THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Cieza A, Causey K, Kamenov K, Hanson SW, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; published online Dec 1. http://dx.doi.org/10.1016/S0140-6736(20)32340-0.

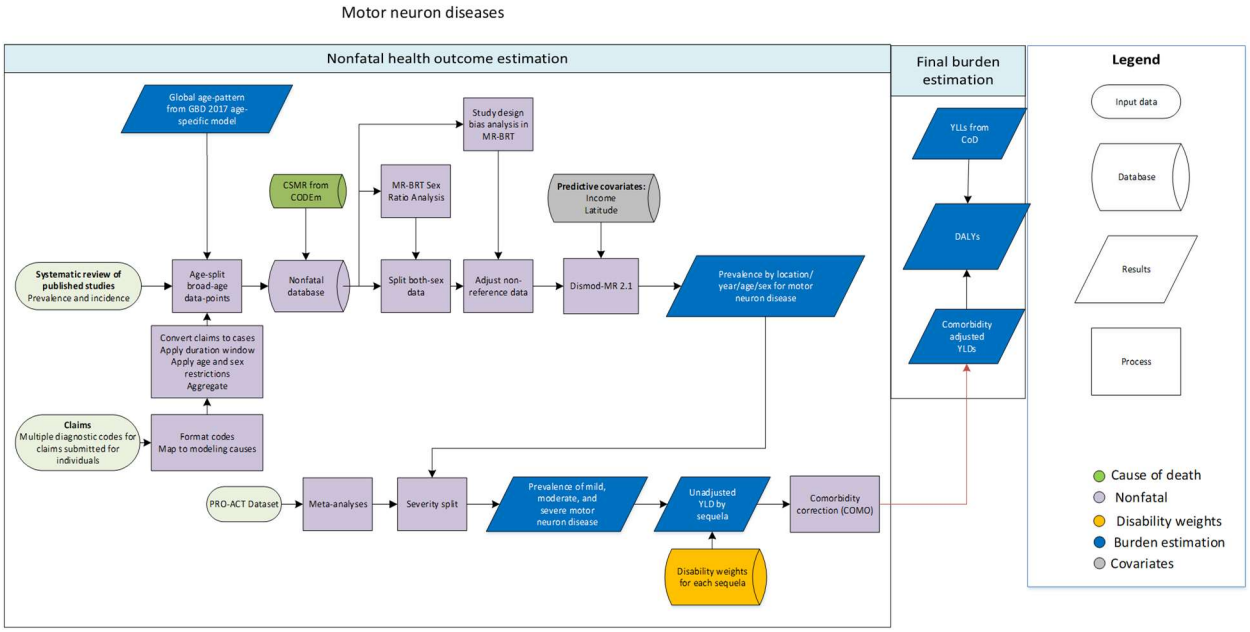
Appendix

Search string used in PubMed to identify systematic review or meta-analysis quantifying the need of rehabilitation services:

Search: ((((((estimation[Title/Abstract]) OR (prediction[Title/Abstract])) OR ("needs assessment"[Title/Abstract])) OR (prevalence[Title/Abstract])) AND (rehabilitation[Title/Abstract])) OR ("rehabilitation need*"[Title/Abstract])) OR ("rehabilitation service*"[Title/Abstract]) Filters: Meta-Analysis, Review, Systematic Reviews, from 1980 – 2019
Total number of hits: 1481

Motor neuron diseases

Flowchart



Case definition

Motor neuron diseases (MND) are a set of chronic, degenerative, and progressive neurological conditions typified by the destruction of motor neurons and the subsequent deterioration of voluntary muscle activity. The most common MND is amyotrophic lateral sclerosis (ALS). The El Escorial Criteria are the gold standard diagnostic criteria. The ICD-10 code corresponding to motor neuron diseases is G12.

Input data and data processing

A full systematic review was last conducted for GBD 2015 and will be updated in a future round of GBD. The following search string guided our search, which resulted in 3,146 hits with 58 sources meeting extraction criteria: (1) the study is a representative population-based study with well-defined sample, (2) reports on prevalence, incidence, remission, excess mortality, relative risk of mortality, standardised mortality ratio, or with-condition mortality rate for motor neuron diseases in aggregate or a specified motor neuron disease.

(('motor neuron disease'[MeSH Terms] OR ('motor'[All Fields] AND 'neuron'[All Fields] AND 'disease'[All Fields]) OR 'motor neuron disease'[All Fields] OR ('motor'[All Fields] AND 'neuron'[All Fields] AND 'diseases'[All Fields]) OR 'motor neuron diseases'[All Fields]) OR ('amyotrophic lateral sclerosis'[MeSH Terms] OR ('amyotrophic'[All Fields] AND 'lateral'[All Fields] AND 'sclerosis'[All Fields]) OR 'amyotrophic lateral sclerosis'[All Fields]) OR ALS[All Fields] OR ('motor neuron disease'[MeSH Terms] OR ('motor'[All Fields] AND 'neuron'[All Fields] AND 'disease'[All Fields]) OR 'motor neuron disease'[All Fields] OR ('primary'[All Fields] AND 'lateral'[All Fields] AND 'sclerosis'[All Fields]) OR 'primary lateral sclerosis'[All Fields]) OR ('Politics Life Sci'[Journal] OR 'pls'[All Fields]) OR ('muscular atrophy, spinal'[MeSH Terms] OR

('muscular'[All Fields] AND 'atrophy'[All Fields] AND 'spinal'[All Fields]) OR 'spinal muscular atrophy'[All Fields] OR ('progressive'[All Fields] AND 'muscular'[All Fields] AND 'atrophy'[All Fields]) OR 'progressive muscular atrophy'[All Fields]) OR PBP[All Fields] OR ('pseudobulbar palsy'[MeSH Terms] OR ('pseudobulbar'[All Fields] AND 'palsy'[All Fields]) OR 'pseudobulbar palsy'[All Fields])) AND (('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'epidemiology'[MeSH Terms]) OR population-based[All Fields])

Data from the systematic review were manually extracted for GBD 2015. For GBD 2017, data-points referring to broad age-groups were split according to the age-pattern estimated for that datum's location in a preliminary model that used only age-specific data. For GBD 2019, all previously extracted studies were reviewed and assigned a design variable to indicate if the case definition was limited to ALS only or encompassed all MND.

Beyond data from the systematic review, as in previous rounds of GBD, we made use of claims data as obtained and processed by the GBD Clinical Informatics team and described in a separate section of this Appendix. These data link claims for all inpatient and outpatient encounters for a single individual, and provide primary and secondary diagnoses for all encounters. An individual was extracted from claims data as a prevalent case if they had any MND code as any diagnosis in one or more inpatient encounters or two or more outpatient encounters. New data added in GBD 2019 included Polish claims and additional years of USA claims (years 2015-2016).

Total sources used for modeling in GBD 2019 are listed in the table below:

Measure	Total sources	Countries with data
All measures	73	18
Prevalence	24	1
Incidence	48	18
Proportion	1	1

In GBD 2019, all sex-specific data were used to estimate a pooled sex-ratio using MR-BRT. This ratio was combined with sex-specific population estimates for the year-age-location combinations corresponding to each data point reported for both sexes combined, to estimate sex-specific data-points prior to modeling. These were applied by calculating male prevalence:

$$prev_{male} = prev_{both} * \frac{pop_{both}}{(pop_{male} + ratio * pop_{female})}$$

and then calculating female prevalence:

$$prev_{female} = ratio * prev_{male}$$

(Or the equivalent equations for incidence or other epidemiologic measure.)

Two pre-modeling adjustments were then made adjust for systematic biases in some data sources: data reporting on ALS only and data from USA claims in the year 2000 (a database that only covers a small commercially insured sub-population). Two studies of ALS only were found to be closely matched in year, age, sex and time with three studies of MND more broadly, and the log-ratios for all matched pairs

were entered into an MR-BRT meta-analysis. Commercial claims data from the USA in 2000 were matched to USA claims data from later years with more complete coverage of the population, and these log-ratios were entered into a separate MR-BRT model.

MR-BRT Crosswalk Adjustment Factors

Data input	Reference or alternative case definition	Beta Coefficient, Log (95% CI)	Adjustment factor*
Surveys of all MND using combined clinical, imaging, electrophysiology and imaging criteria OR Claims data from location-years other than USA 2000	Ref	---	---
USA claims from year 2000	Alt	-0.026 (-1.2 to 1.1)	0.97 (0.31 to 3.1)
Surveys limited to ALS only	Alt	-0.13 (-0.23 to -0.029)	0.88 (0.79 to 0.97)

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

After extraction and processing, some studies were marked as outliers and excluded on a case-by-case basis if they were inconsistent with established regional or temporal trends or if concerns about study quality were identified during extraction and processing.

Modelling strategy

We use DisMod 2.1 as the main analytical tool for MND estimation. Inputs included prevalence and incidence data, as described above, as well as the cause-specific mortality rate (CSMR) estimated in the GBD causes of death analysis, and excess mortality rate (EMR) obtained by dividing CSMR by prevalence data-points. Prior settings are limited to 0 remission at all ages and maximum incidence of 0.0004. We also constrain the super-region random effects for prevalence and incidence to -0.5 and 0.5 to account for spurious inflation of regional differences.

We employed the following covariates to improve model predictions:

Covariate	Measure	Beta coeff (95% CI)	Exponentiated
Absolute value of average latitude	Prevalence	0.032 (0.031 to 0.033)	1.03 (1.03 to 1.03)
LDI (I$ per capita)	Excess mortality rate	-0.5 (-0.5 to -0.5)	0.61 (0.61 to 0.61)

Although there are no known cures for MND, we expect disease management to differ globally – largely as a function of available resources. To capture this, we use the natural log of lagged distributed income per capita as a proxy to capture this relationship in the estimation of excess mortality.

As described in the literature, extreme latitude may be associated with higher prevalence and incidence of motor neuron disease, although the pathway to explain the association is not understood. Our

operationalisation of latitude is created by a population-weighted average of latitude by country and taking the absolute value. The underlying population distribution rasters are part of the Gridded Population of the World dataset.

Severity splits

To calculate severity and disability due to MND we analysed a dataset from Pooled Resource Open-access ALS Clinical Trials (PRO-ACT). This dataset contains the largest ALS clinical trials dataset, with a total of 8,635 ALS patient records from multiple completed clinical trials. Among these, we conducted the final analysis with n=4838 (56%) of the patients with complete ALS Function Rating Score (ALSFRS) with average follow-up time of 184 days (min: -22, max: 648), in which 2,999 (62%) received experimental (medication) treatments and 1,301 (27%) received placebo (in these trials, the medications tested were found to be no better than placebo with respect to their effects on ALS progressions).

The ALSFRS is an instrument for evaluating the functional status of patients with amyotrophic lateral sclerosis. It can be used to monitor functional changes in a patient over time. It measures (1) speech, (2) salivation, (3) swallowing, (4) handwriting, (5) cutting food and handling utensils (with or without gastrostomy), (6) dressing and hygiene, (7) turning in bed and adjusting bed clothes, (8) walking, (9) climbing stairs, and (10) breathing. Each task is rated on a 5-point scale from 0 = can't do, to 4 = normal ability. Individual item scores are summed to produce a reported total score of between 0 and 40 (worst to best). ALSFRS has been revised to ALSFRS-R, which includes 12 questions (ALSFRS Q10 changes to (10) Dyspnea, (11) Orthopnea, and (12) Respiratory insufficiency), with individual item scores summed to a score between 0 and 48.

In order to eliminate any bias from the treatment effects on the ALSFRS, only the first observation at the time of trial is selected. If the first observation is missing at the time of trial (or prior), the next non-missing observation is selected to be included in the final analysis.

We subsequently mapped ALSFRS scores into GBD severities, and sequelae into different combinations of speech problems, chronic obstructive pulmonary disease, and motor impairment using the following logic:

Motor impairment

The ALSFRS assess motor function of the legs through questions on walking (Q8) and stair climbing (Q9).

Combined score	Severity level
8	None
5-7	Mild
2-4	Moderate
0-1	Severe

The ALSFRS also assesses motor impairment through questions on handwriting (Q4), cutting food and handling utensils (Q5), and dressing and hygiene (Q6).

Combined score	Severity level
12	None
9-11	Mild

3-8	Moderate
0-2	Severe

After determining case severity on these two separate metrics, we aggregate by taking the most severe ranking (eg, severe + mild = a severe case).

Respiratory problems:

Question 10 of the ALSFRS describes breathing difficulty as a function of MND.

ALSFRS score	Description	Severity level
4	Normal	None
3	Shortness of breath with minimal exertion	Mild
2	Shortness of breath at rest	Moderate
0-1	Intermittent ventilator assistance required/ventilator-dependent	Severe

Speech problems

Speech impairment due to MND is derived from ALSFRS question 1, which describes speech impediments. A score of 4 on this question denotes no impairment, while all other values suggest some impairment.

Creating sequelae

After determining the severity status of each case for the three symptom umbrellas, we subsequently estimated the relative proportion of each combination of symptom class and their respective severities. Those without any symptoms (eg, no severity) were categorised as having worry about the diagnosis for disability estimation. The following table displays the various sequelae and their associated proportions.

Sequela	Proportion (Mean)	Proportion (Lower)	Proportion (Upper)
Mild motor impairment, mild respiratory problems and speech problems due to motor neuron disease	0.01779	0.01658	0.01909
Mild motor impairment, moderate respiratory problems and speech problems due to motor neuron disease	0.00270	0.00225	0.00324
Mild motor impairment, severe respiratory problems and speech problems due to motor neuron disease	0.00082	0.00059	0.00113
Mild motor impairment, and speech problems due to motor neuron disease	0.02052	0.01922	0.02190
Moderate motor impairment, mild respiratory problems and speech problems due to motor neuron disease	0.03377	0.03210	0.03552
Moderate motor impairment, moderate respiratory problems and speech problems due to motor neuron disease	0.00715	0.00640	0.00799
Moderate motor impairment, severe respiratory problems and speech problems due to motor neuron disease	0.00286	0.00240	0.00342

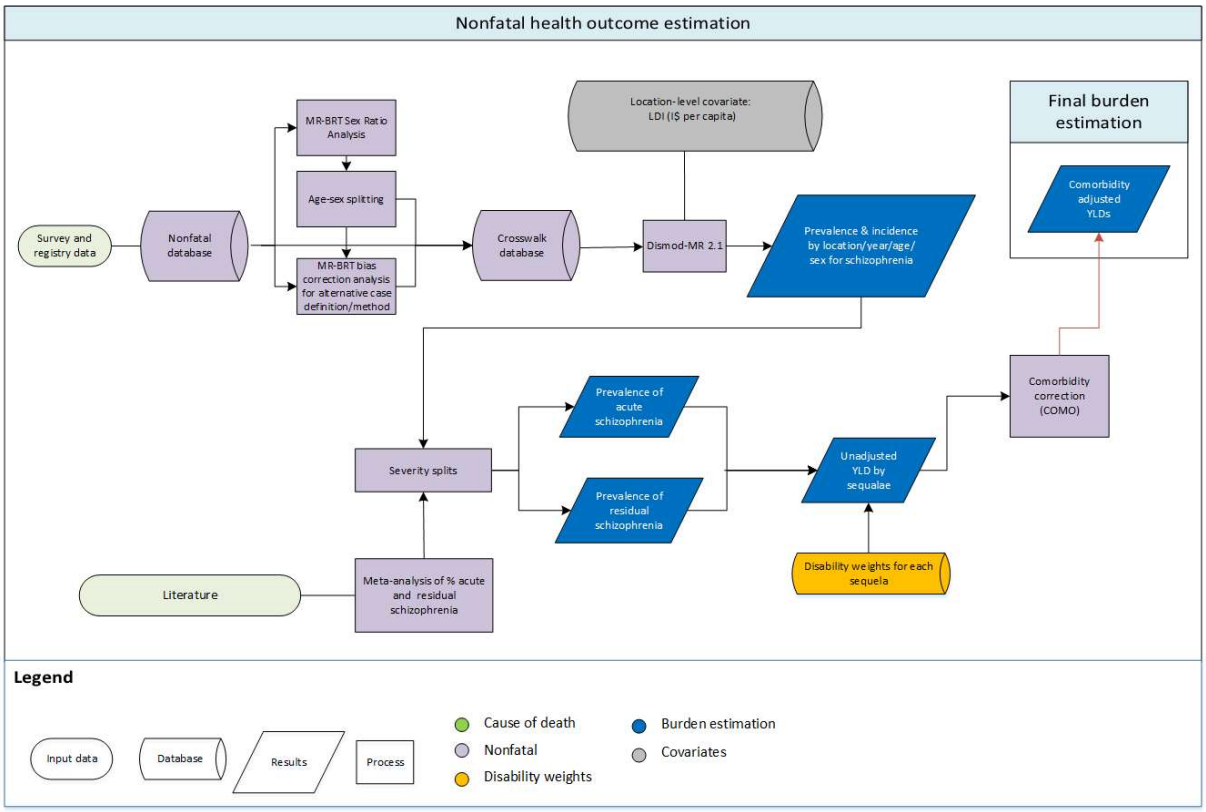
Moderate motor impairment, and speech problems due to motor neuron disease	0.03041	0.02883	0.03208
Severe motor impairment, mild respiratory problems and speech problems due to motor neuron disease	0.05242	0.05035	0.05457
Severe motor impairment, moderate respiratory problems and speech problems due to motor neuron disease	0.02247	0.02111	0.02392
Severe motor impairment, severe respiratory problems and speech problems due to motor neuron disease	0.01365	0.01259	0.01479
Severe motor impairment and speech problems due to motor neuron disease	0.04765	0.04567	0.04970
Mild respiratory problems and speech problems due to motor neuron disease	0.01157	0.01060	0.01263
Moderate respiratory problems and speech problems due to motor neuron disease	0.00142	0.00111	0.00182
Severe respiratory problems and speech problems due to motor neuron disease	0.00023	0.00013	0.00043
Speech problems due to motor neuron disease	0.02457	0.02315	0.02608
Mild motor impairment and mild respiratory problems due to motor neuron disease	0.02245	0.02109	0.02389
Mild motor impairment and moderate respiratory problems due to motor neuron disease	0.00275	0.00230	0.00329
Mild motor impairment and severe respiratory problems due to motor neuron disease	0.00068	0.00047	0.00097
Mild motor impairment due to motor neuron disease	0.10388	0.10103	0.10681
Moderate motor impairment and mild respiratory problems due to motor neuron disease	0.06744	0.06511	0.06985
Moderate motor impairment and moderate respiratory problems due to motor neuron disease	0.01302	0.01199	0.01413
Moderate motor impairment and severe respiratory problems due to motor neuron disease	0.00412	0.00356	0.00477
Moderate motor impairment due to motor neuron disease	0.20136	0.19760	0.20518
Severe motor impairment and mild respiratory problems due to motor neuron disease	0.06902	0.06666	0.07146
Severe motor impairment and moderate respiratory problems due to motor neuron disease	0.02000	0.01872	0.02137
Severe motor impairment and severe respiratory problems due to motor neuron disease	0.01062	0.00969	0.01163
Severe motor impairment due to motor neuron disease	0.15037	0.14702	0.15378
Mild respiratory problems due to motor neuron disease	0.00643	0.00571	0.00723
Moderate respiratory problems due to motor neuron disease	0.00044	0.00028	0.00069
Severe respiratory problems due to motor neuron disease	0.00005	0.00001	0.00017
Asymptomatic, but worry about diagnosis due to motor neuron disease	0.03738	0.03562	0.03921

To determine disability due to these sequelae, we use the standard multiplicative aggregation formula as described in the main text. The following table provides description and disability weight assigned to the sequelae as appropriate.

Symptom group	Severity level	Lay description	DW (95%)
Respiratory problems	Asymptomatic		
Respiratory problems	Mild	Has cough and shortness of breath after heavy physical activity, but is able to walk long distances and climb stairs.	0.019 (0.011–0.033)
Respiratory problems	Moderate	Has cough, wheezing, and shortness of breath, even after light physical activity. The person feels tired and can walk only short distances or climb only a few stairs.	0.225 (0.153–0.31)
Respiratory problems	Severe	Has cough, wheezing, and shortness of breath all the time. The person has great difficulty walking even short distances or climbing any stairs, feels tired when at rest, and is anxious.	0.408 (0.273–0.556)
Motor impairment	Asymptomatic		
Motor impairment	Mild	Has some difficulty in moving around but is able to walk without help.	0.01 (0.005–0.019)
Motor impairment	Moderate	Has some difficulty in moving around and difficulty in lifting and holding objects, dressing, and sitting upright, but is able to walk without help.	0.061 (0.04–0.089)
Motor impairment	Severe	Is unable to move around without help, and is not able to lift or hold objects, get dressed, or sit upright.	0.402 (0.268–0.545)
Speech problems	No		
Speech problems	Yes	Has difficulty speaking, and others find it difficult to understand.	0.051 (0.032–0.078)
Asymptomatic, but worry	Yes	Has a disease diagnosis that causes some worry but minimal interference with daily activities.	0.012 (0.006–0.023)

Schizophrenia

Flowchart



Input Data and Methodological Summary for Schizophrenia

Case definition

Schizophrenia is a chronic psychotic disorder which involves the experience of positive symptoms (e.g., delusions, hallucinations, thought disorder) and negative symptoms (e.g., flat affect, loss of interest, and emotional withdrawal). Included in the GBD disease modelling were cases meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) diagnostic criteria for schizophrenia (DSM-IV-TR: 295.10-295.30, 295.60, 295.90; ICD 10: F20)[1, 2]. Diagnostic criteria are:

A. Two (or more) of the following, each present for a significant portion of time during a one-month period (or less if successfully treated): i) delusions, ii) hallucinations, iii) disorganised speech, iv) grossly disorganised or catatonic behavior, v) negative symptoms

B. Social/occupational dysfunction

C. Continuous signs of the disturbance persist for at least 6 months

D. Exclusions must be met for schizo-affective and mood disorders, substance and general medical conditions, and a relationship to a pervasive development disorder

Input data

The epidemiological systematic review for schizophrenia was conducted in three stages involving electronic searches of the peer-reviewed literature (i.e., PsycInfo, Embase, and PubMed), the grey literature, and expert consultation. For mental disorders, we update our GBD electronic database searches on a two year

rolling basis. A systematic review update for schizophrenia was conducted for GBD 2017 [3] , with the next literature update due for the next round of GBD. The grey literature, and expert consultation was conducted for GBD 2019 and produced new data sources. Consultation with GBD collaborators allowed us to include a large number of studies from Iranian journals which are typically not indexed in the electronic databases searched.

The GBD inclusion criteria stipulated that: (1) the publication year must be from 1980 onward; (2) "caseness" must be based on clinical threshold as established by the DSM or ICD; (3) sufficient information must be provided on study method and sample characteristics to assess the quality of the study; and (4) study samples must be representative of the general population (i.e., inpatient or pharmacological treatment samples, case studies, veterans, or refugee samples were excluded). No limitation was set on the language of publication. Table 1 below summarizes data inputs by parameter for schizophrenia.

Table 1: Data Inputs for schizophrenia morbidity modelling by parameter.

