs. The 95% uncertainty interval was reported as the 0.025 and 0.975 quantile values of the distribution.

The uncertainty intervals for YLDs at various time points (1990, 1995, 2000, 2005, 2010, 2015, 2020, and 2021) for a given disease or sequela are correlated due to the shared uncertainty in DW, and DW draws are not specific to years. Consequently, changes in YLDs over time may be significant even if the uncertainty intervals of the two YLD estimates mostly overlap, as prevalence uncertainty intervals are utilized to assess the significance of changes in YLDs over time since DW draws are not specific to years.

Section 6: Socio-demographic index (SDI)

Section 6.1: SDI definition

The SDI serves as a composite measure reflecting the social and economic conditions that impact health outcomes in various locations. Specifically, the SDI is calculated as the geometric mean of three indices: the total fertility rate (TFR) for individuals under 25 years of age (TFU25), the mean years of education for those aged 15 and older (EDU15+), and lag-distributed income (LDI) per capita. For the GBD 2021, the calculated SDI values were scaled by multiplying by 100, resulting in a range from 0 to 100.

Section 6.2: SDI calculation

For each covariate input, an index score of 0 indicates the minimum level of that input beyond which selected health outcomes cannot worsen, while an index score of 1 signifies the maximum level beyond which selected health outcomes no longer improve. As a composite measure, a location with an SDI of 0 represents the theoretical minimum level of sociodemographic development relevant to these health outcomes, whereas an SDI of 1 (prior to scaling by 100 for reporting) indicates the theoretical maximum level of sociodemographic development pertinent to these health outcomes.

We computed the index scores underlying SDI as follows:

$$I_{cly} = \max\left(\frac{C_{ly} - C_{low}}{C_{high} - C_{low}}, 0.005\right)$$

Where:

I_{cly} is the index for covariate C , location l , and year y and is equal to the difference between the value of that covariate in that location-year and the lower bound of the covariate divided by the difference between the upper and lower bounds for that covariate.

When the values of input covariates fell outside the established upper or lower bounds, they were adjusted to correspond to the respective bounds. It is important to note that the index value for TFU25 was calculated as $(1 - I_{TFU25})$, as lower TFU25 values are indicative of higher levels of development, resulting in higher index scores. For the GBD 2021, the computation of the SDI was expanded to encompass 1075 national and subnational locations over the period from 1950 to 2021.

The composite SDI for each location-year is determined as the geometric mean of the three indices. To establish quintile cut-off values for analysis, country-level estimates of SDI for the year 2019 were utilized, excluding countries with populations of less than 1 million. For GBD 2021, the final SDI values were scaled by multiplying by 100 for reporting purposes, thereby enhancing comprehension and facilitating broader engagement with the values. Consequently, the SDI for GBD 2021 was calculated in the same manner as in 2019, with the final multiplication by 100 applied at the end (refer to the example calculation below). The reported values are presented on a scale from 0 to 100.

Section 7: Mortality-incidence ratio

Section 7.1: Definition of mortality-incidence ratios

The mortality-incidence ratios (MIRs) is a widely recognized epidemiological metric that quantifies the proportion of deaths among incident cases of a particular disease or condition within a defined population. Conceptually, MIRs serve as a surrogate marker for case fatality at the population level, and has been employed extensively to monitor disease lethality, assess healthcare system responsiveness, and evaluate temporal trends in clinical outcomes.

In the context of AEMT—a class of iatrogenic outcomes considered fully preventable—MIRs offer a valuable indicator of healthcare safety and quality. A high MIRs imply that a substantial fraction of individuals experiencing AEMT die as a result, potentially reflecting failures in timely diagnosis, escalation of care, or clinical management. In contrast, low MIRs may indicate effective surveillance, prompt intervention, and robust post-treatment monitoring systems. Unlike static mortality or incidence rates, MIRs is a dynamic parameter that varies over time and across settings, influenced by multiple determinants including the pharmacological agent or procedure involved, patient comorbidities, healthcare infrastructure, and treatment adherence. As such, it provides a more nuanced and comparative lens through which to assess health system performance across diverse populations.

Section 7.2: Mortality-incidence ratios calculation

The MIR was calculated as the ratio of deaths to incident cases of AEMT, stratified by country, year, age group, and sex, using data from the GBD 2021 study. The MIR was computed using the following formula:

$$\mathbf{MIR}_{l,y,g,s} = \frac{D_{l,y,g,s}}{I_{l,y,g,s}}$$

Where:

- ... $\mathbf{MIR}_{l,y,g,s}$ represents the mortality-incidence ratio for location l , year y , age group g , and sex s ;
- ... D is the number of deaths attributable to AEMT;
- ... I is the number of incident AEMT cases.