Measure	Total sources
All measures	203
Prevalence	142
Incidence	16
Remission	8
Relative risk	9
Standardized mortality ratio	34
With-condition mortality rate	5
Proportion	1

Age and sex splitting

The extracted data, where possible, underwent three types of age and sex splitting processes:

1. Estimates were further split by sex and age based on the data that was available. For instance, if studies reported prevalence for broad age groups by sex (e.g., prevalence in 15 to 65 year old males and females separately), and also by specific age groups but for both sexes combined (e.g., prevalence in 15- to 30-year-olds, then in 31- to 65-year-olds, for males and females combined); age-specific estimates were split by sex using the reported sex ratio and bounds of uncertainty.
2. A Meta-Regression with Bayesian priors, Regularization, and Trimming (MR-BRT) analysis was used to split the remaining both-sex estimates in the dataset. For each parameter, sex specific estimates were matched by location, age, year and a MR-BRT regression analysis was used to estimate pooled sex ratios and bounds of uncertainty. These were then used to split the both sex estimates in the dataset. The male: female prevalence ratio estimated was 1.17 (95% uncertainty interval [UI]: 0.60 – 1.75).
3. Studies reporting prevalence estimates across age groups spanning 25 years or more, were split into five-year age groups using the prevalence age pattern estimated by DisMod-MR 2.1. The DisMod-MR model used to estimate the age pattern did not contain any previously age split data.

Bias corrections / Crosswalks

Estimates with known and significant biases are typically adjusted / crosswalked prior to DisMod-MR 2.1. For schizophrenia, tested adjustments (e.g., the difference between 12-month vs point prevalence, or between registry- and community-based samples) failed to demonstrate significance, resulting in a model without the inclusion of adjustments.

Severity splits and disability weights

The GBD disability weight survey assessments are lay descriptions of sequelae highlighting major functional consequences and symptoms. The lay descriptions and disability weights for schizophrenia severity levels are shown in Table 2. Severity splits used in GBD 2019 were consistent with those used in GBD 2017 for schizophrenia. Information on the distribution of acute and residual states of schizophrenia was obtained from a separate systematic review of the literature[4] .Meta-XL (a Microsoft Excel add-in for meta-analysis) was used to pool estimates across all studies to calculate the overall proportion of schizophrenia cases in each health state acute 63% (29% – 91%) and residual state 37% (9% – 71%).

Table 2. Severity distribution for Schizophrenia in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% UI)
acute state	Hears and sees things that are not real and is afraid, confused, and sometimes violent. The person has great difficulty with communication and daily activities, and sometimes wants to harm or kill himself (or herself).	0.778(0.606 – 0.9)
residual state	Hears and sees things that are not real and has trouble communicating. The person can be forgetful, has difficulty with daily activities, and thinks about hurting himself (or herself).	0.588(0.411 – 0.754)

Modeling strategy

After the above data processes were applied, DisMod MR 2.1 was used to model the epidemiological data for Schizophrenia. The DisMod-MR modeling strategy for schizophrenia followed the standard GBD 2019 decomposition structure. At each decomposition step, we compared the new model against the GBD 2017 best model and the best model from the previous step. All substantial changes between models were explored and explained. Adjustments to model priors or the dataset were made where appropriate. Where outliers were identified in the data, we re-assessed the study's methodology and quality before a decision was made to exclude or include the data.

Data across all epidemiological parameters were initially included in the modelling process. We assumed no incidence before age 10 and after age 80. This minimum age of onset was corroborated with expert feedback and existing literature on schizophrenia. Remission was also restricted to a maximum of 0.04 as guided by data available in the dataset.

Location-level covariates were used to inform the estimation of prevalence in locations with no available data. For schizophrenia, one location-level covariate, lag distributed income (LDI), was used. This covariate represents a moving average of gross domestic product (GDP) over time. LDI was applied to excess mortality data with a negative relationship assumed. Table 3 below illustrates the covariate, parameter, beta and exponentiated beta values for the model.

Table 3. Summary of covariates used in the Schizophrenia DisMod-MR meta-regression model

Covariate	Type	Parameter	Exponentiated beta (95% UI)
LDI	Location-level	Excess mortality rate	0.58 (0.37 – 0.90)

Changes between GBD 2017 and GBD 2019

There were three main changes in the GBD 2019 modelling strategy compared to GBD 2017:

1. In GBD 2019 we updated the age splitting by regional pattern methodology by increasing the age threshold for splitting to 25 years (in GBD 2017 it was 20 years). This meant that there were fewer

estimates eligible for age splitting in this way. Previous age split estimates were on average lower than the global mean leading to an upward shift in prevalence in locations which now had fewer age-split estimates informing prevalence estimation.

4. In GBD 2017 sex ratios were estimated by DisMod-MR as part of the prevalence modelling. In GBD 2019 we conducted a MR-BRT analysis instead. The prevalence male: female ratio remained relative consistent from 1.02 (0.96 – 1.08) in GBD 2017 to 1.17 (0.60 – 1.75) in GBD 2019.
2. In GBD 2019 we included new epidemiological data from 22 locations which further informed the DisMod-MR model.

While we continue to improve on the data and methods used to estimate the burden of mental disorders, some challenges need to be acknowledged. Firstly, we still have a large number of locations with no high-quality raw data available. Secondly, it is difficult to quantify and remove all variation due to measurement error in our prevalence estimates. Whilst we have improved the methodology used to account for known sources of bias (e.g., survey methods or case definitions), we still have very few data points to inform such adjustments. Additionally, there is a paucity of research on the risk factors of mental disorders which can be used as predictive covariates in our epidemiological models.

References

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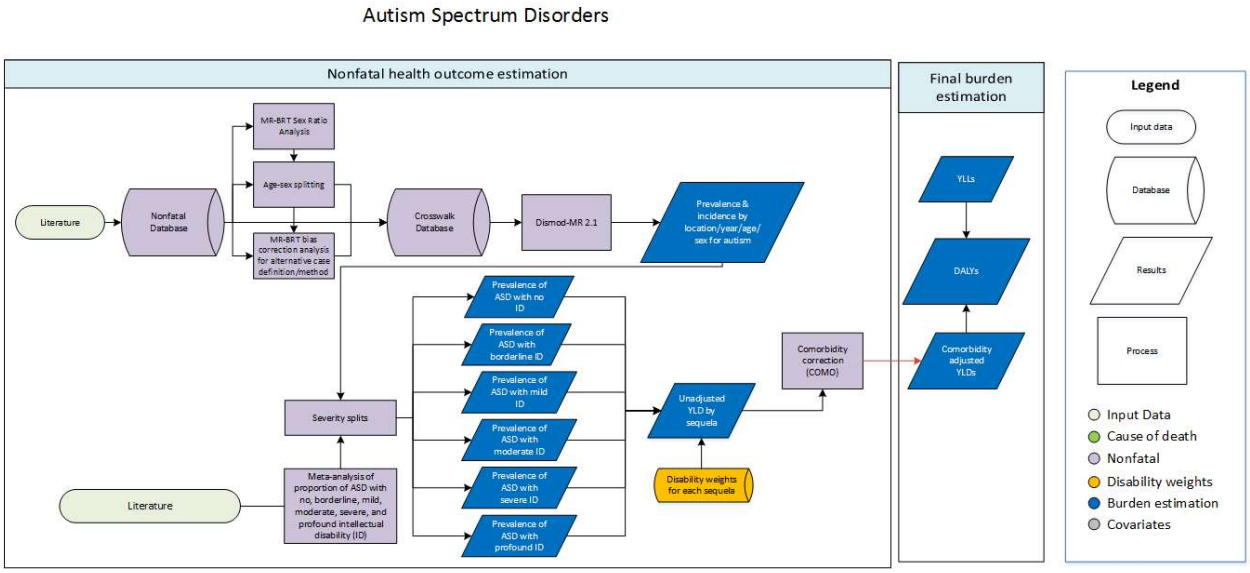
2. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
3. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophrenia bulletin. 2018;44(6):1195-203.
4. Ferrari AJ, Saha S, McGrath JJ, Norman R, Baxter AJ, Vos T, et al. Health states for schizophrenia and bipolar disorder within the Global Burden of Disease 2010 Study. Population health metrics. 2012;10(1):16.

Autism spectrum disorders

Flowchart



Input Data and Methodological Summary for Autism Spectrum Disorders

Case definition

Autism spectrum disorders (ASD; also known as pervasive developmental disorders) are a group of neurodevelopmental disorders with onset occurring in early childhood. ASD is characterised by pervasive impairment in several areas of development, including social interaction and communication skills, along with restricted and repetitive patterns of behaviours and/or interests.

ASD was an umbrella for five sub-disorders according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition, text revision[2] (DSM-IV-TR): Autistic disorder (299.00), Pervasive Developmental Disorder, Pervasive Developmental Disorder Not Otherwise Specified (299.80), Rett's disorder (299.8), Asperger's Disorder (299.8) and Childhood Disintegrative Disorder (299.10). ASD is still an umbrella for eight sub-disorders according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision[1] (ICD10): Childhood autism (F84.0), Atypical autism (F84.1), Rett syndrome (F84.2), Other childhood disintegrative disorder (F84.3), Overactive disorder associated with mental retardation and stereotyped movements (F84.4), Asperger syndrome (F84.5), Other pervasive developmental disorders (F84.8), and Pervasive disorder unspecified (F84.9). However, it has been amalgamated into a single disorder in the Diagnostic and Statistical Manual for Mental Disorders 5th edition[3] (DSM-5). A diagnosis of ASD according to the DSM-5[3] requires the following criteria to be met:

Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following, currently or by history:

1. *Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.*
2. *Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in*

eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

3. *Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.*

Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history:

1. *Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).*
2. *Insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal or nonverbal behavior (eg, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).*
3. *Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).*
4. *Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (eg, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).*

The symptoms must be present in the early developmental period, cause clinically significant impairment, and not be better explained by intellectual impairment or global developmental delay.

Input data

The epidemiological systematic review for ASD was conducted in three stages involving electronic searches of the peer-reviewed literature (i.e., PsycInfo, Embase, and PubMed), the grey literature, and expert consultation. For mental disorders, we update our GBD electronic database searches on a two-year rolling basis. A new systematic review for ASD was conducted for GBD 2017, with the next electronic literature update due for the next round of GBD. The grey literature search, and expert consultation was conducted for GBD 2019 and produced an additional four studies.

The GBD inclusion criteria stipulated that: (1) the diagnostic criteria must be from 1980 onward; (2) "caseness" must be based on clinical threshold as established by the DSM, ICD, Chinese Classification of Mental Disorders (CCMD), or diagnosed by a clinician using established tools; (3) sufficient information must be provided on study method and sample characteristics to assess the quality of the study; and (4) study samples must be representative of the general population (i.e., case studies, veterans, or refugee samples were excluded). No limitation was set on the language of publication. Due to insufficient data on ASD, estimates of the prevalence of the DSM-IV-TR sub-disorder Autistic disorder (299.00), ICD-10 Childhood autism (F84.0), and their DSM-III, DSM-II-R, DSM-IV, ICD9, and CCMD equivalents were also included with an adjustment so that they reflected what these estimates would be if the data represented ASD. Table 1 below summarizes data inputs by parameter for Autism spectrum disorders.

Table 1: Data Inputs for Autism spectrum disorders morbidity modelling by parameter.

Measure	Total sources	Countries with data
All measures	167	34
Prevalence	164	34
Standardized mortality ratio	3	2

Age and sex splitting

The extracted data underwent three types of age and sex splitting processes:

1. Where possible, estimates were further split by sex and age based on the data that was available. For instance, if studies reported prevalence for broad age groups by sex (e.g., prevalence in 15 to 65 year old males and females separately), and also by specific age groups but for both sexes combined (e.g., prevalence in 15- to 30-year-olds, then in 31- to 65-year-olds, for males and females combined); age-specific estimates were split by sex using the reported sex ratio and bounds of uncertainty
2. A Meta-Regression with Bayesian priors, Regularization, and Trimming (MR-BRT) analysis was used to split the remaining both-sex estimates in the dataset. For each parameter, sex specific estimates were matched by location, age, year and a MR-BRT network meta-analysis was used to estimate pooled sex ratios and bounds of uncertainty. These were then used to split the both sex estimates in the dataset. The male: female prevalence ratio was 4.39 (95% uncertainty interval [UI]: 3.36 – 5.41).
3. Studies reporting prevalence estimates across age groups spanning 25 years or more, were split into five-year age groups using the prevalence age pattern estimated by DisMod-MR 2.1. The DisMod-MR model used to estimate the age pattern did not contain any previously age split data.

Bias corrections / Crosswalks

Estimates with known biases were adjusted / crosswalked accordingly prior to DisMod-MR 2.1. Within the ASD epidemiological dataset, within and between study estimates were paired by age, sex, location, and year, between the reference and alternative estimates. Pairs were also made between the different alternative estimates. The ratios between these estimates were then used as inputs in a MR-BRT network meta-analysis. This analysis produced pooled ratios between the reference estimates and alternative estimates. These ratios (see Table 2) were used to adjust all alternative estimates in the dataset. ASD had 4 alternative definitions to crosswalk:

1. Estimates of autism (rather than of ASD).
2. General population survey without additional case-finding – These are studies that conduct household or school surveys but do not conduct additional active case-finding (such as reviewing special education records) to find cases likely to be missed by survey methodology.
3. Record report – These are studies where prevalence of ASD is estimated from diagnoses within a clinical or educational registry where no population screening procedure is in place.
4. Review of record notes – These are studies where researchers review notes of high-risk populations from one or more data sources records (e.g., clinical/education records) and determine prevalence based on notes without confirming the diagnosis via clinical evaluation.

Table 2: MR-BRT Crosswalk Adjustment Factors for ASD

Data input	Reference or alternative case definition	Beta Coefficient, Log (95% UI)	Adjustment factor* (95% UI)	Gamma
Population survey	Reference: Estimate represents ASD from general population surveys, with additional case finding or total population screening			0.29
Population survey	Alternative: Estimate represents autism (rather than ASD)	-0.93 (-1.49 – -0.36)	0.40 (0.23 – 0.70)	
Population survey	Alternative: General population survey without additional case finding	-0.29 (-0.91 – 0.33)	0.75 (0.40 – 1.39)	
Registry	Alternative: Record report	-0.17 (-0.74 – 0.41)	0.85 (0.48 – 1.50)	
Surveillance	Alternative: Review of record notes	0.22 (-0.40 – 0.83)	1.24 (0.67 – 2.30)	

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

UIs incorporate Gamma which represents the between study variance across all input data in the model. This added uncertainty widens the UIs for crosswalks with significant fixed effects.

Severity splits and disability weights

ASD is one of the causes that contributes to the intellectual disability (ID) envelope. As such, a gradation of ASD by level of severity was needed. Meta-analyses were conducted using data from 19 studies that used gold-standard sampling methodology and reported information on the IQ level of those with ASD in order to calculate the severity splits by six sequelae: ASD with 1) no ID, 2) borderline ID, 3) mild ID, 4) moderate ID, 5) severe ID, and 6) profound ID.

The disability weights for each sequela of ASD were calculated using the disability weights for the health states Autism, Asperger's syndrome & other ASD, borderline ID, mild ID, moderate ID, severe ID, and profound ID. These disability weights and their lay descriptions are presented in the table below.

Table 3: Health states and disability weights used to estimate sequela-specific disability weights for ASD.

Health state	Lay description	DW (95% UI)
Autism	Has severe problems interacting with others and difficulty understanding simple questions or directions. The person has great difficulty with basic daily activities and becomes distressed by any change in routine.	0.262 (0.176 – 0.365)
Asperger's syndrome & other ASDs	Has difficulty interacting with other people and is slow to understand or respond to questions. The person is often preoccupied with one thing and has some difficulty with basic daily activities.	0.104 (0.071 – 0.147)
ID, borderline	Is slow in learning at school. As an adult, the person has some difficulty doing complex or unfamiliar tasks but otherwise functions independently.	0.011 (0.005 – 0.020)

ID, mild	Has low intelligence and is slow in learning at school. As an adult, the person can live independently, but often needs help to raise children and can only work at simple supervised jobs.	0.043 (0.026 – 0.064)
ID, moderate	Has low intelligence, and is slow in learning to speak and to do even simple tasks. As an adult, the person requires a lot of support to live independently and raise children. The person can only work at the simplest supervised jobs.	0.100 (0.066 – 0.142)
ID, severe	Has very low intelligence and cannot speak more than a few words, needs constant supervision and help with most daily activities, and can do only the simplest tasks.	0.160 (0.107 – 0.226)
ID, profound	Has very low intelligence, has almost no language, and does not understand even the most basic requests or instructions. The person requires constant supervision and help for all activities.	0.200 (0.133 – 0.283)

To estimate the disability weights for each sequela of ASD, the following steps were conducted, with each step pulling 1,000 draws of each input:

1. A pooled disability weight for ASD was estimated:
$$DW_{ASD} = DW_{Autism} \times P_{Autism} + DW_{Asperger} \times (1 - P_{Autism})$$
Where *DW* is disability weight and *P* is the proportion of ASD cases estimated to meet DSM-IV criteria for the autism subtype.
2. The disability weight for ASD without ID was estimated:
$$DW_{ASD\ no\ ID} = \frac{DW_{ASD} - \sum_{k=B}^{Prof.ID}{}_{.ID}(P_k \times DW_k)}{P_{ASD\ no\ ID} + \sum_{k=Bo}^{Prof.ID}{}_{.ID}(P_k \times (1 - DW_k))}$$
Where *DW* is disability weight and *P* is the severity proportion estimated from the meta-analysis.
3. The disability weight for ASD and each remaining level of ID was estimated:
$$DW_{ASD+ID} = 1 - (1 - DW_{ASD\ no\ ID}) \times (1 - DW_{ID})$$

The severity proportions from the meta-analysis used in the above process and the resulting disability weights for each sequela are presented in table 4 below.

Table 4: MR-BRT Crosswalk Adjustment Factors for ASD

Sequela	Severity proportion (95% UI)	DW (95% UI)
ASD without ID	0.428 (0.369 – 0.491)	0.143 (0.094 – 0.202)
ASD with borderline ID	0.187 (0.144 – 0.236)	0.152 (0.103 – 0.212)
ASD with mild ID	0.180 (0.134 – 0.231)	0.179 (0.125 – 0.245)
ASD with moderate ID	0.133 (0.094 – 0.177)	0.228 (0.160 – 0.310)
ASD with severe ID	0.057 (0.034 – 0.091)	0.279 (0.195 – 0.378)
ASD with profound ID	0.014 (0.006 – 0.025)	0.313 (0.215 – 0.422)

Modelling strategy

After the above data processes were applied, DisMod MR 2.1 was used to model the epidemiological data for ASD. The DisMod-MR modeling strategy for ASD followed the standard GBD 2019 decomposition structure. At each decomposition step, we compared the new model against the GBD 2017 best model and the best model from the previous step. All substantial changes between models were explored and explained. Adjustments to model priors or the dataset were made where appropriate. Where outliers were identified in the data, we re-assessed the study's methodology and quality before a decision was made to exclude or include the data.

We assumed all incidence of ASD occurred at birth. Remission was set to 0 after expert consultation revealed we would not expect remission for ASD.

Changes between GBD 2017 and GBD 2019

There were three main changes in the GBD 2019 modelling strategy compared to GBD 2017:

1. In GBD 2017 the sex ratio was estimated by DisMod MR 2.1 as part of the prevalence modelling. In GBD 2019 we made use of MR-BRT to run a nested meta-regression analysis on the within-study sex ratios to estimate a pooled sex ratio with 95% UI as previously discussed. The prevalence male : female sex ratio was 4.03 (3.47 – 4.69) in GBD 2017 compared to 4.39 (3.36 – 5.41) in GBD 2019.
2. In GBD 2019 we made use of MR-BRT to run a nested network meta-regression to estimate adjustments to alternative data prior to running DisMod MR 2.1. Ratios estimated between 2017 and 2019 were largely consistent, although the UIs derived by MR-BRT tended to be larger. MR-BRT UIs incorporate Gamma which represents the between study variance across all input data in the model. This added uncertainty widens the UIs for crosswalks with significant fixed effects.
    a. The adjustment ratio for autism to ASD estimates was 0.43 (0.35 – 0.51) in GBD 2017 vs 0.40 (0.23 – 0.70) in GBD 2019
    b. The adjustment ratio for general population survey without additional case finding estimates was 0.87 (0.70 – 1.11) in GBD 2017 vs 0.75 (0.40 – 1.39) in GBD 2019
    c. The adjustment ratio for record report estimates was 0.71 (0.71 – 0.71) in GBD 2017 vs 0.85 (0.48 – 1.50) in GBD 2019

    d. The adjustment ratio for review of record notes estimates was 1.48 (1.23 – 1.78) in GBD 2017 vs 1.24 (0.67 – 2.30) in GBD 2019
3. In GBD 2019 we included new epidemiological data from 4 locations (Sweden, Lithuania, Tehran in Iran, and Rio Grande do Sul in Brazil).

While we continue to improve on the data and methods used to estimate the burden of mental disorders, some challenges need to be acknowledged. Firstly, we still have a large number of locations with no high-quality raw data available. Secondly, it is difficult to quantify and remove all variation due to measurement error in our epidemiological estimates. Whilst we have attempted to account for known sources of bias, in some case we still have very few data points to inform these adjustments and to explore other interactions/ bias adjustments. For example there is not enough data to explore the interaction between record report estimates and time or healthcare access quality. This could potentially inflate prevalence in locations with good healthcare access quality where the majority of ASD cases are diagnosed, and underestimate prevalence in locations where healthcare access quality is poor and the majority of ASD cases are missed. We also did not explore interactions between the estimated sex ratio and case detection method which may lead to a change in the sex ratio for ASD. Thirdly, there is a paucity of research on the risk factors of mental disorders which can be used as predictive covariates in our epidemiological models.

References

1. World Health Organisation. ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organisation; 1992.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th, Text Revision ed. Washington DC: American Psychiatric Association; 2000.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders : DSM-5. Arlington, VA: American Psychiatric Publishing; 2013.
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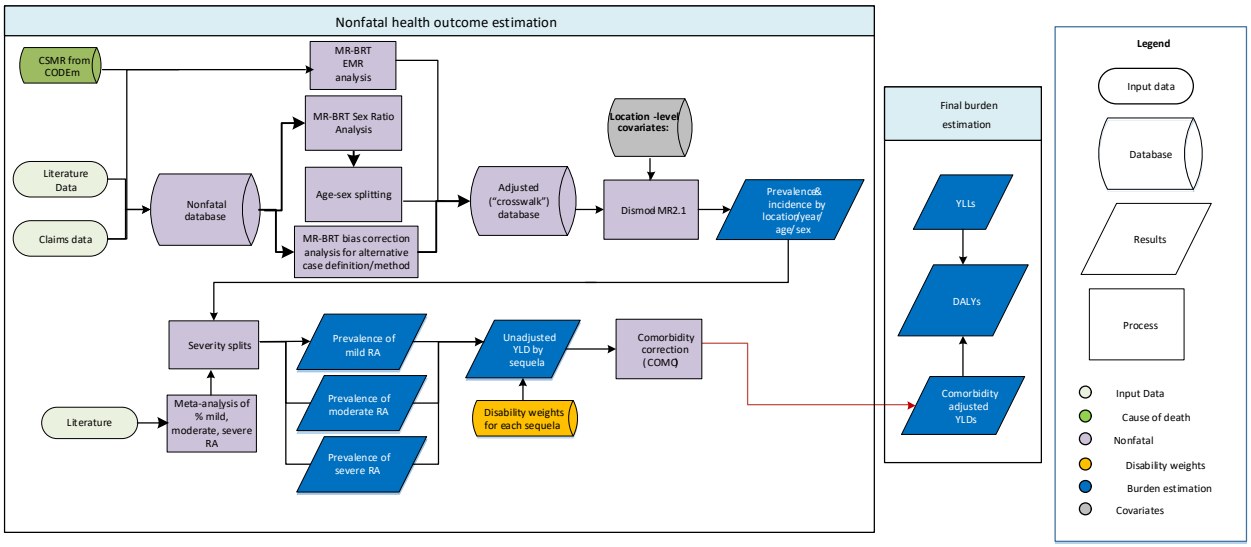
Rheumatoid Arthritis

Flowchart



Input Data and Methodological Summary for Rheumatoid Arthritis

Case definition

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that causes pain, swelling, and deformation of the joints and may be accompanied by systemic symptoms. While RA is known to affect internal organs in addition to the joints, these extra-articular effects are currently not quantified in GBD. The reference case definition for rheumatoid arthritis is based on the 1987 criteria by the American College of Rheumatology (ACR 1987) which stipulate seven diagnostic criteria, of which four need to be satisfied for a diagnosis and the first 4 of which need to have been present for at least six weeks:

1. Morning stiffness
2. Arthritis of 3 or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

For RA, ICD-10 codes are M05, M06, and M08, and ICD-9 codes are 714.0–714.9.

Input data

For GBD 2010, a systematic review of the prevalence of RA throughout the world was conducted. Ovid MEDLINE, EMBASE, CINAHL, CAB abstracts, WHOLIS, and SIGLE databases were searched using the

following search terms: (rheumatoid arthritis OR rheumatic disease* OR rheumatism) AND (prevalen* OR inciden* OR cross-sectional OR cross sectional OR epidemiol* OR survey OR population-based OR population based OR population study OR population sample OR cohort OR follow-up OR follow up OR longitudinal OR regist* OR data collection). Opportunistically, we added scientific literatures and population surveys encountered for GBD 2015 and GBD 2016. The most recent PubMed search was conducted in GBD 2017 using the following search terms: ("Arthritis, Rheumatoid"[Mesh] AND ("Prevalence"[Mesh] OR "Incidence"[Mesh])) NOT (Meta-Analysis[ptyp] OR Letter[ptyp] OR Editorial[ptyp] OR Case Reports[ptyp] OR Review[ptyp] OR Controlled Clinical Trial[ptyp]) AND ("2013/01/01"[PDAT] : "2018/1/10"[PDAT]. An age and sex split were applied to extracted data.

The exclusion criteria were:

1. Studies clearly not representative of the national population
2. Studies that were not population-based, eg, hospital or clinic-based studies
3. Studies that did not provide primary data on epidemiological parameters, eg, a commentary piece
4. Studies of a specific type of RA, eg, seropositive RA
5. Studies with a sample size of less than 150
6. Reviews

Opportunistically, additional studies encountered during data review were added for GBD 2019. In addition, data from USA claims data for 2000, 2010–2012, and 2014-2016 by state and Taiwan claims for 2016 were included. We decided not to use hospital inpatient data as we considered they would not be representative of true prevalence and that variation between countries in the proportion of true prevalent cases captured in hospital inpatient data systems would likely vary more than can be captured by a single crosswalk. We compared the rates of RA in the outpatient data from Norway, Sweden, Canada, and the USA and found implausibly large differences with the rates from the claims data. The USA outpatient rates were half the value of the claims data and those for the other countries much lower still. For those reasons we decided not to use the outpatient data.

Table 1: Data Inputs for Rheumatoid Arthritis

Measure	Total sources	Countries with data
All measures	123	45
Prevalence	92	42
Incidence	25	14
Relative risk	1	1
Standardized mortality ratio	12	5
With-condition mortality rate	3	3

Age and sex splitting

Reported estimates of prevalence were split by age and sex where possible. First, if studies reported prevalence for broad age groups by sex (eg, prevalence in 15- to 65-year-old males and females separately), and also by specific age groups for both sexes combined (eg, prevalence in 15- to 30-year-olds, then in 31- to 65-year-olds, for males and females combined), age-specific estimates were split by

sex using the reported sex ratio and bounds of uncertainty. Second, prevalence data for both sexes that could not be split using a within-study ratio were split using a sex ratio derived from a meta-analysis of existing sex-specific data using MR-BRT. The female to male ratio was 2.60 (2.58 to 2.62). Finally, after the application of bias adjustments, where studies reported estimates across age groups spanning 25 years or more, these were split into five-year age groups using the prevalence age pattern estimated by DisMod-MR 2.1 in GBD 2017.

Data adjustment

We used a single study covariate for studies using diagnostic criteria that did not match our reference case definition based on ACR 1987 criteria. We added an additional covariate for claims data in the USA from the year 2000. We treat claims data from the USA from 2010 onward and Taiwan as reference case definition data; rarely would cases of RA not intersect with the health system in the USA and Taiwan. Betas and exponentiated values (which can be interpreted as an odds ratio) for these two covariates are shown in the table below:

Table 2: MR-BRT Crosswalk Adjustment Factors for Rheumatoid Arthritis

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Log (95% CI)	Adjustment factor*
ACR 1987	Ref	0.38	---	---
RA criteria other than RA 1987	Alt		0.13 (-0.14 to 0.41)	1.14 (0.87 to 1.50)
USA claims data – 2000	Alt		0.54 (-0.25 to 1.34)	1.72 (0.78 to 3.83)

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

After adjusting data for case definition, we outliered data that with a median absolute deviation of 2 or more above the mean to cull data that were implausibly high.

Modeling strategy

Prior settings in the DisMod model included setting remission to 0 – 0.02 for ages up to 65 and 0 – 0.05 for ages 65+. It was assumed that there was no incidence or prevalence of RA before the age of 5 years. These settings were retained for GBD 2019. We continued to include the Mean BMI country covariate with bounds set at 0 and 1 and increased the coefficient of variation from 0.4 at the Global, Super Region, and Region priors to 0.8 to allow the model to better follow the data. The time window for fit was increased from 10 to 25 years to optimize temporal smoothing.

In previous rounds, priors on excess mortality rate (EMR) were estimated in DisMod by matching prevalence data points with their corresponding CSMR values within the same age, sex, year, location (by dividing CSMR by prevalence). For short duration conditions (remission>1), the corresponding prevalence was derived by running an initial model and then applying the same CSMR/prevalence method. However, for many causes, DisMod estimated a rather unrealistic pattern of EMR compared to an expected pattern of decreasing EMR with greater access to quality health care. Such unexpected patterns often signal inconsistencies between CSMR estimates and the measures of prevalence and/or

incidence. In effort to provide greater guidance to DisMod on the expected pattern of EMR, EMR data generated in the previous round were modeled using the MR-BRT approach by age and sex with a prior on healthcare access and quality index (HAQi) having a negative coefficient. Results from MR-BRT were then predicted for each location year, sex and for ages 0, 10, 20 ….100. We included HAQi as a country-level covariate to inform EMR with a mean and standard deviation produced from MR-BRT. However, even without this setting DisMod would tend to estimate a coefficient that was consistent with the MR-BRT analysis.

Table 3. Covariates. Summary of covariates used in the rheumatoid arthritis DisMod-MR meta-regression model

Covariate	Type	Parameter	Exponentiated beta (95% Uncertainty Interval)
Healthcare access and quality index	Country-level	Excess mortality rate	0.98 (0.98 to 0.98)
Mean BMI	Country-level	Prevalence	1.12 (1.11 to 1.13)

Severity and Disability

The basis of the GBD disability weight survey assessments are lay descriptions of health states highlighting major functional consequences and symptoms. The lay descriptions and disability weights for RA severity levels are shown below.

Table 4. Severity distribution, details on the severity levels for rheumatoid arthritis in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)
Mild	This person has moderate pain and stiffness in the arms and hands which causes difficulty lifting, carrying, and holding things, and trouble sleeping because of the pain.	0.117 (0.080–0.163)
Moderate	This person has pain and deformity in most joints, causing difficulty moving around, getting up and down, and using the hands for lifting and carrying. The person often feels fatigue.	0.317 (0.216–0.440)
Severe	This person has severe, constant pain, and deformity in most joints, causing difficulty moving around, getting up and down, eating, dressing, lifting, carrying, and using the hands. The person often feels sadness, anxiety, and extreme fatigue.	0.581 (0.403–0.739)

To determine the proportion of people with RA within each of the severity levels, seven studies from three regions provided information on the severity of RA. Severity was classified according to Health Assessment Questionnaire scores, with the cutoff for each severity level: <1 mild; 1-1.875 moderate; and ≥2 severe. Estimates were across studies. We used a random effects meta-analysis model. The pooled percentages were mild 48.8% (37.9 – 59.6), moderate 37.6% (29.3 – 46.2), and severe 12.2% (7.8

– 17.4). After streaming out 1,000 draws assuming a binomial distribution, percentages were scaled to sum to 1 at each draw.

Figure 1. Severity distribution meta-analysis, details on the studies included in the meta-analysis calculating the proportion of mild RA.

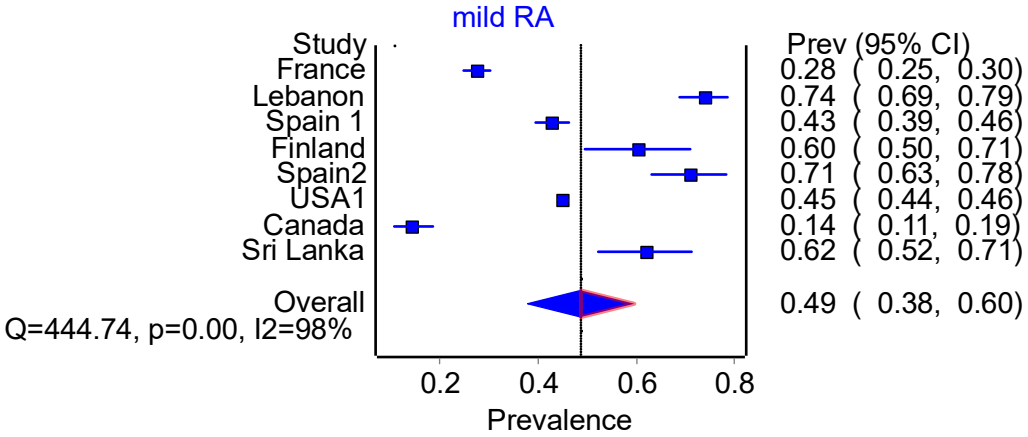


Figure 2. Severity distribution meta-analysis, details on the studies included in the meta-analysis calculating the proportion of moderate RA.

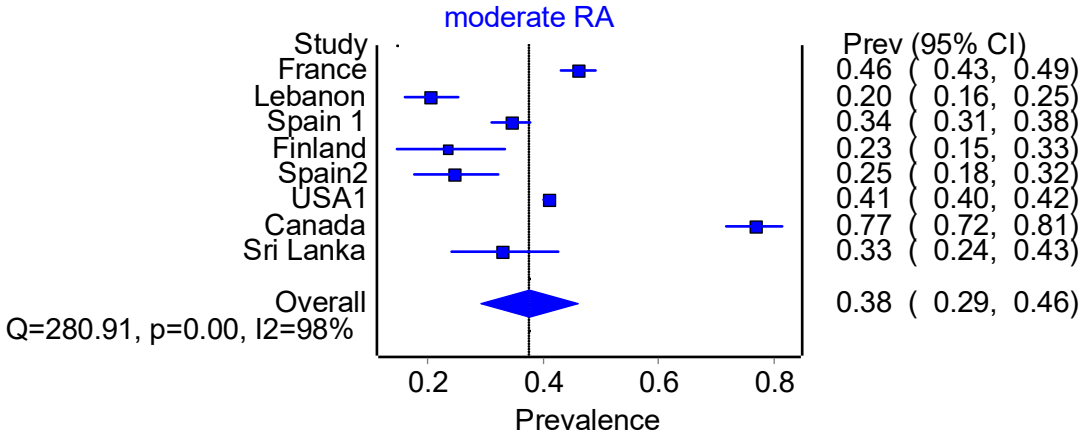
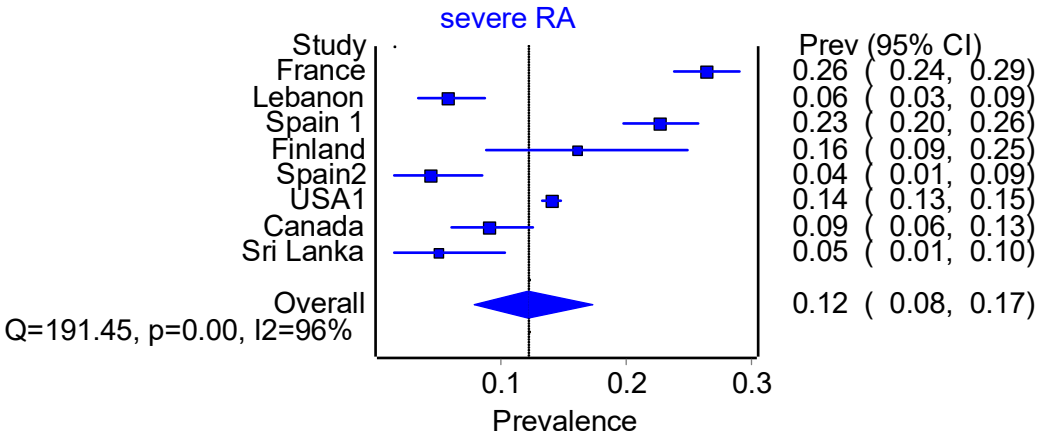
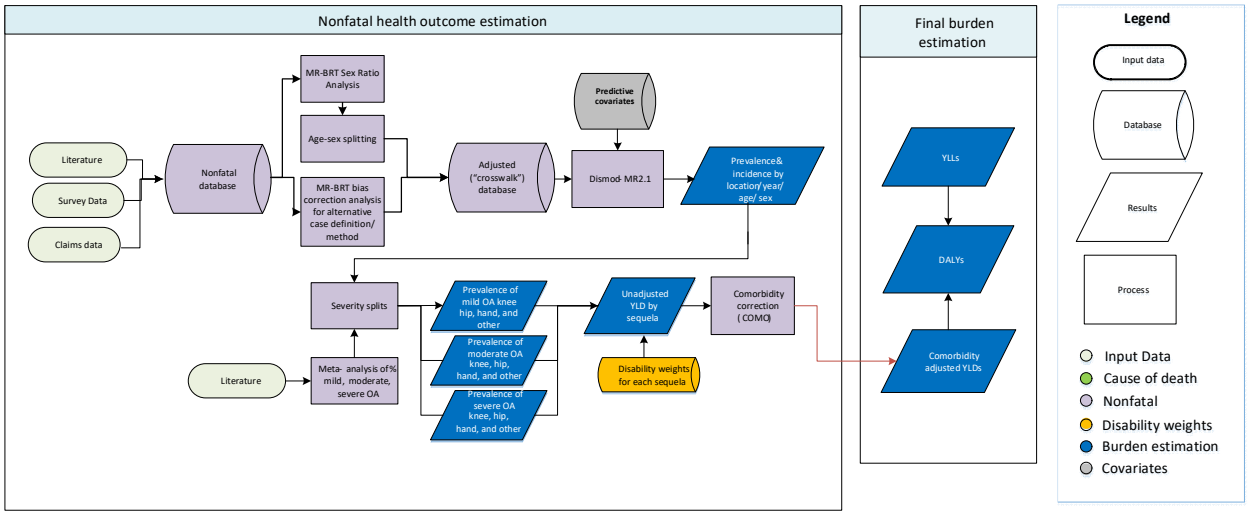


Figure 3. Severity distribution meta-analysis, details on the studies included in the meta-analysis calculating the proportion of severe RA.



Osteoarthritis

Flowchart



Input Data and Methodological Summary for Osteoarthritis

Case definition

OA is the most common form of arthritis, involving chronic inflammation, breakdown, and structural changes of whole joints. For the purposes of OA estimates for this GBD study, hip, knee, hand, and other sites were reviewed. The hip, knee, and hand are the common sites of OA. OA in the larger joints, such as the hip and knee, are considered to produce the greatest disability. Failure of these joints can lead to need for joint replacement surgery, if available, and thus contributes to a significant proportion of the high direct health care costs attributable to arthritis. OA of the spine is also common; however, it was considered that any symptoms and disability related to the cervical and/or lumbar spine would be captured in the estimates of low back pain and neck pain.

The osteoarthritis (OA) reference case definition is symptomatic osteoarthritis radiologically confirmed as Kellgren-Lawrence grade 2-4. Prior to GBD 2019, we only estimated OA of the hip and knee. For GBD 2019, two new sites of OA were added, OA of the hand, with the same reference criteria present in any single hand joint type, and OA other, with the same reference criteria present in any joint other than those of the hand, hip, knee, or spine. Grade 2 symptomatic requires one defined osteophyte in the affected joint and pain for at least one month out of the last 12. Grade 3-4 symptomatic requires osteophytes and joint space narrowing in the affected joint with deformity also present for grade 4, and pain for at least one month out of the last 12 months.

ICD-10 codes for OA of the hip, knee, hand, and other are M16, M17, M18, and M19, respectively. The ICD-9 code for OA is 715, without specific codes for various sites.

Input data

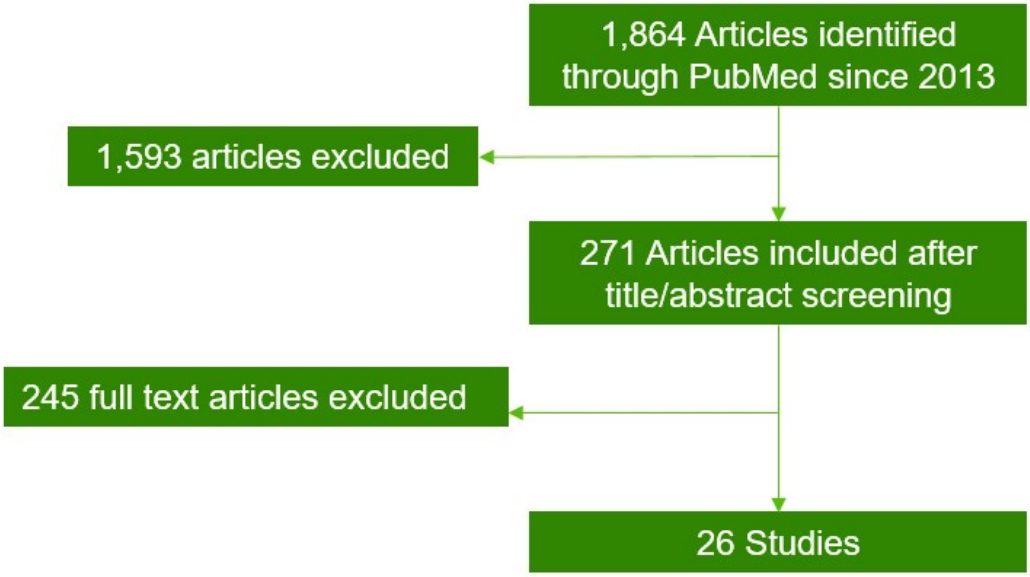
The most recent systematic review for OA hip and OA knee was conducted in 2017 for studies published between 2013 - 2017. A systematic review of the prevalence, incidence, and mortality was performed on MEDLINE, EMBASE, CINAHL, CAB Abstracts, WHO Library (WHOLIS) and OpenSIGLE. For prevalence and incidence, the following search terms were used: (osteoarth* OR gonarthr*) AND (prevalen* OR inciden* OR cross-sectional OR cross sectional OR epidemiol* OR survey OR population-based OR population based OR population study OR population sample OR cohort OR follow-up OR follow up OR longitudinal OR regist*) AND (list of names of all GBD countries).

Exclusion criteria were:

1. Sub-populations clearly not representative of the national population
2. Not a population-based study
3. Low sample size (less than 150)
4. Review rather than original studies

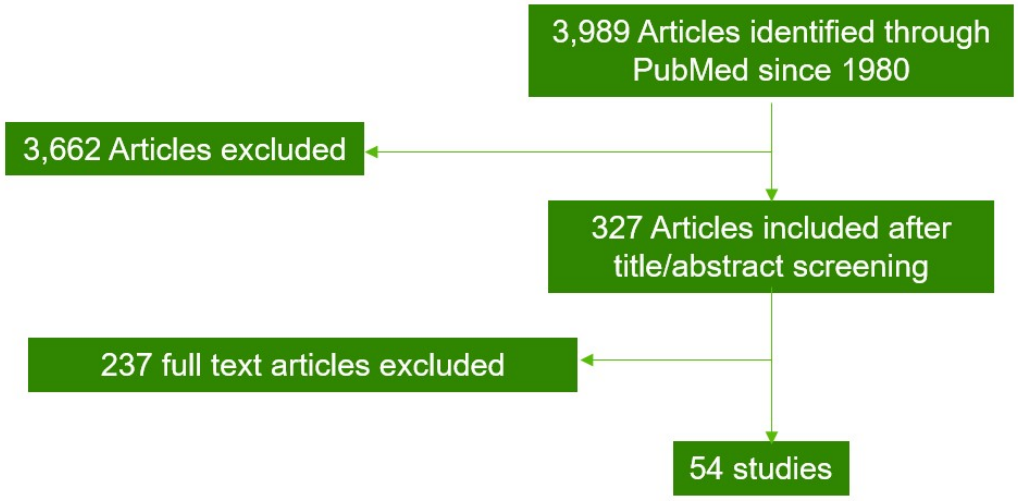
We identified 1,864 articles and extracted data from 26. These studies were from 19 locations: Australia, Brazil, Canada, China, Ecuador, Egypt, India, Iran, United Kingdom, France, Japan, United States, Mongolia, Portugal, Spain, Mexico, Turkey, Venezuela, and Vietnam.

Figure 1: PRISMA diagram of osteoarthritis systematic review from 2013–2017



All existing sources used in the hip and knee models were re-reviewed for mention of prevalence and incidence of OA hand or OA other specifically. In order to gather more input data on prevalence for the new OA hand and OA other models, a broad systematic review was also conducted in 2019 specifically for data on these sites. A PubMed search was conducted for studies published between 1980 and 2019 using the following search terms: (("osteoarthritis" AND ("epidemiology" OR "prevalence")) AND "humans") AND ("population" OR "population groups" OR ("population" AND "groups")).

Figure 2: PRISMA diagram of osteoarthritis systematic review from 1980–2019



As in past rounds of the GBD, we decided not to use hospital inpatient data as we considered it would not be representative of true prevalence, and that variation between countries in the proportion of true prevalent cases captured in hospital inpatient data system would likely vary more than can be captured by a single crosswalk in DisMod-MR 2.1. Data from USA claims data for 2000 and 2010–2016 by state and Taiwan claims data from 2016 were included. There were very few sources identified through data re-review and systematic review for OA other, with minimal overlap in reported site. As a result, US claims data constituted the only data input source for this model.