This dimensionless ratio provides a population-level estimate of the fatality burden relative to disease occurrence. A higher MIR suggests that a greater proportion of individuals experiencing AEMT died as a result, potentially reflecting suboptimal treatment safety, delays in clinical response, or systemic limitations in managing iatrogenic harm. Conversely, a lower MIR may indicate early detection, effective management, or robust healthcare safety protocols.

Importantly, MIR values were not expressed as percentages, but rather as unitless ratios ranging from 0 to 1. This approach preserves interpretability and comparability across demographic strata. MIR estimates were further stratified by HAQ age bands (0–14, 15–64, 65–74 years) to align with the Health Access and Quality Index framework and facilitate correlation analyses with system-level performance indicators.

Section 8: Healthcare Access and Quality Index

Section 8.1: Overview

The HAQ Index is a comprehensive metric designed to evaluate personal health-care access and quality across diverse regions. Building on the GBD 2019, the HAQ Index was assessed both overall and for three select age groups: young (0–14 years), working age (15–64 years), and post-working age (65+ years), across 204 locations from 1990 to 2021. Recent refinements include adding new systematic reviews for risk–outcome pairs, enabling a more detailed and accurate representation of conditions where health-care access and quality are critical. These enhancements improve the index’s ability to identify areas requiring targeted health system interventions. Detailed methodological explanations of these advancements are provided elsewhere.[1]

Section 8.2: Utilizing HAQ index

HAQ Index Construction

The HAQ Index is constructed using age-specific mortality-to-incidence ratios (MIR) and risk-standardized death rates (RSDR), adjusted by adding an offset of one death per million to address cases of zero values in specific age-cause combinations. All RSDR and MIR values were log-transformed and scaled using the 1st and 99th percentiles, with 0 representing the worst outcomes and 100 the best. These calculations were performed separately for all estimates, countries, and years across 32 causes and four HAQ age groups. The HAQ Index captures performance differences by presenting the values for the best and worst performers in each group, conceptualizing health system performance relative to these benchmarks for 1990–2019. Differences in scaling for each group ensure that varying outcomes across age groups do not distort representation of health-care access and quality.

Section 8.3: 2021 HAQ estimates via linear interpolation and extrapolation

To estimate the HAQ Index for 2021, linear interpolation and extrapolation methods were applied based on values from 1990 to 2019. Linear interpolation was used to estimate missing data points within this range, while extrapolation extended the trends observed in 1990–2019 to predict values for 2021. The estimation formula used for extrapolation was:

$$HAQ_{2021} = HAQ_{2019} + \frac{HAQ_{2019} - HAQ_{1990}}{2019 - 1990} \times (2021 - 2019)$$

Where:

- HAQ_{1990} is the value of the HAQ index in 1990.
- HAQ_{2019} is the value of the HAQ index in 2019.
- The slope term $\frac{HAQ_{2019} - HAQ_{1990}}{2019 - 1990}$ represents the annual rate of change over the period.

The same approach was applied to the upper and lower bounds (e.g., $upper_{2021}$, $lower_{2021}$) to ensure consistency in uncertainty ranges. This methodology ensures continuity and comparability of HAQ Index values while extending insights into health-care system performance through 2021. By relying on observed trends and leveraging interpolation and extrapolation, this approach provides a robust framework for projecting health-care access and quality into recent years.

Age groupings

This study builds on prior research by extending the analysis of the HAQ Index to examine variations in health-care access and quality across different stages of life. Specifically, it addresses two primary questions: (1) how does health-care access and quality differ by age group, and (2) to

what extent does convergence or divergence occur over time across age groups? To answer these questions, the HAQ Index was computed separately for three distinct age groups: young (0–14 years), working age (15–64 years), and post-working age (65–74 years). These groupings align with the Organisation for Economic Co-operation and Development definition of the working-age population (15–64 years) and the upper age limit of 75 years identified by Nolte and McKee for amenable mortality.[2]

In addition to the overall HAQ Index (ages 0–74 years), these age groupings were chosen to reflect the unique dynamics of health-care access and quality across the life course. The working-age group captures access tied to employment and economic activity, while the post-working age group highlights health-care access linked to social health insurance and aging-related needs. The young group focuses on access to and quality of child health care. The age cap at 75 years ensures consistency with Nolte and McKee's framework, which identifies deaths beyond this age as less amenable to health-care interventions.

Section 9: Author's Contributions

Providing data or critical feedback on data sources

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