The total source counts used for modeling in GBD 2019 are listed below:

Cause	Measure	Total sources	Countries with data
Osteoarthritis hip	All measures	59	23
	Prevalence	52	23
	Incidence	5	3
	Relative risk	1	1
	Standardized mortality ratio	1	1
Osteoarthritis knee	All measures	73	26
	Prevalence	69	25
	Incidence	5	4
Osteoarthritis hand	All measures	88	40
	Prevalence	87	40
	Incidence	1	1
Osteoarthritis other	All measures	12	1
	Prevalence	12	1

Age and sex splitting

Reported estimates of prevalence were split by age and sex where possible. First, if studies reported prevalence for broad age groups by sex (eg, prevalence in 15- to 65-year-old males and females separately), and also by specific age groups but for both sexes combined (eg, prevalence in 15- to 30-year-olds, then in 31- to 65-year-olds, for males and females combined), age-specific estimates were split by sex using the reported sex ratio and bounds of uncertainty. Second, input data reporting prevalence of OA for both sexes that could not be split using a within-study ratio were split using a sex ratio derived from a meta-analysis of existing sex-specific data for each type of OA using MR-BRT. The female to male ratio was 1.10 (1.09 to 1.12) for the hip, 1.44 (1.43 to 1.45) for the knee, and 2.36 (2.33 to 2.38) for the hand. There weren't any both sex input data for OA other. Finally, after the application of bias adjustments, where studies on OA hip and OA knee reported estimates across age groups spanning 25 years or more, these were split into five-year age groups using the prevalence age pattern estimated by DisMod-MR 2.1 for each type of OA in GBD 2017. Remaining wide age bin data for OA hand were split into five-year age groups using the prevalence age pattern of the USA claims input data. There weren't any wide age bin input data for OA other.

Data adjustment

For OA hip and OA knee, we marked studies that reported on X-rays only, self-reported OA with pain, or self-reported OA with no information on pain. Other studies identified cases of osteoarthritis through a review of medical charts. We assumed that these cases were diagnosed by X-ray with pain present. We added three additional covariates for claims data in the USA from the year 2000 and from 2010 onward and for Taiwan claims data. For all these alternative case definitions we derived adjustment factors using MR-BRT. Claims data from Taiwan were excluded from the model, as we did not have data on the reference case definition from Taiwan to inform a reliable adjustment. Betas and exponentiated values (which can be interpreted as an odds ratio) for these two covariates are shown in the table below:

Table 1: MR-BRT Crosswalk Adjustment Factors for OA Hip

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Log (95% CI)	Adjustment factor*
Radiography with pain	Ref	0.26	---	---
Radiography only	Alt		1.09 (0.89 to 1.28)	2.96 (2.44 to 3.6)
Self-reported OA with pain	Alt		1.32 (1.15 to 1.48)	3.73 (3.16 to 4.39)
Self-reported OA, no mention of pain	Alt		1.60 (1.18 to 2.01)	4.94 (3.26 to 7.49)
USA Claims data – 2000	Alt		-2.50 (-2.96 to -2.01)	0.082 (0.052 to 0.13)
USA Claims data – 2010–2016	Alt		-2.03 (-2.08 to -1.97)	0.13 (0.12 to 0.14)

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

Table 2: MR-BRT Crosswalk Adjustment Factors for OA Knee

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Log (95% CI)	Adjustment factor*
Radiography with pain	Ref	0.38	---	---
Radiography only	Alt		0.21 (0.14 to 0.27)	1.23 91.15 to 1.32)
Self-reported OA with pain	Alt		0.063 (-0.027 to 0.15)	1.065 (0.97 to 1.17)
Self-reported OA, no mention of pain	Alt		-0.77 (-0.81 to -0.72)	0.46 (0.44 to 0.48)
USA Claims data – 2000	Alt		-2.26 (-2.64 to -1.88)	0.10 (0.072 to 0.15)
USA Claims data – 2010–2016	Alt		-1.60 (-2.43 to -0.77)	0.20 (0.088 to 0.46)

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

For OA hand, we allowed for alternatives to two dimensions of case definition: affected joint and diagnostic criteria. These alternative case definitions concerned studies reporting on the presence of OA in any single joint type (e.g. distal interphalangeal), present in the first carpometacarpal joint of the thumb specifically, present in multiple joint types, or diagnosed as generalized hand OA. Adjustments were also considered for studies that used X-rays, studies in which a physician diagnosed OA without X-rays, studies that used reported pain, and studies that used self-report. We added two additional covariates for claims data in the USA from the year 2000 and from 2010 onward. The mean and standard error for the coefficients were calculated using the MR-BRT crosswalk adjustment method. Data concerning the presence of OA in the thumb base and through self-report were not included in the final model, as we were unable to find matches to inform a reliable crosswalk. Betas and exponentiated values (which can be interpreted as an odds ratio) for these two covariates are shown in the table below:

Table 3: MR-BRT Crosswalk Adjustment Factors for OA Hand

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Log (95% CI)	Adjustment factor*
Radiography with pain in a single joint type	Ref	0.36	---	---
OA in a single joint type	Alt		0.32 (0.29 to 0.34)	1.37 (1.34 to 1.40)

OA in multiple joint types	Alt		0.32 (0.30 to 0.34)	1.38 (1.35 to 1.41)
Generalized hand OA	Alt		-0.74 (-0.80 to -0.68)	0.48 (0.45 to 0.51)
Radiography only	Alt		1.09 (1.03 to 1.15)	2.97 (2.79 to 3.16)
Physician diagnosis only	Alt		0.58 (0.51 to 0.65)	1.78 (1.66 to 1.92)
Pain only	Alt		0.055 (0.0077 to 0.10)	1.06 (1.01 to 1.11)
Radiography with pain	Alt		0.31 (0.23 to 0.39)	1.36 (1.26 to 1.48)
Physician diagnosis with pain	Alt		0.28 (0.20 to 0.35)	1.32 (1.22 to 1.42)
USA Claims data – 2000	Alt		-0.48 (-0.49 to -0.47)	0.62 (0.61 to 0.62)
USA Claims data – 2010–2016	Alt		-2.74 (-2.81 to -2.66)	0.065 (0.60 to 0.70)

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

Modeling strategy

For OA hip and OA knee, prior settings in the DisMod model included setting remission to 0, and it was assumed that there was no incidence or prevalence of OA before the age of 30 years. We assumed that excess mortality is zero. While there are some data on excess mortality risk, the values of hazard ratios or standardised mortality ratios are close to one, with some studies reporting mean estimates less than one.

We made few substantive changes in the modeling strategy from GBD 2017. For OA hip, the coefficient of variation was increased from 0.4 at the Global, Super Region, and Region levels, to 0.8 to allow the model to better follow the data. For OA knee, bounds were set on remission between 0 and 0.05 to account for knee replacement. We included Mean BMI and the SEV scalar for osteoarthritis as country covariates on prevalence. The OA SEV scalar combines the exposure measures for risks estimated to impinge on OA in GBD: increased BMI.

Table 4. Covariates. Summary of covariates used in the OA hip and OA knee DisMod-MR meta-regression models

Covariate	Beta, log (95% Uncertainty Interval), OA Hip	Exponentiated beta (95% Uncertainty Interval), OA Hip	Beta, log (95% Uncertainty Interval), OA Knee	Exponentiated beta (95% Uncertainty Interval), OA Knee
Mean BMI	0.98 (0.94 to 1.00	2.66 (2.56 to 2.72)	0.69 (0.51 to 0.87)	1.99 (1.66 to 2.39)

Log-transformed age-standardized SEV scalar: OA	1.95 (1.25 to 2.00)	7.05 (3.51 to 7.38)	0.78 (0.75 to 0.83)	2.17 (2.12 to 2.29)

For the new OA hand and OA other models, settings in DisMod included setting remission to 0, and assuming no incidence or prevalence of OA before the age of 30 years. In addition, we included the SEV scalar for OA as a country covariate on prevalence for OA other in order to provide a basis for some geographic variation in a model that only has input data in the USA. This covariate was not used in the OA hand model because we did not have reason to believe that there is a reliable relationship between increased BMI and OA in hand joints.

Table 5. Covariates. Summary of covariates used in the OA other DisMod-MR meta-regression model

Covariate	Beta, log (95% Uncertainty Interval)	Exponentiated beta (95% Uncertainty Interval)
Log-transformed age-standardized SEV scalar: OA	1.23 (1.20 to 1.25)	3.42 (3.31 to 3.49)

Severity and Disability

The basis of the GBD disability weight survey assessments are lay descriptions of sequelae highlighting major functional consequences and symptoms. The lay descriptions and disability weights for OA severity levels are shown below.

Table 6. Severity distribution, details on the severity levels for OA in GBD 2019 and the associated disability weight (DW) with that severity.

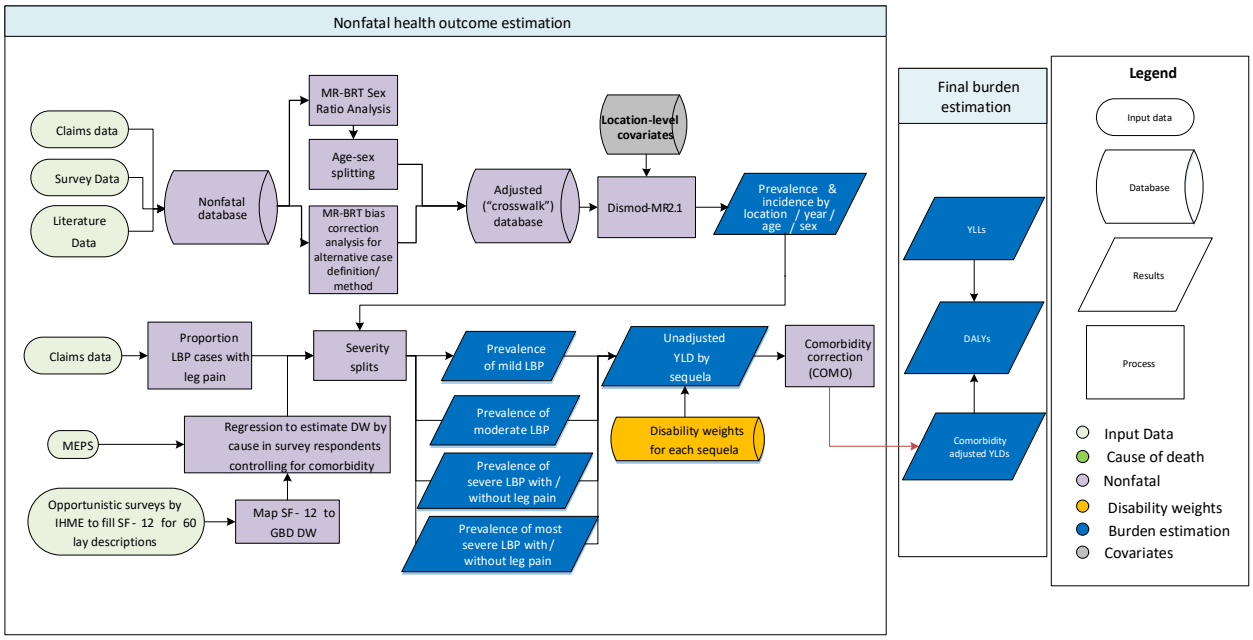
Severity level	Lay description	DW (95% CI)
Asymptomatic		0
Mild	This person has pain in the leg, which causes some difficulty running, walking long distances, and getting up and down.	0.023 (0.013–0.037)
Moderate	This person has moderate pain in the leg, which makes the person limp, and causes some difficulty walking,	0.079 (0.054–0.110)

	standing, lifting and carrying heavy things, getting up and down, and sleeping.	
Severe	This person has severe pain in the leg, which makes the person limp and causes a lot of difficulty walking, standing, lifting and carrying heavy things, getting up and down, and sleeping.	0.165 (0.112–0.232)

In past GBD rounds, to determine the proportion of people with OA within each of the severity levels, four studies representing the High-income, South Asia, and Southeast Asia, East Asia, and Oceania super regions provided information on the severity of OA. In GBD 2017, data from the USA Osteoarthritis Initiative study were included as well. The OA Initiative is a large cohort study that follows individuals with OA of the knee recruited from four centers around the USA. In all five studies, severity was classified based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) with scores 0-5 taken as mild, 6-13 as moderate, and 14 and higher as severe. Estimates were pooled across studies using a random effects meta-analysis model. The pooled percentages were mild 47.0% (42.2–51.9), moderate 35.9% (31.3–40.7), and severe 17.1% (12.9–21.6) pooled between patient and physician ratings in a study from Bangladesh, which we apply to low- and middle-income countries. The pooled proportions from three high-income countries were mild 74.3% (64.8–82.7), moderate 24.3% (16.4–33.1), and severe 1.1% (0.6–1.7). After streaming out 1,000 draws assuming a binomial distribution, percentages were scaled to sum to 1 at each draw. For the sake of consistency, the same severity distribution and disability weights were applied to OA hand and OA other, to be reconsidered in the subsequent modeling round.

Low Back Pain

Flowchart



Input Data and Methodological Summary for LBP

Case definition

Low back pain (LBP) is defined as low back pain (with or without pain referred into one or both lower limbs) that lasts for at least one day. The "low back" is defined as the area on the posterior aspect of the body from the lower margin of the twelfth ribs to the lower gluteal folds.

ICD-10 codes for LBP are M54.3, M54.4 and M54.5. The ICD-9 code is 724.

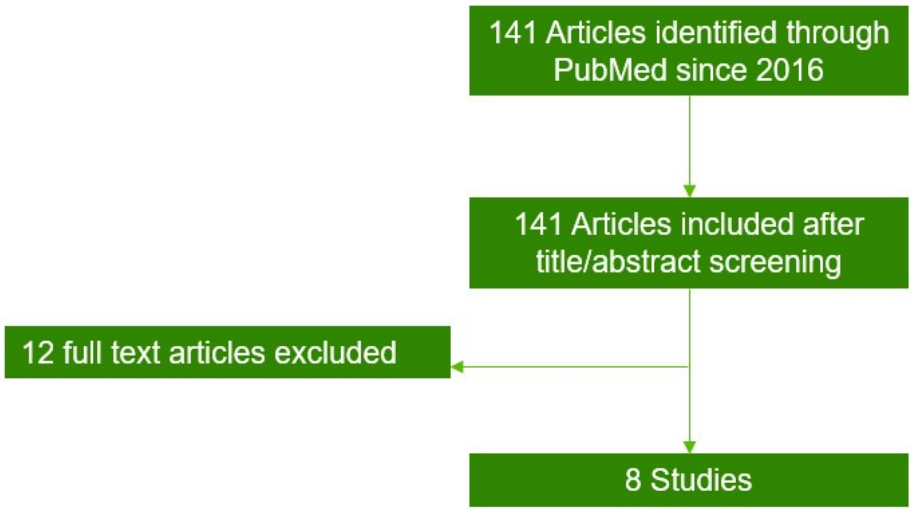
Input data

The last systematic review was conducted from October 2016-October 2017. We searched PUBMED, Ovid Medline, EMBase, and CINAHL electronic databases. There were no age, sex, or language restrictions. The terms "back pain," "lumbar pain," "back ache," "backache," and "lumbago" were used individually and combined with each of the following: "prevalence," "incidence," "cross-sectional," and "epidemiology."

Exclusion criteria were:

1. Sub-populations clearly not representative of the national population
2. Not a population-based study
3. Low sample size (less than 150)
4. Review rather than original studies

Figure 2: PRISMA diagram of low back pain systematic review from 2016–2017



Additional information was derived from unit record data of surveys in the GHDx, GBD's repository of population health data including the World Health surveys and national health surveys. Opportunistically, additional studies encountered during data review were added for GBD 2019. In addition, data from USA claims data for 2000, 2010–2012, and 2014-2016 by state were included.

Table 1: Data Inputs for LBP

Measure	Total sources	Countries with data
All measures	463	103
Prevalence	446	102
Incidence	4	3
Remission	3	2
Proportion	15	1

Age and sex splitting

Reported estimates of prevalence were split by age and sex where possible. First, if studies reported prevalence for broad age groups by sex (eg, prevalence in 15- to 65-year-old males and females separately), and also by specific age groups for both sexes combined (eg, prevalence in 15- to 30-year-olds, then in 31- to 65-year-olds, for males and females combined), age-specific estimates were split by sex using the reported sex ratio and bounds of uncertainty. Second, prevalence data for both sexes that could not be split using a within-study ratio were split using a sex ratio derived from a meta-analysis of existing sex-specific data using MR-BRT. The female to male ratio was 1.18 (1.18 to 1.18). Finally, after the application of bias adjustments, where studies reported estimates across age groups spanning 25 years or more, these were split into five-year age groups using the prevalence age pattern estimated by DisMod-MR 2.1 in GDB 2017.

Data adjustment

We corrected for bias among studies that defined low back back with too broad anatomical region, episode duration of greater than three months, recall periods of one week to one month, recall periods between two months and one year, or as activity-limiting LBP, as well as studies conducted among schoolchildren. We added three additional covariates for claims data in the USA from the year 2000 and from 2010 onward and for Taiwan claims data. These adjustment factors were estimated as the logit difference between the prevalence of alternate case definition data and that of the reference definition for comparable age, sex, year, and location calculated using the MR-BRT network crosswalk adjustment method. Unadjusted low back pain prevalence data is often already close to one, especially for older age groups, and a logit difference strategy ensures that any prevalence data requiring adjustment to a higher value do not exceed one. Claims data from Taiwan were not included in the final model, as we were unable to find matches to inform a reliable crosswalk. Betas and exponentiated values for these covariates are shown in the table below:

Table 2: MR-BRT Crosswalk Adjustment Factors for LBP

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor
Point prevalence	Ref	0.86	---	---
Anatomical region too broad	Alt		0.099 (0.080 to 0.12)	0.52 (0.52 to 0.53)
Episode duration >= 3 months	Alt		-0.19 (-1.03 to -0.97)	0.27 (0.26 to 0.28)
Recall periods of 1 week to 1 month	Alt		0.31 (0.28 to 0.34)	0.58 (0.57 to 0.58)
Recall periods between 2 months and one year	Alt		0.80 (0.76 to 0.84)	0.69 (0.68 to 0.70)
Activity-limiting LBP	Alt		-1.53 (-1.55 to -1.51)	0.18 (0.17 to 0.18)
Studies among school children	Alt		0.00 (-0.05 to 0.05)	0.5 (0.49 to 0.51)
USA claims data – 2000	Alt		-1.31 (1.66 to -0.97)	0.21 (0.16 to 0.27)
USA claims data – 2010–2012, 2014-2016	Alt		-0.54 (-0.57 to -0.50)	0.37 (0.36 to 0.38)

After adjusting data for case definition, we outliered data with a median absolute deviation of 1.5 or more above the mean. This was done in a systematic way to cull data that were implausibly high.

Modeling strategy

Prior settings in the DisMod model included setting excess mortality to 0, and it was assumed that there was no incidence or prevalence of low back pain before the age of 5 years. We made no substantive changes in the modeling strategy from GBD 2017. We included the SEV scalar for low back pain as a

country covariate. This combines the exposure measures for risks estimated to impinge on LBP in GBD: occupational ergonomic exposure and increased BMI. We set bounds of 0.75 to 1.25 as the SEV is constructed in a way that if our risk estimates are accurate the value should be 1.

Table 3. Covariates. Summary of covariates used in the LBP DisMod-MR meta-regression model

Covariate	Type	Parameter	Exponentiated beta (95% Uncertainty Interval)
Log-transformed age-standardized SEV scalar: Back pain	Country-level	Prevalence	2.12 (2.12 – 2.13)

Severity and Disability

The basis of the GBD disability weight survey assessments are lay descriptions of sequelae highlighting major functional consequences and symptoms. The lay descriptions and disability weights for LBP severity levels are shown below.

Table 4. Severity distribution, details on the severity levels for LBP in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)
Low back pain, mild	This person has mild back pain, which causes some difficulty dressing, standing, and lifting things.	0.020 (0.011–0.035)
Low back pain, moderate	This person has moderate back pain, which causes difficulty dressing, sitting, standing, walking, and lifting things.	0.054 (0.035–0.079)
Low back pain, severe without leg pain	This person has severe back pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly and feels worried.	0.272 (0.182–0.373)
Low back pain, severe with leg pain	This person has severe back and leg pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly and feels worried.	0.325 0.219–0.446)
Low back pain, most severe without leg pain	This person has constant back pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly, is worried, and has lost some enjoyment in life.	0.372 (0.250–0.506)
Low back pain, most severe with leg pain	This person has constant back and leg pain, which causes difficulty dressing, sitting, standing, walking, and lifting things. The person sleeps poorly, is worried, and has lost some enjoyment in life.	0.384 (0.256–0.518)

The severity distributions are derived from an analysis of the Medical Expenditure Panel Surveys (MEPS) in the USA. MEPS is an overlapping continuous panel survey of the United States non-institutionalised population whose primary purpose is to collect information on the use and cost of health care. Panels are two years long and are conducted in five rounds, which are conducted every five to six months. A new panel begins annually, while the last panel is in its second year. Each panel typically contains about

30,000 to 35,000 individual respondents.
(http://www.meps.ahrq.gov/survey_comp/hc_data_collection.jsp)

MEPS was initiated in 1996 but only began collecting health status data in the form of SF-12 responses in 2000. For GBD 2016 we used data from 2000–2014. Respondents self-administer the SF-12 twice per panel, at rounds 2 and 4, typically about a year apart. Only adults 18 years and older completed the SF-12. MEPS also usually collects information on diagnoses based on self-report of reasons for encounters with health services. In addition, diagnoses are derived through additional questions on "problems that bother you" or conditions that led to "disability days," ie, days out of role due to illness. Professional coders translate the verbatim text into three-digit ICD-9 codes. The main reason for LBP being measured in MEPS relates to health care contact. From MEPS, the severity distribution for LBP without leg pain and with leg pain were derived as shown in the below table.

Table 5. Severity distribution, details on the distribution of severity splits for LBP in GBD 2019 with and without leg pain

Severity level	Distribution without leg pain	Distribution with leg pain
Low back pain, mild	0.41 (0.31–0.53)	0.27 (0.19–0.37)
Low back pain, moderate	0.35 (0.25–0.44)	0.36 (0.28–0.43)
Low back pain, severe	0.10 (0.08–0.12)	0.14 (0.10–0.16)
Low back pain, most severe	0.14 (0.09–0.20)	0.23 (0.15–0.32)

We used USA claims data (2012) to derive the proportion of cases with low back pain who report leg pain. The proportions were different by age group as shown in Figure 1. The proportion in each severity level in each age group is calculated by multiplying the proportion in the severity level and the proportion with or without leg pain.

Figure 2: Proportion of LBP with leg pain

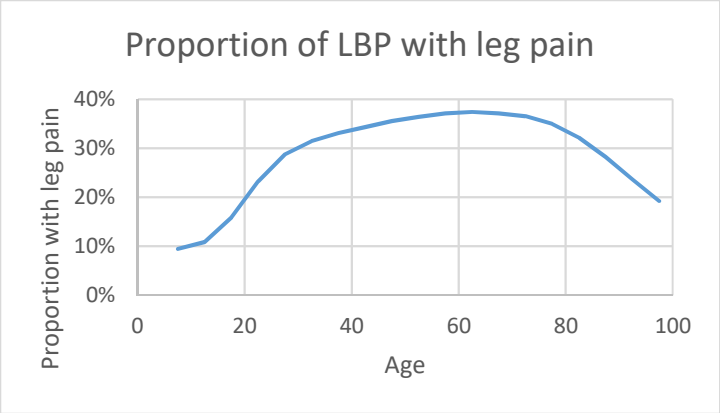


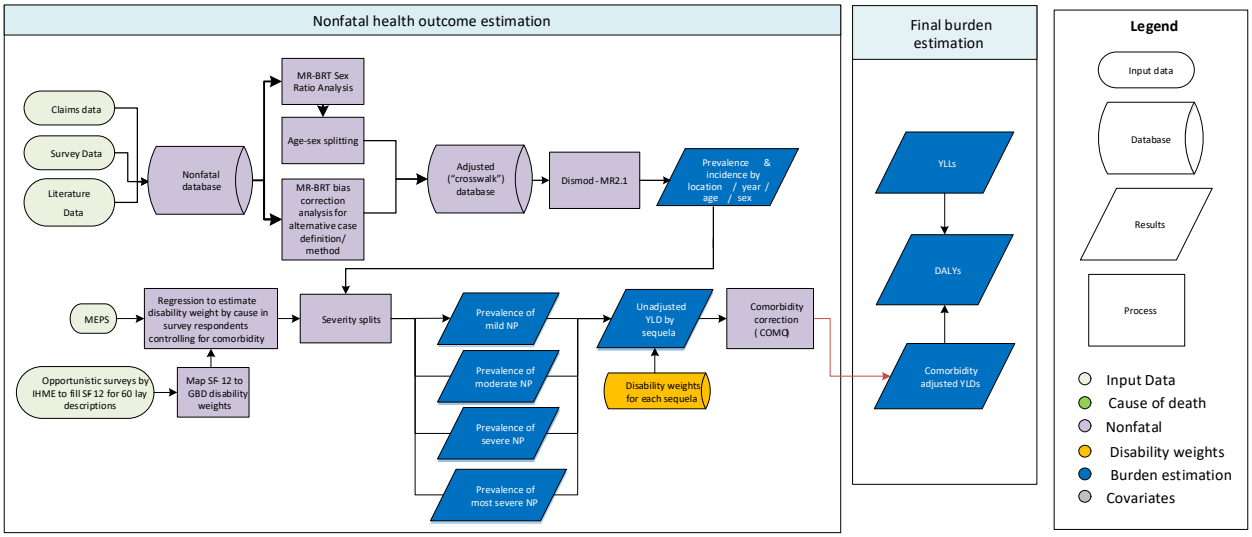
Table 6. Proportion of LBP with leg pain

Age (years)	Proportion with leg pain
5–9	9.4 (9.1–9.8) %
10–14	10.9 (10.7–11.1) %

15–19	15.9 (15.8–16.1) %
20–24	23.2 (23.0–23.4) %
25–29	28.8 (28.6–28.9) %
30–34	31.4 (31.3–31.6) %
35–39	33.1 (32.9–33.2) %
40–44	34.3 (34.2–34.4) %
45–49	35.5 (35.4–35.6) %
50–54	36.4 (36.3–36.5) %
55–59	37.1 (37.0–37.2) %
60–64	37.4 (37.3–37.5) %
65–69	37.1 (36.9–37.3) %
70–74	36.5 (36.4–36.7) %
75–79	35.0 (34.8–35.2) %
80–84	32.1 (31.9–32.4) %
85–89	28.3 (28.0–28.5) %
90–94	23.7 (23.2–24.2) %
95–100	19.2 (18.2–20.2) %

Neck Pain (NP)

Flowchart



Input Data and Methodological Summary for Neck Pain

Case definition

Neck pain (NP) was defined as: neck pain (+/- pain referred into the upper limb(s)) that lasts for at least one day.

ICD-10 code for neck pain is M54.2. The ICD-9 code is 723.1.

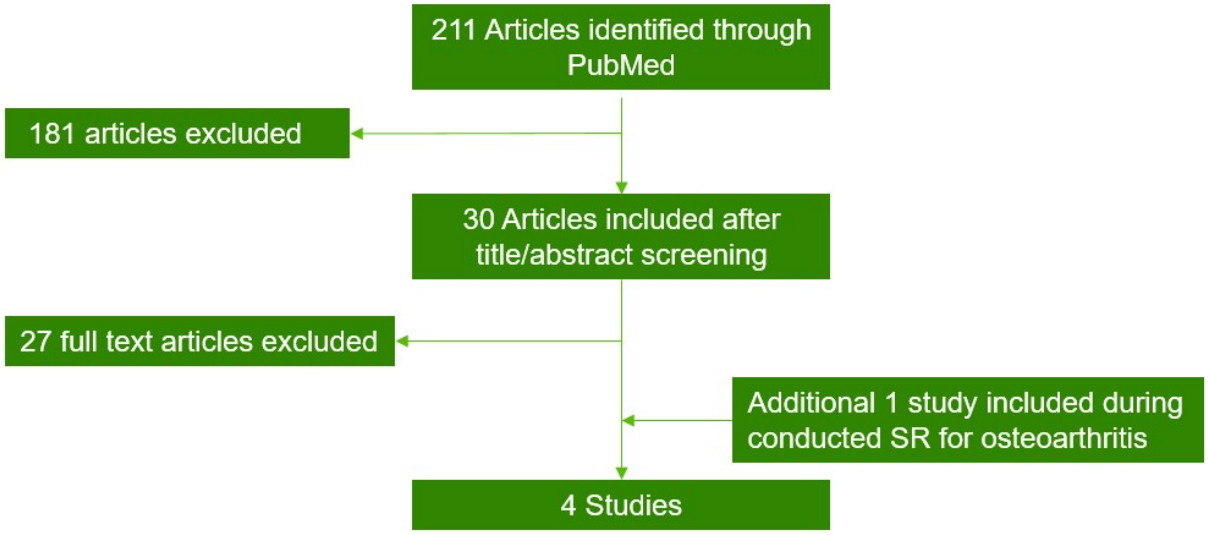
Input data

Ovid MEDLINE, EMBASE, CINAHL, CAB abstracts, WHOLIS, and SIGLE databases were searched for GBD 2010 and PUBMED was searched through October 2017 for GBD 2017. There were no age, sex, or language restrictions. The terms neck pain, neck ache, neckache, and cervical pain individually and combined with each of the following terms: prevalen*, inciden*, cross-sectional, cross sectional, epidemiol*, survey, population-based, population based, population study, population sample.

Exclusion criteria were:

1. Sub-populations clearly not representative of the national population
2. Not a population-based study
3. Studies on a specific type of neck pain (eg, following neck fracture)
4. Low sample size (less than 150)
5. Review rather than original studies

Figure 1: PRISMA diagram of neck pain systematic review from 2016–2017



Additional information was derived from unit record data of surveys in the GHDx, GBD's repository of population health data including National Health and Nutrition Examination Survey (NHANES) and National Health Interview Survey (NHIS) in the USA. Opportunistically, additional studies encountered during data review were added for GBD 2019. In addition, data from USA claims data for 2000 and 2010–2015 by state and Taiwan claims data from 2016 were included.

Table 1: Data inputs for neck pain

Measure	Total sources	Countries with data
All measures	92	26
Prevalence	77	26
Remission	1	1
Proportion	15	1

Age and sex splitting

Reported estimates of prevalence were split by age and sex where possible. First, if studies reported prevalence for broad age groups by sex (eg, prevalence in 15- to 65-year-old males and females separately), and also by specific age groups for both sexes combined (eg, prevalence in 15- to 30-year-olds, then in 31- to 65-year-olds, for males and females combined), age-specific estimates were split by sex using the reported sex ratio and bounds of uncertainty. Second, prevalence data for both sexes that could not be split using a within-study ratio were split using a sex ratio derived from a meta-analysis of existing sex-specific data using MR-BRT. The female to male ratio was 1.31 (1.30 to 1.32). Finally, after the application of bias adjustments, where studies reported estimates across age groups spanning 25 years or more, these were split into five-year age groups using the prevalence age pattern estimated by DisMod-MR 2.1 in GBD 2017.

Data adjustment

We used MR-BRT to calculate adjustment factors to correct for biases introduced by alternative case definitions. These alternative case definitions were studies that reported a too broad anatomical region, episode duration of greater than three months, recall periods of one week to one month, recall periods between two months and one year, activity-limiting neck pain, and studies conducted among schoolchildren. We added three additional covariates for claims data in the USA from the year 2000 and from 2010 onward and for Taiwan claims data. The mean and standard error for the coefficients were calculated using the MR-BRT network crosswalk adjustment method. The covariate for claims data from Taiwan was not included in the final adjustments, as we were unable to find matches to inform a reliable crosswalk. Betas and exponentiated values (which can be interpreted as an odds ratio) for these two covariates are shown in the table below:

Table 2: MR-BRT crosswalk adjustment factors for neck pain

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Log (95% CI)	Adjustment factor*
Point prevalence	Ref	0.30	---	---
Anatomical region too broad	Alt		0.89 (0.66 to 1.12)	2.43 (1.93 to 3.07)
Episode duration >= 3 months	Alt		-0.69 (-0.85 to -0.53)	0.50 (0.43 to 0.59)
Recall periods of 1 week to 1 month	Alt		0.94 (0.51 to 1.38)	2.56 (1.65 to 3.96)
Recall periods between 2 months and one year	Alt		1.23 (0.80 to 1.68)	3.46 (2.24 to 5.36)
Studies among schoolchildren	Alt		0.13 (-0.61 to 0.87)	1.14 (0.54 to 2.39)
Activity-limiting neck pain	Alt		-1.23 (-1.23 to -1.18)	0.30 (0.29 to 0.31)
USA Claims data – 2000	Alt		-1.58 (-2.08 to -1.08)	0.21 (0.13 to 0.34)
USA Claims data – 2010–2016	Alt		-0.65 (-1.09 to -0.21)	0.52 (0.23 to 0.81)

**Adjustment factor is the transformed Beta coefficient in normal space, and can be interpreted as the factor by which the alternative case definition is adjusted to reflect what it would have been if measured as the reference.*

After adjusting data for case definition, we outliered data with a median absolute deviation of 2 or more above or below the mean. This was done in a systematic way to cull data that were implausibly high or low.

Modeling strategy

Prior settings in the DisMod model included setting excess mortality to 0, and it was assumed that there was no incidence or prevalence of neck pain before the age of 5 years. We made no substantive changes in the modeling strategy from GBD 2017, with the exception of increasing the coefficient of variation

from 0.4 to 0.8 for the priors being passed down the geographical hierarchy to allow the model to better follow the data.

Severity and Disability

The basis of the GBD disability weight survey assessments are lay descriptions of health states highlighting major functional consequences and symptoms. The lay descriptions and disability weights for neck pain severity levels are shown below.

Table 3. Severity distribution, details on the severity levels for NP in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)	Proportions
Neck pain, mild	This person has neck pain, and has difficulty turning the head and lifting things	0.052 (0.036–0.074)	0.67 (0.57–0.75)
Neck pain, moderate	This person has constant neck pain, and has difficulty turning the head, holding arms up, and lifting things	0.112 (0.079–0.162)	0.12 (0.08–0.19)
Neck pain, severe	This person has severe neck pain, and difficulty turning the head and lifting things. The person gets headaches and arm pain, sleeps poorly, and feels tired and worried	0.226 (0.147–0.323)	0.06 (0.05–0.07)
Neck pain, most severe	This person has constant neck pain and arm pain, and difficulty turning the head, holding arms up, and lifting things. The person gets headaches, sleeps poorly, and feels tired and worried	0.300 0.199–0.434)	0.15 (0.11–0.20)

The severity distributions are derived from an analysis of the Medical Expenditure Panel Surveys (MEPS) in the USA. MEPS is an overlapping continuous panel survey of the United States non-institutionalised population whose primary purpose is to collect information on the use and cost of health care. Panels are two years long and are conducted in five rounds, which are conducted every five to six months. A new panel begins annually, while the last panel is in its second year. Each panel typically contains about 30,000 to 35,000 individual respondents (http://www.meps.ahrq.gov/survey_comp/hc_data_collection.jsp).

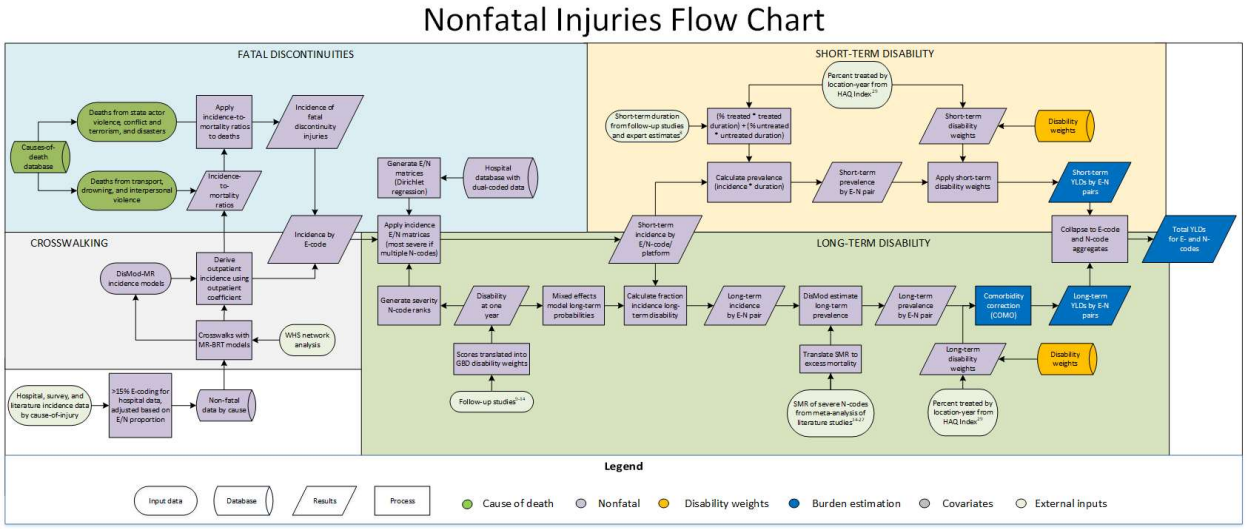
MEPS was initiated in 1996 but only began collecting health status data in the form of SF-12 responses in 2000. For GBD 2019 we used data from 2000–2014. Respondents self-administer the SF-12 twice per panel, at rounds two and four, typically about a year apart. Only adults 18 years and older completed the SF-12. MEPS also usually collects information on diagnoses based on self-report of reasons for encounters with health services. In addition, diagnoses are derived through additional questions on “problems that bother you” or conditions that led to “disability days,” ie, days out of role due to illness. Professional coders translate the verbatim text into three-digit ICD-9 codes. The main reason for neck pain being measured in MEPS relates to health care contact.

In order to derive a crosswalk of SF-12 values into a scale comparable with that used by the GBD disability weights, small studies on convenience samples were conducted asking respondents to fill in SF-12 to reflect 62 lay descriptions of diverse severity that were used to derive the GBD disability weights. From these responses a relationship between SF-12 summary score and the GBD DWs was

derived. With regression methods, average disability weights were calculated for each of 156 conditions for which there were corresponding diagnoses in MEPS, while controlling for any co-morbid other condition by adding dummy variables for each condition. As our case definition is for point prevalence of neck pain, we ignored the proportion of MEPS respondents with a neck pain diagnosis for whom in our regression we found no disability attributable to neck pain. For the remaining cases we binned the amount of DW attributed to neck pain across the four health states assuming thresholds at the midpoints between DW values.

Injuries

Flowchart



Case definition

For GBD 2019, the Injuries estimation process for non-fatal health outcomes encompasses a range of 30 causes, including transport injuries, falls, drowning, self-harm, interpersonal violence, and animal contact. Injury incidence is defined using ICD-9 codes E000-E999 and ICD-10 chapters V to Y. For non-fatal estimation, Chapters S and T in ICD-10 and codes 800-999 in ICD9 are used to estimate morbidity. Each of these 30 causes of injury can result in a variety of physical injury sequelae (e.g., traumatic brain injury), which we call the "nature of injury." Although the initial DisMod models are at the "cause of injury" level (e.g., drowning), each cause of injury is distributed into cause-nature pairs to capture the actual disability that develops. We report incidence, prevalence, and YLDs due to injuries at the cause-nature pair level.

We make additional distinctions between inpatient and outpatient injuries and between short-term and long-term injuries. Inpatient injuries are defined as injuries that led to overnight hospitalisation, whereas outpatient injuries are defined as ones treated in outpatient settings or emergency care. We define short-term injuries as injuries lasting less than one year and long-term injuries as those lasting longer than one year, at which point we assume lifelong disability.

Input data

Model inputs

To estimate morbidity from injuries, we used data from hospital records, emergency department records, insurance claims, and surveys to produce years lost to disability (YLDs) by country, year, sex, age, external cause-of-injury, and nature-of-injury category. Many countries report hospital data using a mix of cause-of-injury and nature-of-injury codes. In order to retain as much of the data as possible, we included all datasets that had at least 15% of cases coded to the cause of injury. In GBD 2015, we chose 45% as the threshold but have since lowered the threshold to 15%. We made this distinction after assessing the proportions of major injury causes (road injury and falls) in each of the data sources. We concluded that there were no obvious differences between country data with 15%–45% coverage of external cause codes and those with more than 45% coverage. Below the 15% threshold, the cause of nature coding

became more disproportionate when compared to sources with higher cause of nature coding. We assessed the raw hospital data to make sure that there was no disproportionate coding to certain causes in the 15%–45% cause-of-injury coding range. We increased the cause-specific injury cases from these datasets proportionately to sum to the total number of injury cases.

Conflict, war and executions, and police conflict data were obtained from the Uppsala Conflict Data Program [2], the International Institute for Strategic Studies [3], the Armed Conflict Location and Event Dataset [4], the Social Conflict Analysis Database [5], and vital registration systems. Disaster data were obtained from the International Disaster Database from the Center for Research on the Epidemiology of Disasters [6].

Data searches

GBD 2019 utilized the same data as GBD 2017 [1] with some updates to existing data and additions of new data. For GBD 2019, hospital and emergency department records were supplemented with more recent and available site-years, including adding subnational detail in select countries. A hospital utilisation envelope that gave reliable denominators for hospital data allowed for the use of more data sources. We applied correction factors to account for repeat hospital visits within a three-month time window (derived from US claims data) to the incidence estimates to avoid double-counting multiple health service contacts for the same injury. For GBD 2019, we also incorporated a correction for access to health care facilities to account for inidividuals who sustain an injury but do not have access to a hospital or health care facility. This correction is based on the health care access and quality index (HAQi) [29].

Additionally, prior to estimation, we reviewed existing usage in GBD 2017 of other types of data that could be incorporated into nonfatal estimates of injuries. In GBD 2017, we added injury claims data from the Accident Compensation Corporation in New Zealand into the transport, self-harm, and animal contact incidence models [1]. These claims data span ten years (2008-2017) and provide detailed information on age and ethnicity (Maori/non-Maori). We also added national survey data from China, Ghana, India, Mexico, Russian Federation, and South Africa from the World Health Organization's Study on Global AGEing and Adult Health were included in the estimation of injuries due to road accidents and falls. Injury cases from the Vietnam National Injury Survey (VNIS) were also added for GBD 2019. We also added literature studies from India and South Africa based on inputs from the GBD collaborator network.

Infrequently, data points were marked as outliers. Reasons for this were that the data point did not follow the age or time pattern as expected and/or if the incidence rate of people sustaining an injury from a certain cause of injury was not plausible. Table 1 contains information about data coverage for each cause of injury, not including fatal discontinuities: state actor violence, exposure to forces of nature, and conflict and terrorism.

Table 1. Data inputs for injuries incidence modelling

Cause	Total sources	Countries with data
Road injuries	284	75
Pedestrian road injuries	169	23
Cyclist road injuries	178	23
Motorcyclist road injuries	173	23
Motor vehicle road injuries	179	23
Other road injuries	168	19

Other transport injuries	182	20
Falls (EMR)	220	38
Drowning (EMR)	37	11
Fire, heat, and hot substances	212	34
Poisonings	208	34
Poisoning by carbon monoxide (EMR)	154	19
Poisoning by other means	161	20
Exposure to mechanical forces	182	23
Unintentional firearm injuries	178	19
Other exposure to mechanical forces	181	22
Adverse effects of medical treatment	294	44
Animal contact	214	31
Venomous animal contact	180	21
Non-venomous animal contact	180	21
Pulmonary aspiration and foreign body in airway	185	21
Foreign body in eyes	202	21
Foreign body in other body part	203	24
Environmental heat and cold exposure	191	24
Other unintentional injuries	160	21
Self-harm (EMR)	230	38
Self-harm by firearm (EMR)	175	27
Self-harm by other specified means	162	21
Interpersonal violence	212	33
Physical violence by firearm (EMR)	30	6
Physical violence by sharp object	187	25
Physical violence by other means	181	22

Modelling strategy

As in previous GBD iterations, two categories of injury severity were separately modelled: injuries warranting inpatient care and injuries warranting other health care. Injuries warranting inpatient care refer to injury cases of sufficient severity to require inpatient care, if there are no restrictions in access to health care. Injuries warranting other health care refer to injury cases of sufficient severity to require health care attention but not hospitalisation. This category includes emergency department visits. In order to best measure the burden of injuries, the GBD 2019 estimates excluded trivial injuries by restricting morbidity analysis to cases warranting some form of health care in a system with full access to health care. We intended to include cases with injuries that did not receive care in areas with restricted access to health care, but that would have warranted some type of health care in a system with full access to health care. In some surveys, after asking about recall of injuries in the past month or year, respondents were further probed on whether they sought care and why they did not. This allowed us to include cases who cited financial or geographical barriers as reasons for not seeking care.

Cause-of-injury incidence

The list of unique (i.e., not counting aggregate categories like road injuries or interpersonal violence) cause-of-injury categories did not change from the 30 unique causes in GBD 2017 [1]. We treat executions and police conflict (“state actor violence”) as a typical cause of injury rather than as a fatal

discontinuity; however, the cause is modelled using the fatal discontinuity estimation strategy using incidence-to-mortality ratios because we do not have incidence data for state actor violence.

The majority of incidence data exist at the external cause-of-injury level. Incidence for cause-of-injury categories was modelled using DisMod-MR 2.1. Multiple datasets from hospital and emergency/outpatient departments, insurance claims, and surveys were fed into these incidence models. We separately estimated two categories of injury severity: inpatient and outpatient injuries.

Excess mortality modeling

In previous rounds, priors on excess mortality rate (EMR) were estimated in DisMod by matching prevalence data points with their corresponding CSMR values within the same age, sex, year, location (by dividing CSMR by prevalence). For short duration conditions like injuries (remission > 1), the corresponding prevalence was derived by running an initial model and then applying the same CSMR/prevalence method. However, for many causes, DisMod estimated a rather unrealistic pattern of EMR compared to an expected pattern of decreasing EMR with greater access to quality health care. Such unexpected patterns often signal inconsistencies between CSMR estimates and the measures of prevalence and/or incidence. This was especially the case for the injuries that we implemented an EMR modeling framework, which included drowning, falls, poisoning by carbon monoxide, assault by firearm, self-harm, and self-harm by firearm.

In effort to provide greater guidance to DisMod on the expected pattern of EMR, EMR data generated in the previous round were modeled using the MR-BRT approach by age and sex with a prior on healthcare access and quality index (HAQi) [29] having a negative coefficient. Results from MR-BRT were then predicted for each location year, sex and for ages 0, 10, 20 … 100. We included HAQi as a country-level covariate to inform EMR with a mean and standard deviation produced from MR-BRT. However, even without this setting DisMod would tend to estimate a coefficient that was consistent with the MR-BRT analysis. For the six injuries using EMR inputs modeled from MR-BRT, we set the trimming parameter to trim 0.1% of the datapoints, added a cubic-spline on age with knots set by data density, and a fixed effect on sex.

Adjusting data

For GBD 2017, we used two covariates in each DisMod-MR 2.1 model as a multiplier from inpatient to outpatient incidence, namely covariates “outpatient” and “in- and outpatient” [1]. For GBD 2019, the adjustment of data via study-level covariates was performed out of DisMod using adjustment coefficients derived from a network analysis on World Health Survey data on road injuries spanning over 50 countries. First, ST-GPR was used to estimate the proportion of people who were able to receive care for their injuries using the ratio of inviduals who received in- or outpatient care to individuals who were injured overall. These proportions allowed us to adjust data to the definition “injuries that received inpatient or outpatient care.” Then, MR-BRT was used to crosswalk “received care” incidence and outpatient incidence both to inpatient incidence, using inpatient versus outpatient incidence comparisons from the United States National Hospital Ambulatory Medical Care Survey. This process is summarized in Figure 1, and an example of a MR-BRT output can be seen Figure 2. Country-level covariates are shown in Table 2.

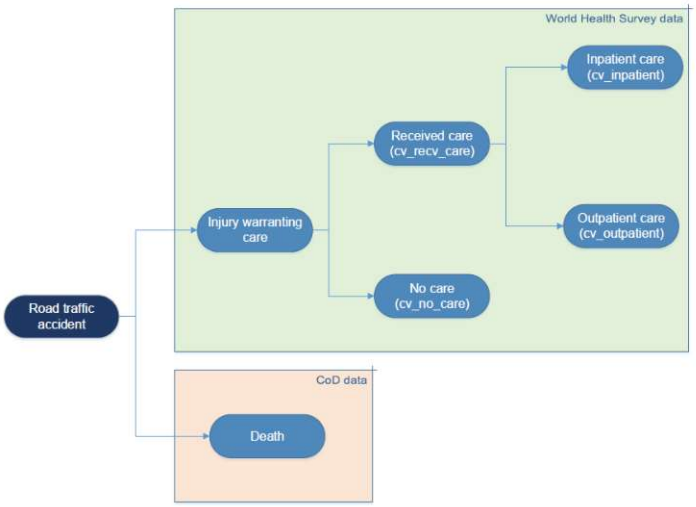


Figure 1. Overview of data adjustment process using road injuries data from World Health Survey data

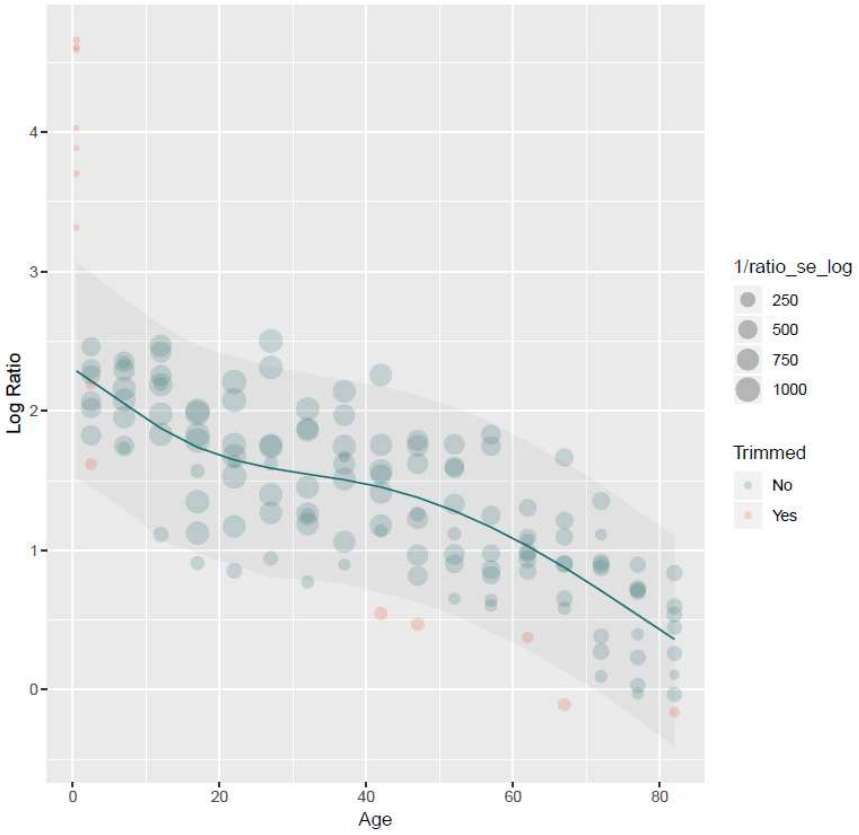


Figure 2. MR-BRT model for road injuries by age. The y-axis shows the log of the ratio of outpatient cases to inpatient cases for each age along the x-axis. This shows how outpatient or ED visits without admission are more probable per inpatient admission in younger ages, while in the oldest ages, it is less likely for a road injury case to be seen only as an outpatient relative to each observed inpatient admission. The red data points show data that were trimmed by MR-BRT. See Figures 5–15 for additional MR-BRT plots.

Table 2. Country-level covariates for DisMod-MR 2.1 incidence models for injuries

Model	Covariate	Exponentiated Value
Road injuries	Log-transformed age-standardized SEV scalar: Road Inj	3.40 (3.29 — 3.48)
	Vehicles - 2+4 wheels (per capita)	1.04 (1.03 — 1.06)
Pedestrian road injuries by road vehicle	Log-transformed age-standardized SEV scalar: Pedest	2.58 (2.14 — 3.18)
Cyclist road injuries	Log-transformed age-standardized SEV scalar: Cyclist	2.43 (2.14 — 2.82)
	Vehicles - 2+4 wheels (per capita)	1.00 (1.00 — 1.01)
Motorcyclist road injuries	Log-transformed age-standardized SEV scalar: Mot Cyc	2.14 (2.12 — 2.20)
	Vehicles - 2 wheels (per capita)	1.54 (1.49 — 1.59)
Motor vehicle road injuries	Log-transformed age-standardized SEV scalar: Mot Veh	2.27 (2.12 — 2.57)
	Vehicles - 4 wheels (per capita)	1.21 (1.18 — 1.23)
Other road injuries	Log-transformed age-standardized SEV scalar: Oth Road	2.17 (2.12 — 2.26)
Other transport injuries	Log-transformed age-standardized SEV scalar: Oth Trans	3.41 (3.26 — 3.49)
Falls (EMR)	Log-transformed age-standardized SEV scalar: Falls	3.48 (3.47 — 3.49)
Drowning (EMR)	Log-transformed age-standardized SEV scalar: Drown	2.77 (2.24 — 3.42)
	Coastal Population within 10km (proportion)	1.02 (1.00 — 1.08)
Fire, heat, and hot substances	Log-transformed age-standardized SEV scalar: Fire	3.39 (3.24 — 3.49)
	Indoor Air Pollution (All Cooking Fuels)	1.05 (0.97 — 1.18)
Poisonings	Log-transformed age-standardized SEV scalar: Poison	3.32 (3.04 — 3.48)
Poisoning by carbon monoxide (EMR)	Log-transformed SEV scalar: Poison	2.35 (2.13 — 2.79)
Poisoning by other means	Log-transformed SEV scalar: Poison	3.07 (2.56 — 3.46)
Exposure to mechanical forces	Log-transformed age-standardized SEV scalar: Mech	3.45 (3.39 — 3.49)
Unintentional firearm injuries	Log-transformed age-standardized SEV scalar: Mech Gun	2.27 (2.13 — 2.52)
Other exposure to mechanical forces	Log-transformed age-standardized SEV scalar: Oth Mech	3.45 (3.38 — 3.49)
Adverse effects of medical treatment	Socio-demographic Index	1.64 (1.63 — 1.65)
Animal contact	Log-transformed age-standardized SEV scalar: Animal	3.45 (3.40 — 3.49)
	LDI (I$ per capita)	0.74 (0.74 — 0.74)

Venomous animal contact	Log-transformed age-standardized SEV scalar: Venom	2.14 (2.12 — 2.19)
Non-venomous animal contact	Log-transformed age-standardized SEV scalar: Non Ven	3.47 (3.43 — 3.49)
Pulmonary aspiration and foreign body in airway	Log-transformed age-standardized SEV scalar: F Body Asp	2.83 (2.25 — 3.44)
Foreign body in eyes	—	—
Foreign body in other body part	Log-transformed SEV scalar: Oth F Body	2.29 (2.12 — 2.69)
Environmental heat and cold exposure	Population-weighted mean temperature	1.17 (1.12 — 1.21)
	90th percentile climatic temperature in the given country-year.	1.54 (1.44 — 1.64)
Other unintentional injuries	Log-transformed age-standardized SEV scalar: Oth Unint	3.29 (2.92 — 3.48)
Self-harm (EMR)	Log-transformed age-standardized SEV scalar: Self Harm	2.15 (2.12 — 2.21)
Self-harm by firearm (EMR)	Log-transformed age-standardized SEV scalar: Self Other	3.36 (3.27 — 3.45)
Self-harm by other specified means	Log-transformed age-standardized SEV scalar: Self Harm	3.43 (3.34 — 3.49)
Interpersonal violence	Log-transformed age-standardized SEV scalar: Violence	2.13 (2.12 — 2.16)
Assault by firearm (EMR)	Log-transformed age-standardized SEV scalar: Viol Gun	2.20 (2.12 — 2.36)
Assault by sharp object	Log-transformed age-standardized SEV scalar: Viol Knife	2.12 (2.12 — 2.14)
Assault by other means	Log-transformed age-standardized SEV scalar: Oth Viol	2.91 (2.74 — 3.10)

Fatal discontinuities

Due to the sporadic nature of the incidence of injuries and a lack of time trend that results from fatal discontinuities, DisMod-MR 2.1 was not used to model incidence due to fatal discontinuities, including state actor violence, exposure to forces of nature (i.e., natural disaster), and conflict and terrorism. Instead, incidence-to-mortality ratios were averaged over super-region, year, and sex to limit the variability in the ratios applied to fatal discontinuities. For disaster incidence, the incidence-to-mortality ratio was calculated as an average of road injuries and drowning if there was a water-related natural disaster in that specific country-year noted in the International Disaster Database [6]. For conflict and terrorism, the incidence-to-mortality ratio was calculated as an average of the road injuries and interpersonal violence causes. We treated executions and police conflict as similar to the fatal discontinuities in that we imputed the incidence using the incidence-to-mortality ratio of interpersonal violence. These incidence-to-mortality ratios were applied to mortality estimates from shock events from the Cause of Death database and shocks modelling process to calculate fatal discontinuity injuries incidence.

Follow-up studies

Similar to GBD 2017, we used follow-up data obtained from a pooled dataset of six follow-up studies from China, the Netherlands, and the US (see Table 3) [1]. These studies followed patients for at least one year

after the injury. We also used the Medical Expenditure Panel Survey (MEPS) [7]. MEPS is a large-scale overlapping continuous panel survey of the US non-institutionalized population that collects information on use and cost of health care and SF-12 responses. SF-12 responses are elicited twice over the two-year period that any individual is part of the study. Thus, MEPS offered the benefit of including health state measures of non-injured and destined to be injured and the benefit of having pre-injury and post-injury SF-12 responses. We pooled all available MEPS data over a 19-year span.

The follow-up studies used different patient reported outcome measures to assess health status, namely the SF-36, Version 1 SF-12, and the EQ-5D. To enable comparison across the six datasets, it was necessary to analyse the data in a standardised patient-reported outcome measure. First, we mapped all patient-reported outcome measures to Version 2 SF-12 (SF-12v2). Second, we normalised the health status measurements by mapping the SF-12 scores to a corresponding disability weight based on several opportunistic surveys asking respondents to score SF-12 based on the lay descriptions for a selection of 60 GBD health states. We ran a regression of logit-transformed disability weight on nature-of-injury category and age group and never-injured status. The pooled dataset informed both the nature-of-injury category hierarchy and the long-term probability of injuries, discussed below.

Table 3. Details of injury follow-up surveys used in GBD 2019

Dataset	Year	Type of data collected	Type of patients	Setting	Sample size* and response
Guangdong follow up survey, China[9]	2006–2007	Follow up survey among sample of ISS patients	Patients (15+ years) who were hospitalized that had been injured by road traffic injury, fall, blunt or penetrating trauma	Based on three national injury surveillance hospitals in Zhuhai, Guangdong Province in China	998 (response 87%)
LIS follow up survey, Netherlands[10]	2001–2002	Follow-up survey among stratified sample of ISS patients (oversampling less common, severe injuries)	Patients (15+ years) who visited the Emergency Department of a hospital and were discharged to the home environment and patients who were admitted to hospital	Based on 17 public hospitals in the Netherlands	8,564 (response 37%)
LIS follow-up survey, Netherlands[11]	2007–2008	Follow-up survey among stratified sample of ISS patients (oversampling less common, severe injuries)	Patients (15+ years) who visited the Emergency Department of a hospital and were discharged to the home environment and patients who were admitted to hospital	Based on 15 public hospitals in the Netherlands	8,057 (response 36%)
NSCOT – National study on Costs and	2001–2002	A prospective cohort study was conducted among a sample of	Patients treated for a moderate to severe injury (as defined by at least one injury	Based on 69 hospitals in 12 states in the US	5,191 (response 61%)

Outcomes of Trauma, USA[12]		adult trauma patients treated at Level I trauma centers and non-trauma center hospitals	of an Abbreviated Injury Scale (AIS) score of 3 or greater		
SCTBIFR – South Carolina Traumatic Brain injury Follow-up Registry, USA[13]	1999–2002	A prospective cohort study was conducted among injured in-patients with a traumatic brain injury-related injury	Patients (15+ years) who were admitted to hospitals and met the CDC case definition of TBI – trauma to the head associated with altered consciousness, amnesia, neurological abnormalities, skull fracture, intracranial lesion, or death	Discharged from all nonfederal in-state acute care hospitals	7,613 (response 28%)
Burns outcome study, Netherlands[14]	2003–2006	A multicenter prospective cohort was conducted among adult (severe) burn patients	Injury patients who sustained severe burns	Three public hospitals with specialized burn units.	311 (response 78%)

*number of patients that met the inclusion criteria; response rate = percentage of patients who responded to the follow-up survey (in case of multiple follow-up times the response rate of the first follow-up moment is reported).

Nature-of-injury category hierarchy

Multiple injuries can occur in one individual. For GBD 2019, a nature-of-injuries severity hierarchy was developed to establish a one-to-one relationship between cause-of-injury and nature-of-injury category. This means that in the case of multiple injuries the nature-of-injury category that was likely to be responsible for the largest burden was selected. To construct the hierarchy, we used data from the pooled dataset of follow-up studies [9–14]. The output of the regression of logit-transformed disability weight on nature-of-injury category and individual characteristics of the follow-up studies were used to calculate the mean long-term disability attributable to each nature-of-injury category. The ranking of nature-of-injury categories by their long-term disability weights formed the basis of our severity hierarchy. Hierarchies were developed separately, for injuries warranting inpatient care and injuries warranting other health care.

Table 4. Nature-of-injury hierarchies: combination of empirical hierarchies estimated from pooled follow-up studies and expert adjustments, for inpatient and outpatient injuries

Rank	Inpatient Hierarchy	Outpatient Hierarchy
1	Spinal cord lesion below neck level	Fracture of pelvis
2	Amputation of lower limbs, bilateral	Fracture of patella, tibia or fibula, or ankle
3	Amputation of upper limbs, bilateral	Fracture of hip
4	Spinal cord lesion at neck level	Fracture of skull
5	Fracture of hip	Amputation of thumb
6	Fracture of femur, other than femoral neck	Fracture of vertebral column
7	Amputation of upper limb, unilateral	Multiple fractures, dislocations, crashes, wounds, sprains, and strains
8	Amputation of lower limb, unilateral	Internal hemorrhage in abdomen and pelvis

9	Multiple fractures, dislocations, crashes, wounds, sprains, and strains	Fracture of femur, other than femoral neck
10	Effect of different environmental factors	Dislocation of hip
11	Fracture of patella, tibia or fibula, or ankle	Amputation of toe/toes
12	Moderate-Severe traumatic brain injury	Fracture of hand (wrist and other distal part of hand)
13	Fracture of foot bones except ankle	Amputation of fingers (excluding thumb)
14	Internal hemorrhage in abdomen and pelvis	Burns, <20% of total burned surface area without lower airway burns
15	Crush injury	Dislocation of knee
16	Minor traumatic brain injury	Contusion in any part of the body
17	Fracture of pelvis	Minor traumatic brain injury
18	Nerve injury	Foreign body in respiratory system
19	Severe chest injury	Severe chest injury
20	Dislocation of hip	Drowning and nonfatal submersion
21	Burns, >= 20% total burned surface area or >= 10% burned surface are if head/neck or hands/wrist involved w/o lower airway burns	Asphyxiation
22	Lower airway burns	Poisoning requiring urgent care
23	Fracture of skull	Effect of different environmental factors
24	Amputation of thumb	Foreign body in GI and urogenital system
25	Fracture of hand (wrist and other distal part of hand)	Fracture of sternum and/or fracture of one or more ribs
26	Fracture of vertebral column	Nerve injury
27	Contusion in any part of the body	Fracture of face bones
28	Open wound(s)	Dislocation of shoulder
29	Amputation of toe/toes	Injury to eyes
30	Dislocation of knee	Fracture of clavicle, scapula, or humerus
31	Amputation of fingers (excluding thumb)	Fracture of radius and/or ulna
32	Drowning and nonfatal submersion	Fracture of foot bones except ankle
33	Asphyxiation	Foreign body in ear
34	Burns, <20% total burned surface area without lower airway burns	Muscle and tendon injuries, including sprains and strains lesser dislocations
35	Muscle and tendon injuries, including sprains and strains lesser dislocations	Superficial injury of any part of the body
36	Fracture of face bones	Open wound(s)
37	Foreign body in respiratory system	Complications following therapeutic procedures
38	Poisoning requiring urgent care	
39	Foreign body in GI and urogenital system	
40	Fracture of sternum and/or fracture of one or more ribs	
41	Dislocation of shoulder	
42	Injury to eyes	
43	Fracture of clavicle, scapula, or humerus	
44	Fracture of radius and/or ulna	
45	Foreign body in ear	
46	Superficial injury of any part of the body	
47	Complications following therapeutic procedures	

Cause-nature matrices

Because injury disability is linked more to the nature of injury than to the cause of injury, matrices were generated to map the proportion of each cause-of-injury category that results in a particular nature-of-injury category. These matrices are based on a collection of dual-coded (i.e., both cause-of-injury and nature-of-injury coded) hospital and emergency department datasets [28]. The data for this step came from inpatient, outpatient, and emergency room discharge data from Argentina, Bulgaria, China, Colombia, Cyprus, Czech Republic, Denmark, Egypt, Estonia, Hungary, Iceland, Iran, Italy, Latvia, Malta, Mauritius, Mexico, Mozambique, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Macedonia, Uganda, United States, and Zambia. We applied our nature-of-injury severity hierarchy above to assert that every observation had one cause of injury and one nature of injury.

Dirichlet models were used to estimate all of the nature-of-injury category proportions for one cause of injury simultaneously. These models allow for consistent borrowing of information across age, sex, inpatient/outpatient, and high/low-income countries and assert that the nature-of-injury proportions within a cause-of-injury category must add up to 1. One cause-nature matrix was created for each combination of injury warranting hospital admission versus injury warranting other health care, high/low-income countries, male/female, and age category. Applying these matrices to our cause-of-injury incidence from DisMod-MR, we produced cases of injury warranting hospital admission and incidence of injury warranting other health care by cause and nature of injury.

Probability of permanent health loss

Disability due to injury was assumed to affect all cases in the short term with a proportion having long-term (permanent) outcomes. The probability of long-term outcomes was needed to estimate the incidence and subsequently the prevalence of cases with permanent health loss. In our conceptual model, individuals who suffer a non-fatal injury will, in the long-term, return to either full or partial health. If one-year post-injury patients return to a health status with more disability than their pre-injury health status, injury patients are assumed to have permanent disability from their injury. The difference between the pre-injury health states and health status one year after injury is assumed to be their permanent level of injury-related disability. We assessed the probability of developing permanent health loss using the pooled dataset of follow-up studies [9–14] and the MEPS [7] that were also used to generate the nature-of-injury hierarchy. To assess the probability of permanent health loss, we estimated the effects using a logit-linear mixed effects regression:

$$\begin{aligned} Logit(DW)_{im} = \; & \alpha + \beta(injuries_{im}) + \beta(never\ injured_i) + \beta(never\ injured_i * age_i) \\ & + \beta(fracture\ of\ pelvis_i) + \beta(fracture\ of\ pelvis_i * age_i) + \beta(poisoning_i * age_i) \\ & + \beta(moderate\ to\ severe\ TBI_i * age_i) + RE_c + RE_i \end{aligned}$$

where we included dummies for all the nature-of-injury categories $(injuries_{im})$, with the reference category being no injury (from MEPS dataset). We also included a dummy for never injured prior to the current injury, age, interactions between age and never injured status, and interactions with three long-term nature-of-injury categories that were found to significantly vary with age: pelvis fractures, poisonings, and moderate/severe traumatic brain injuries. In notation, subscript m refers to patient-reported outcome measure, i refers to individual, and c refers to country. Random effects (RE) were included to control for variation between countries and individuals.

After predicting overall disability at one-year follow-up, we estimated a counterfactual by setting all observations to "no injury," the reference group for $\beta(injuries_{im})$ in our model. The disability attributable to the nature of injury at one year was assumed to be the difference between our

counterfactual of no injury and predicted disability with injury. The probability of treated long-term outcomes was estimated via the ratio of this attributable disability relative to the long-term disability weight for that injury.

$$Probability\ of\ long-term\ disability = \frac{with\ injury\ disability_{im} - counterfactual\ disability_{im}}{DW_m}$$

We developed estimates of the probability of permanent health loss by nature-of-injury category, injury severity level (injuries warranting inpatient admission and injuries warranting other health care), and age. These probabilities are shown in Figure 3 for three selected age groups (25-30, 50-55, 75-80) and selected nature-of-injury categories by inpatient and outpatient. Moderate-severe TBI and spinal cord lesions only have inpatient injury long-term probabilities, and nerve injury, open wounds, and severe chest injury have long-term probabilities of zero for outpatient cases.

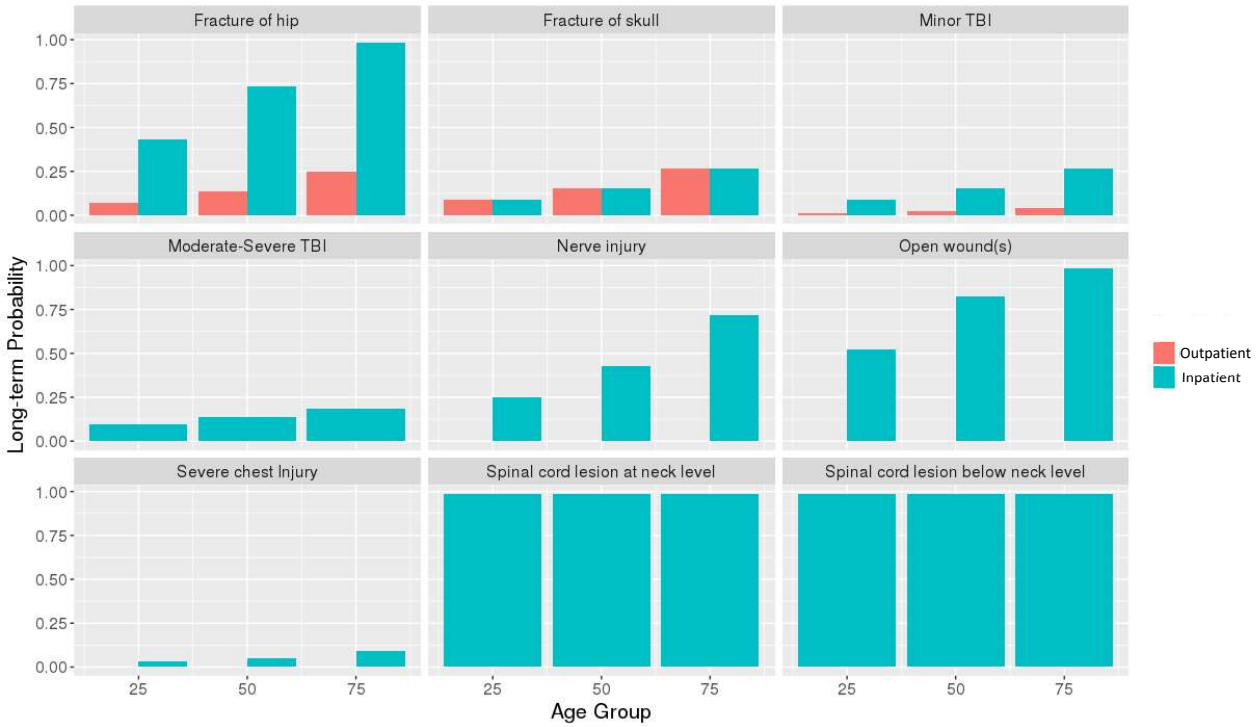


Figure 3. Long-term probabilities derived from the MEPS data for selected nature of injuries and age groups

Disability associated with treated and untreated cases

For many nature-of-injury categories, GBD 2019 has a separate disability weight for treated and for untreated cases. To estimate the percent treated for injuries in a given location-year, we used the Healthcare Access and Quality (HAQ) Index [29] with the same strategy described for the probability of permanent health loss. We chose a reasonable cutoff for the HAQ Index (75 on a scale of 0 – 100) as the threshold at and above which 100% of injuries were treated. This value captured most OECD countries for all years back to 1980. We then scaled all remaining location-years between 10% and 100% treated based on their HAQ Index value and used that as the percent treated in a given location-year. This was done at

the draw level to propagate uncertainty. We made the decision to ignore any long-term disability from injuries with implausibly high estimates of long-term disability.

Duration of short-term health loss

To determine the duration for treated cases of short-term injury, we analysed patient responses from two Dutch Injury Surveillance System follow-up studies conducted from 2001–2003 and 2007–2009 [8]. These studies collected data at 2.5, 5, 9, and 24 months post-injury to determine whether injury patients were still experiencing problems due to their injury. If not, the patients were asked how many days they had experienced problems. The injury patients that still reported having problems one year after the injury were assumed to be captured in our analysis of permanent disability. The duration for treated cases of short-term injury was estimated for injuries warranting inpatient admission and injuries warranting other health care separately. The estimates were supplemented by expert-driven estimates of short-term duration for nature-of-injury categories that did not appear in the Dutch dataset and untreated injuries.

Calculation of prevalence from incidence data – short-term injury

For short-term injury outcomes, which were assumed to be less than one year in duration, the prevalence for each cause-of-injury/nature-of-injury/severity-level grouping was approximated by the incidence for that grouping multiplied by the associated nature-of-injury/severity-level-specific duration.

Calculation of prevalence from incidence data – permanent health loss

For permanent health loss, we assumed no remission and thus integrated incidence over time to arrive at prevalence estimates. We used DisMod ODE (i.e., the "engine" of DisMod-MR 2.1) to carry out this integration for each combination of cause of injury and nature of injury by country, year, and sex. For this step we used random effects meta-analysis to pool data on standardised mortality ratios derived from literature reviews for spinal cord injury, burns covering more than 20% of the body, moderate to severe traumatic brain injury, hip fracture, and multiple significant injuries [14–27]. Here we include examples of these meta-analyses: hip fractures and traumatic brain injuries.

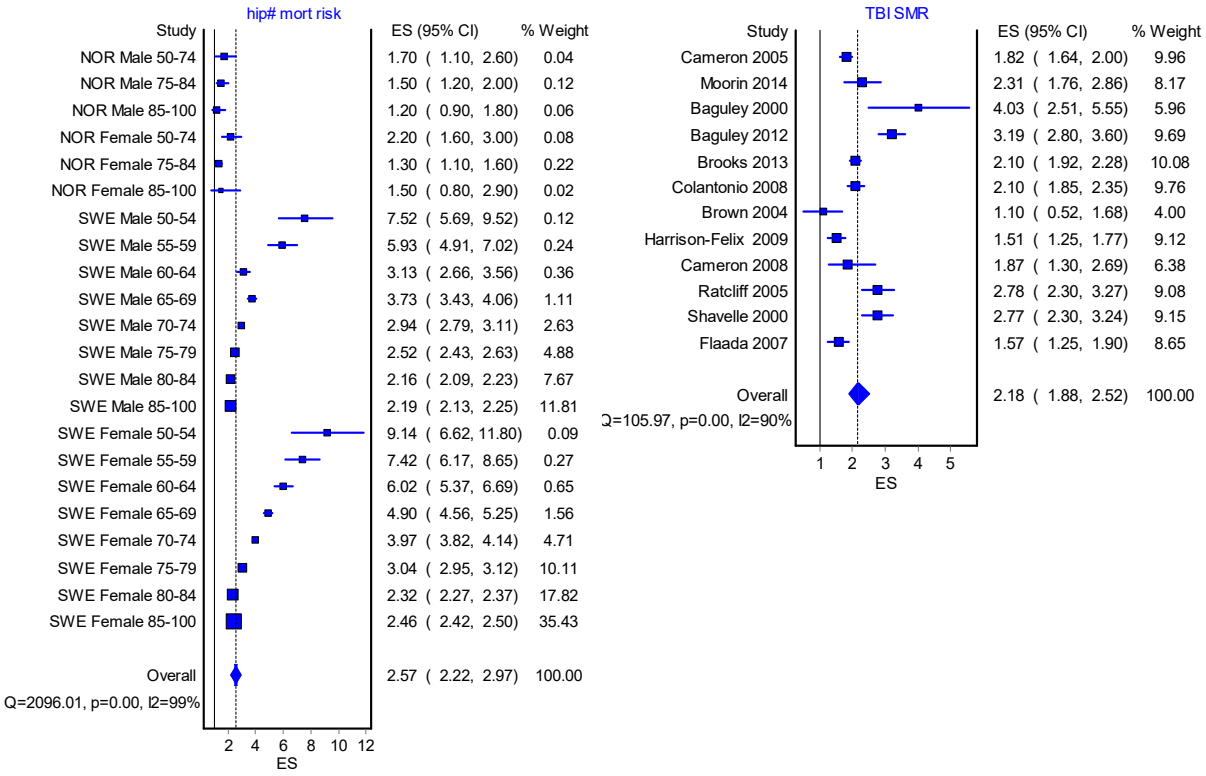


Figure 4. Meta-analyses of standardised mortality ratios derived from literature reviews: hip fractures and traumatic brain injury

For all other nature-of-injury categories, we assumed no long-term excess mortality. For the incidence estimates derived from fatal discontinuities – "exposure to forces of nature" and "conflict and terrorism" – we did not use DisMod as discontinuities by definition violate the assumption of a steady state in DisMod to estimate prevalence from incidence. For these two cause-of-injury categories, we coded the differential equations from DisMod ODE that determine the relationship between incidence, remission, mortality risk, and prevalence into Python and streamed out the prevalence from the incidence in the years of war or disaster by integrating over one year at a time.

MR-BRT models (continued)

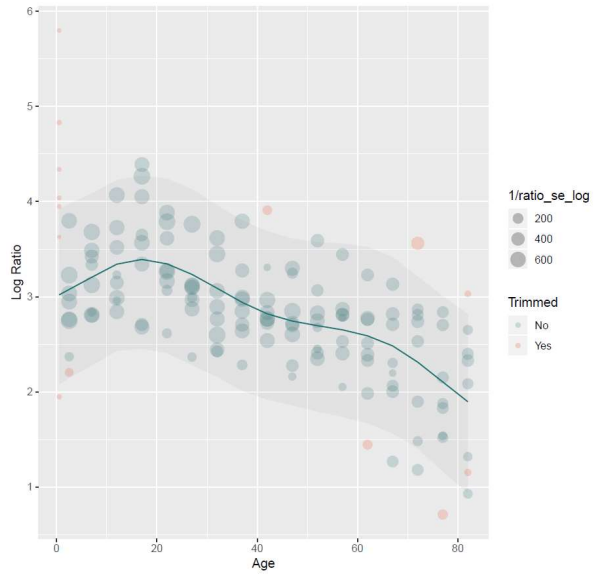


Figure 5. MR-BRT model for animal contact

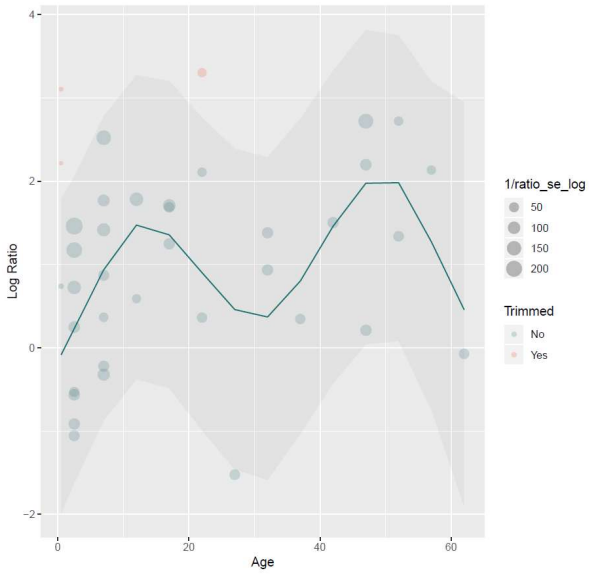


Figure 6. MR-BRT model for drowning

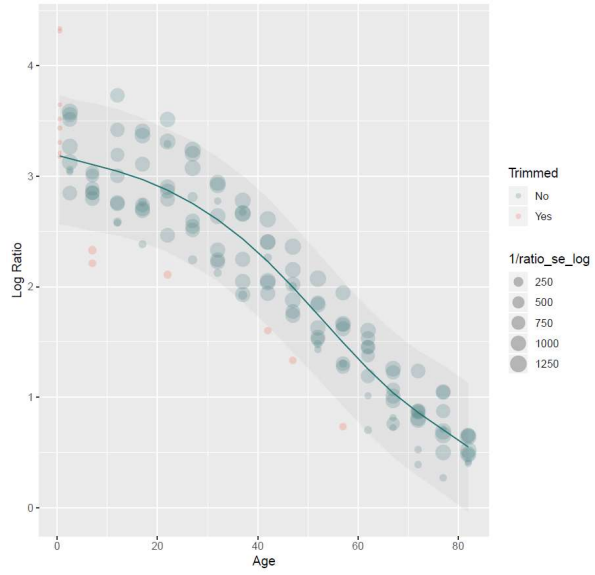


Figure 7. MR-BRT model for falls

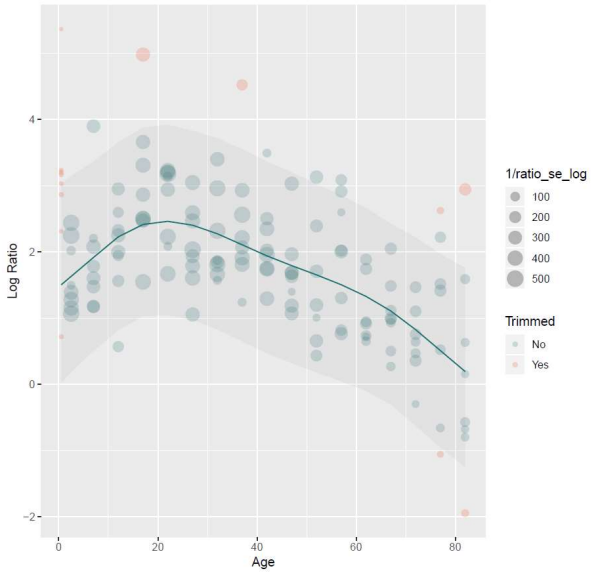


Figure 8. MR-BRT model for fire, heat, and hot substances

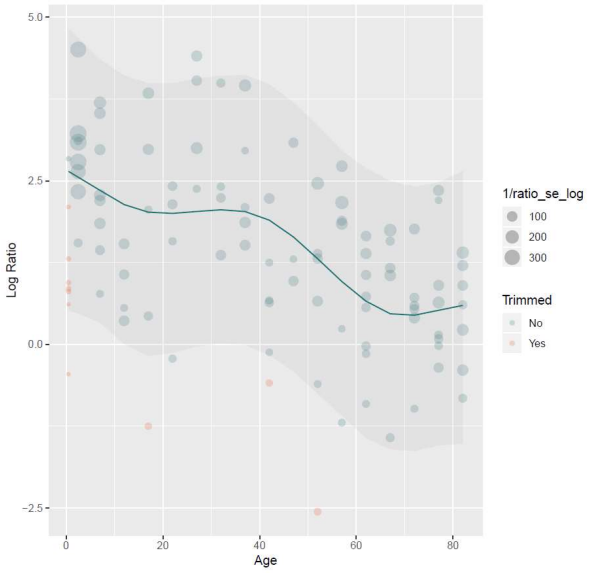


Figure 9. MR-BRT model for pulmonary aspiration and foreign body in airway

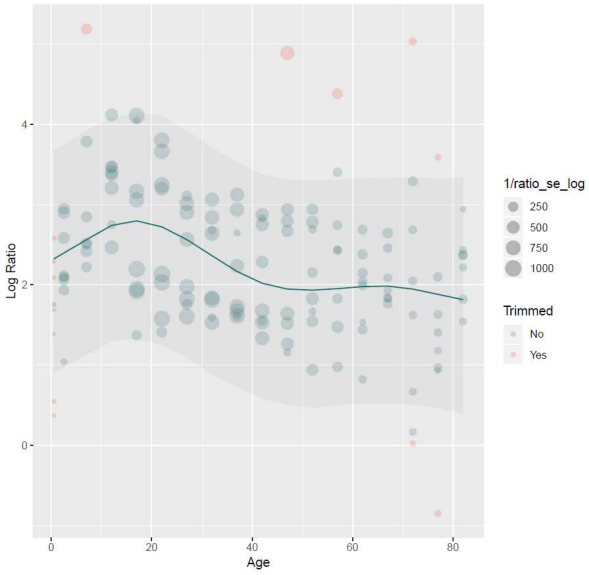


Figure 10. MR-BRT model for interpersonal violence

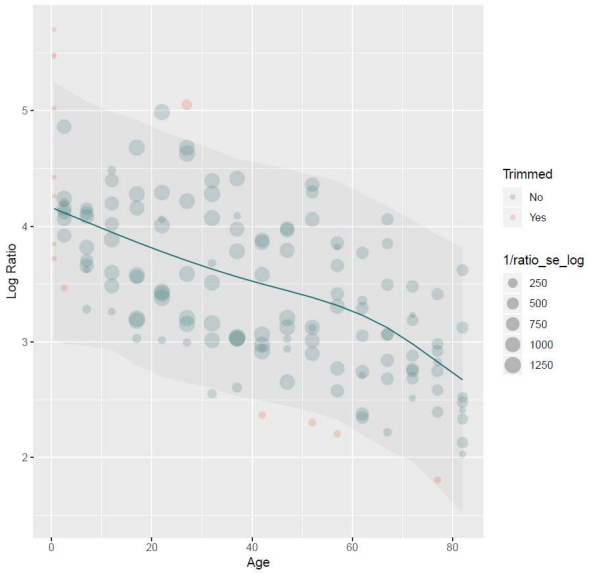


Figure 11. MR-BRT model for exposure to mechanical forces

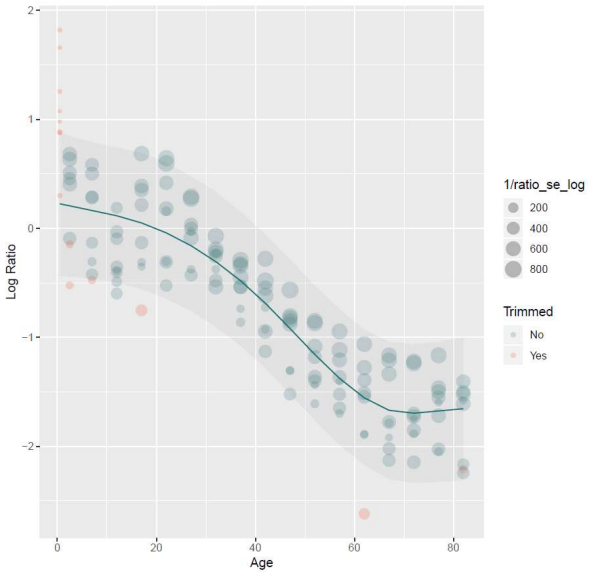


Figure 12. MR-BRT model for adverse effects of medical treatment

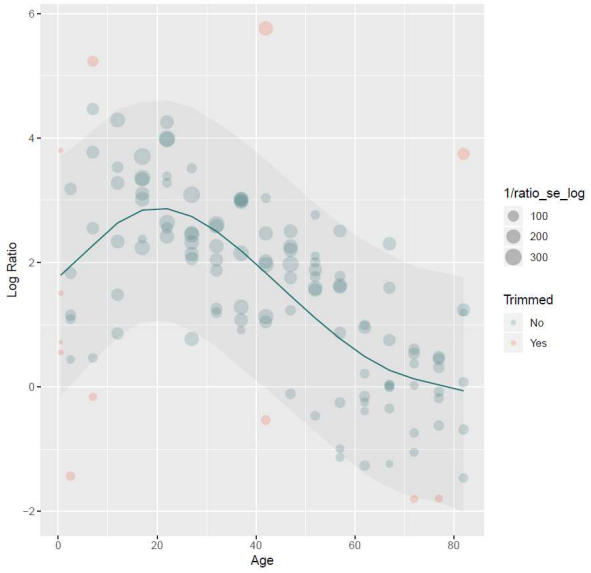


Figure 13. MR-BRT model for exposure to forces of nature

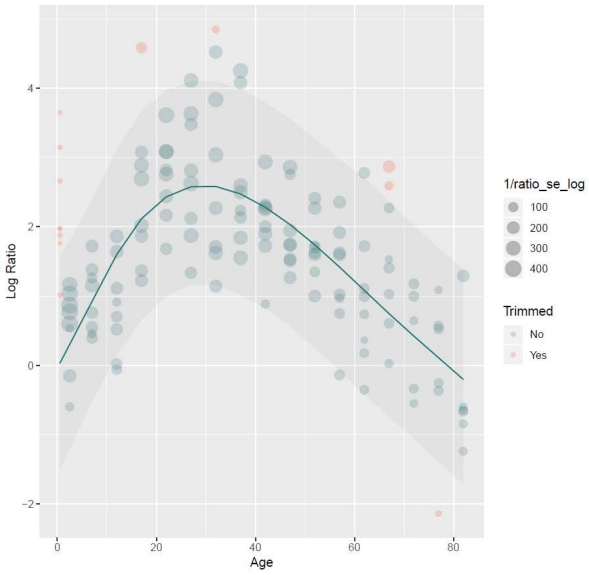


Figure 14. MR-BRT model for poisonings

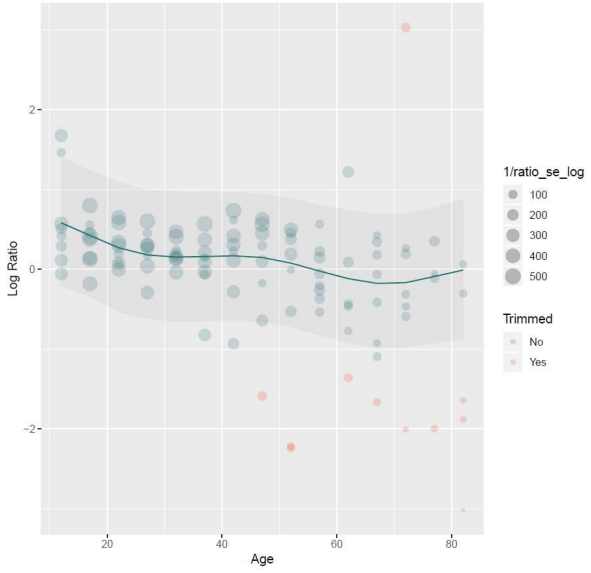


Figure 15. MR-BRT model for self-harm

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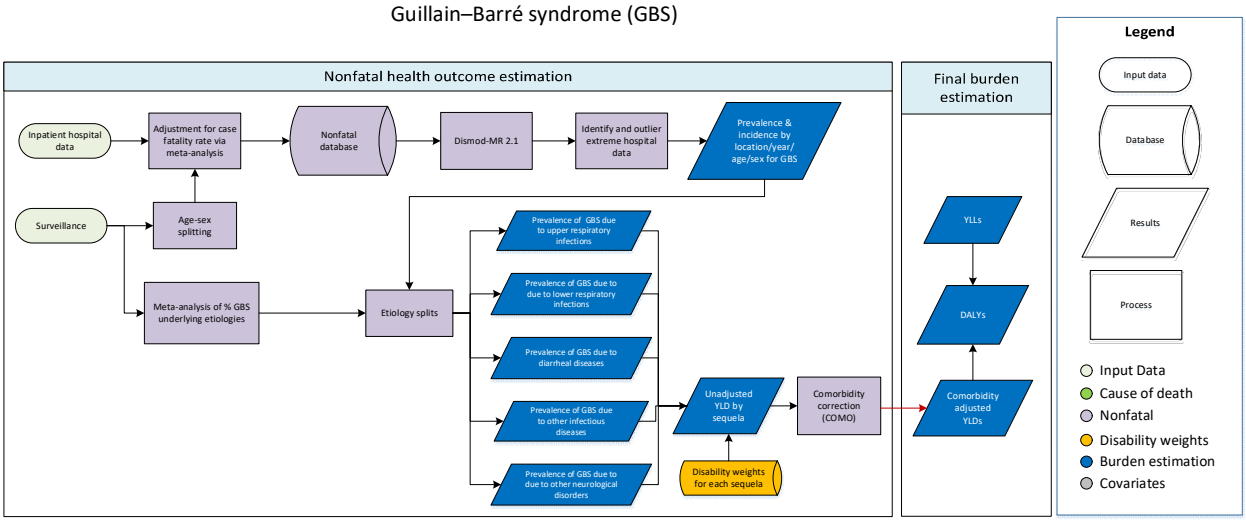
Guillain-Barré syndrome (GBS) impairment

Flowchart



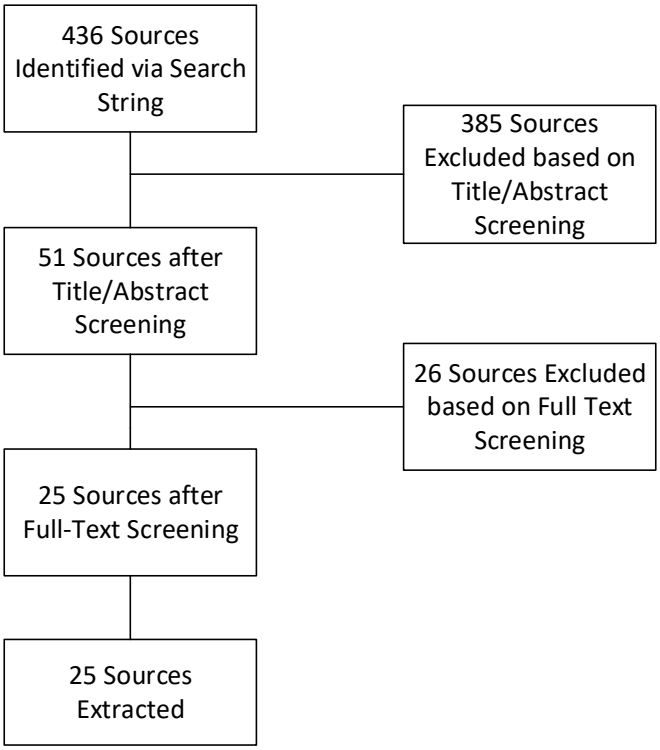
Case definition

Guillain-Barré syndrome is a rare condition that usually occurs as a complication of respiratory or gastrointestinal infection. It is considered an immune-mediated nerve dysfunction with rapid onset of weakness in the feet and legs, and sometimes the arms, which then progresses toward the trunk. In the acute phase, about a quarter of cases required mechanical ventilation for survival. The majority of cases fully recover within months to a year. The following ICD codes are used G61.0 (GBS) and 357.0 (Acute infective polyneuritis). Literature studies are accepted if there is a doctor diagnosed GBS, or other record of GBS.

Input data

Morbidity model inputs

An updated systematic review was done for GBD 2017 from January 2008 to September 2017 using the search string (((((("guillain barre syndrome"[MeSH Terms] OR ("guillain"[Title/Abstract] AND ("barre"[Title/Abstract] OR "barre"[Title/Abstract]) AND Title/Abstract[All Fields] AND "syndrome"[Title/Abstract])) OR "guillain-barre syndrome"[Title/Abstract]) OR "guillain-barre syndrome"[Title/Abstract]) OR "polyradiculoneuropathy"[Title/Abstract]) OR "Guillain-Barre syndrome"[Title/Abstract]) AND ("prevalence"[Title/Abstract] OR "incidence"[Title/Abstract] OR "epidemiology"[Title/Abstract] OR "remission"[Title/Abstract]))) AND ("2008/01/01"[Date - Publication] : "2017/09/26"[Date - Publication]). This search yielded 436 hits with 25 sources marked for extraction. A flowchart documenting this review is displayed below.



An additional informal search was undertaken for more information on remission and duration of GBS. We extracted remission data from four studies.

Inpatient hospital and claims incidence data were extracted using the ICD codes listed above. Only primary diagnoses were considered. This year we added additional years of claims data from the USA (2015, 2016), and for the first time added claims data from Poland (2015, 2016, 2017).

Aetiology data inputs

Information on aetiology splits come from a systematic review and meta-analysis of the literature completed for GBD 2010. This review searched for articles providing information on the proportion of Guillain-Barré cases with any described aetiological cause, the proportion of Guillain-Barré cases attributed to influenza, the proportion of Guillain-Barré cases attributed to upper respiratory infections, the proportion of Guillain-Barré cases attributed to diarrhoeal diseases and the proportion of Guillain-Barré cases attributed to other infections. This review yielded 35 articles; a breakdown of how many articles inform each proportion contributing to the split is provided below:

Split	Number of sources
All specified aetiologies	31
Influenza	3
Upper respiratory infections	26
Diarrhoeal diseases	25
Other infectious diseases	14

Total source counts for GBS used in GBD 2019 modeling are listed in the table below:

Measure	Total sources	Countries with data
All measures	330	46
Incidence	325	44
Remission	3	3
Case fatality rate	10	8
Proportion	35	19

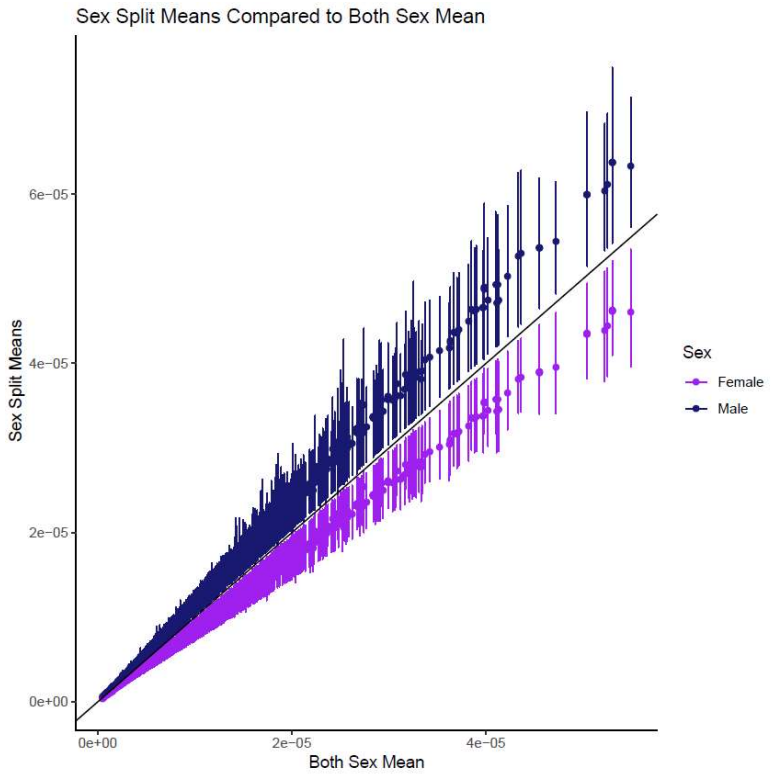
Data processing

Data extracted from published surveys, disease registries, surveillance studies and medical facilities were sometimes reported for both sexes or broadly defined age-groups in aggregate. In these cases, data were sex split and/or age split. Standard GBD sex splitting methods were used for studies with only "both" sex data points. We modeled the ratio of female/male prevalence in MR-BRT and calculated male prevalence:

$$prev_{male} = prev_{both} * \frac{pop_{both}}{(pop_{male} + ratio * pop_{female})}$$

And then calculated female prevalence:

$$prev_{female} = ratio * prev_{male}$$

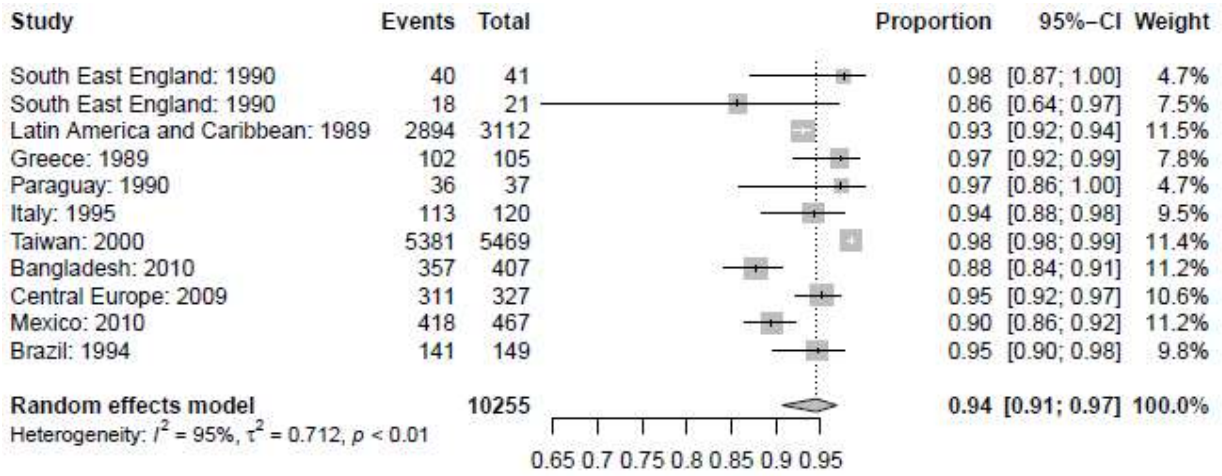


For GBS, the modeled female/male ratio demonstrated a higher prevalence in males, and was used to proportionally split "both" sex data points into male and female data points (as seen in the figure above).

For GBD 2019, raw data with large age ranges were split into 5-year age bins using regional age patterns generated from a Dismod model with only input data with less than a 25-year age range. Finally, we systematically outliered all hospital data-series (entire age span of data) where the age standardized incidence is more than two median absolute deviations away from the median age-standardized incidence across location-years.

Modelling strategy

The first step of our modeling strategy was to correct inputs for survival rate. A random effects meta-analysis calculated a 95% case fatality rate (95% CI 93–98%). A forest plot showing the results of this meta-analysis is displayed below. As mortality mainly occurs during the acute phase of the disease (usually within four weeks of onset), the pooled survival rate was used to get the incidence of the people surviving after the acute phase of the GBS.



Dismod-MR 2.1 was used to estimate prevalence of Guillain-Barré syndrome for every location, year, age, and sex. We then split the overall prevalence of the impairment by underlying aetiology (upper respiratory infections, influenza, diarrhoeal diseases, other infections, and other neurological causes). We used random effects meta-analysis to pool these proportions. We squeeze the proportions for influenza, diarrhoeal diseases, upper respiratory infections, and other infectious diseases to add to the proportion for all identified infectious underlying diseases. We assigned the complement to one of the proportion with any underlying infectious disease to a rest category of "idiopathic Guillain-Barre syndrome" that is classified under neurological disorders.

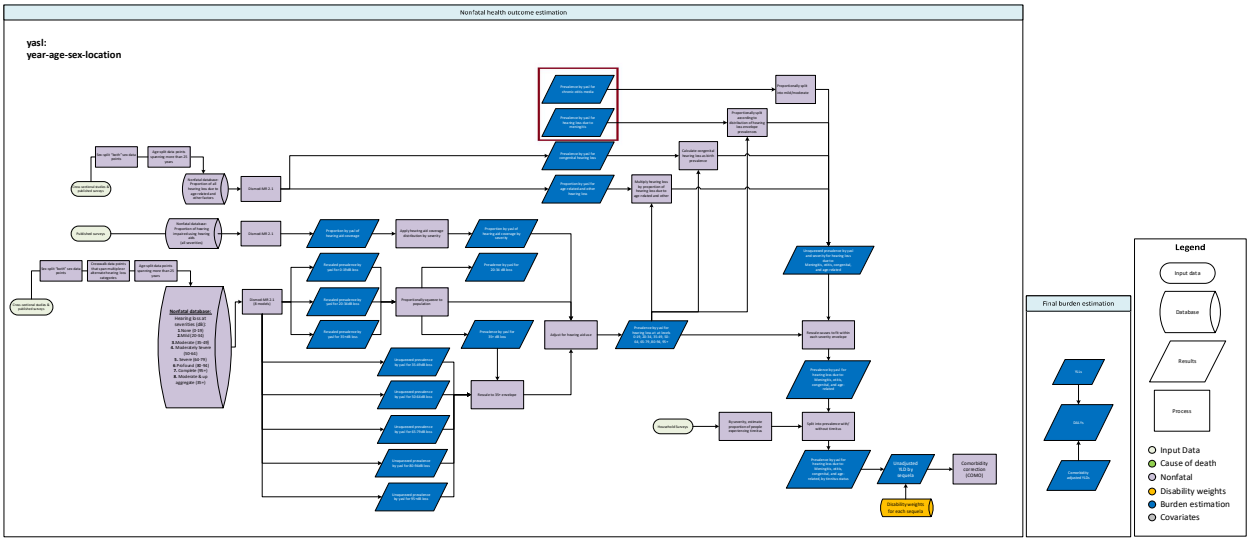
First the envelope for Guillain-Barré cases due to all specified aetiologies is established by doing a meta-analysis on the proportions reported in the studies included. Then, the proportions for each of the other splits are squeezed to fit the envelope created in the all specified meta-analysis. Finally, the difference between all specified and 100% is attributed to other neurological disorders. The final results of these aetiology splits are shown below:

Aetiology	Mean	Lower	Upper
Other neurological disorders	0.382	0.331	0.669
Influenza	0.119	0.071	0.192
Upper respiratory infections	0.319	0.27	0.372
Diarrhoeal diseases	0.109	0.086	0.135
Other infectious diseases	0.071	0.054	0.093

Disability weights

The health state for paraplegia was used for all Guillain-Barré cases. It is described as "paralysed from the waist down, cannot feel or move the legs, and has difficulties with urine and bowel control. The person uses a wheelchair to move around". The disability weight is 0.296 (0.198–0.414).

Hearing impairment



Case definition

Hearing impairment is an estimation of the prevalence of hearing loss at a range of severities, as measured by the softest sound that an individual can hear in their better ear, taken as the average across frequencies from 500 to 4000 Hertz.

Hearing Impairment is modelled for every year, age, sex, and location (y-a-s-l) in the following severity categories:

Table 1: Severity thresholds of hearing loss

Severity thresholds of interest for hearing loss	
Severity	**Threshold (in decibels)**
None	0–19
Mild	20–34
Moderate	35–49
Moderately severe	50–64
Severe	65–79
Profound	80–94
Complete	95+

We modelled the following causes of hearing loss: congenital, meningitis, otitis, and age-related and other. Congenital hearing loss is defined as hearing loss present at birth. Age-related and other hearing loss includes causes not identified as meningitis, otitis, or congenital. This includes presbycusis, the gradual loss of hearing with age, caused by breakdown of neurons in the inner ear. For all causes, we estimate hearing loss with and without tinnitus, the perception of noise or ringing in the ears.

Unadjusted estimates of the prevalence of hearing loss due to meningitis and chronic otitis media are produced separately as part of each underlying cause's modeling process, as described in their respective sections. Along with the congenital and age-related etiologies, these unadjusted estimates are incorporated into the overall hearing loss model, as detailed below.

Input data and processing

Studies on hearing loss typically report the prevalence of hearing loss by severity, in categories that are mutually exclusive and exhaustive. The severity grouping that an individual is put into depends on the softest decibel level that they can hear a sound. However, these severity groupings are not standardized across literature. For example, one study may report the prevalence of mild, moderate, and severe hearing loss across the range of decibels. Another study may simply report the prevalence of the study population with no hearing loss, and those that have hearing loss, regardless of range. In order to standardize severity groupings, we established 7 mutually exclusive and exhaustive categories that the GBD would use to model and report the severity of hearing loss. These are referred to as "severity specific envelopes". The range of decibel values applicable to each severity category can be seen in table 1.

For the estimation of severity-specific envelopes, we used prevalence measurements and individual-level data extracted from published surveys identified in a series of systematic reviews, or from sources provided by the GBD collaborator network.

Data sources up to 2008 were identified by a published systematic review (http://www.ncbi.nlm.nih.gov/pubmed/19444763). For GBD 2013, we conducted a systematic review covering 2008–2013 with the following search terms:

> (hearing impairment[Title/Abstract] OR deafness[Title/Abstract] OR hearing loss[Title/Abstract]) AND (prevalence[Title/Abstract]) AND ("2008"[PDAT] : "3000"[PDAT]) AND (cross sectional OR survey)

For GBD 2016, we conducted an additional systematic review using the following search terms:

(hearing impairment[Title/Abstract] OR deafness[Title/Abstract] OR hearing loss[Title/Abstract] OR audiometry[Title/Abstract]) AND (prevalence[Title/Abstract]) AND ("2008/11/26"[PDAT]: "3000"[PDAT]) AND (cross sectional OR survey)

This was conducted on November 30, 2016 and returned 239 results, of which 17 were accepted.

In addition to the search-string hits above, we identified household surveys that measured hearing loss - the United States National Health and Examination Surveys (NHANES) and the Health Survey for England (HSE) – and extracted prevalence measurements from individual-level data.

Self-reported hearing loss data were excluded. This includes censuses in the Integrated Public Use Microdata Series (IPUMS), the WHO Studies on Global Ageing and Adult Health (SAGE), and the WHO Multi-Country Survey Study on Health and Responsiveness (MCSS). Self-reported use of hearing aids (such as in MCSS, SAGE, and NHANES), however, was used to estimate hearing aid coverage.

We focused on improving methods of processing existing data in GBD 2019. An updated systematic review will be performed in a future round.

Table 2: Data inputs

Cause/ Impairment Name	Measure	Total Sources	Countries with data
Hearing Loss	All measures	208	77
	Prevalence	204	77
	Proportion	11	3
Age-related and other hearing loss	All measures	58	34
	Proportion	58	34

Where studies reported hearing loss spanning multiple thresholds (eg, 80+, rather than 80-94 and 95+) or severity categories that did not align with GBD thresholds, we crosswalked data with the MR-BRT methodology to the appropriate GBD severity categories. A description of the MR-BRT methodology can be found in its respective section.

To create adjustment factors between alternate and reference threshold categories, we used microdata extracted from NHANES surveys. This data reported the exact decibel at which each person experienced hearing loss. We estimated the prevalence of each alternate and reference severity category by aggregating microdata into groups specific to age and sex. The prevalent population for each alternate or reference category was comprised of every individual that fell within the range of decibels for a given severity. Adjustment factors were estimated as the logit difference between the prevalence of an alternate category and the prevalence of its corresponding reference category. A table of each adjustment factor can be found below.

Table 3: **MR-BRT crosswalk adjustment factors**

Reference Category (dB)	Alternate Category (dB)	Gamma	Beta Coefficient, Logit (95% CI)
0-19	0-24	0	0.60 (0.54 to 0.67)
	0-25	0	0.70 (0.64 to 0.77)
	0-29	0.23	1.13 (0.68 to 1.59)
	0-30	0.21	1.24 (0.83 to 1.68)
	0-39	0.91	1.67 (-0.04 to 3.58)
	0-40	0.96	1.71 (-0.05 to 3.53)
20-34	0-24	2.50	3.40 (-1.46 to 8.28)
	0-25	2.45	3.49 (-1.53 to 8.29)
	0-29	2.30	3.82 (-0.85 to 8.29)
	0-30	2.27	3.89 (-0.24 to 8.42)
	0-39	1.95	4.48 (0.61 to 8.55)
	0-40	1.91	4.50 (0.86 to 8.14)
	20-39	0.13	0.27 (0.02 to 0.52)
	20-40	0.15	0.29 (0.003 to 0.59)
	20-200	0.41	0.52 (-0.35 to 1.32)
	21-39	0.20	0.12 (-0.29 to 0.52)

	25-39	0.35	-0.39 (-1.04 to 0.34)
	26-40	0.43	-0.50 (-1.36 to 0.28)
	26-99	0.84	-0.03 (-1.65 to 1.73)
	26-200	0.84	-0.03 (-1.74 to 1.54)
	30-40	0.56	-1.06 (-2.24 to 0.007)
	30-200	0.96	-0.37 (-2.12 to 1.43)

35-49	0-39	2.45	5.18 (0.16 to 10.08)
	0-40	2.42	5.24 (0.41 to 10.17)
	20-39	0.71	1.45 (0.04 to 2.85)
	20-40	0.69	1.49 (0.10 to 2.88)
	21-39	0.66	1.31 (0.02 to 2.67)
	25-39	0.54	0.76 (-0.27 to 1.93)
	26-40	0.51	0.67 (-0.30 to 1.75)
	30-40	0.47	0.09 (-0.89 to 1.05)
	31-50	0.52	0.10 (0.29 to 0.74)
	40-64	0.37	-0.10 (-0.85 to 0.61)
	40-69	0.40	-0.04 (-0.82 to 0.811)
	41-55	0.32	-0.45 (-1.06 to 0.23)
	41-60	0.35	-0.29 (-0.99 to 0.37)
	41-70	0.44	-0.12 (-1.06 to 0.76)
50-64	40-64	0.27	1.13 (0.58 to 1.68)
	40-69	0.29	1.22 (0.64 to 1.80)
	41-55	0.4	0.72 (-0.09 to 1.53)
	41-60	0.31	0.92 (0.30 to 1.55)
	41-70	0.32	1.13 (0.49 to 1.77)
	51-70	0.18	0.06 (-0.31 to 0.42)
	55-69	0.29	-0.42 (-1.00 to 0.15)
	56-70	0.33	-0.43 (-1.10 to 0.24)
65-79	40-69	0.77	2.44 (0.92 to 3.99)
	51-70	0.67	1.35 (0.01 to 2.68)
	55-69	0.69	0.86 (-0.53 to 2.24)
	56-70	0.66	0.84 (-0.47 to 2.16)
	61-80	0.19	0.35 (-0.04 to 0.72)
	61-99	0.14	0.46 (0.17 to 0.75)
	65-84	0.02	0.03 (-0.01 to 0.08)
	70-89	0.21	-0.20 (-0.63 to 0.22)
	70-94	0.21	-0.20 (-0.62 to 0.24)
	70-95	0.21	-0.20 (-0.63 to 0.23)
	71-90	0.3	-0.26 (-0.86 to 0.34)
	71-99	0.3	-0.16 (-0.75 to 0.44)
	71-200	0.31	-0.19 (-0.81 to 0.42)
80-94	61-99	1.01	1.58 (-0.42 to 3.58)
	65-84	0.91	0.92 (-0.89 to 2.73)
	70-89	0.81	0.54 (-1.06 to 2.14)

	70-94	0.73	0.44 (-1.01 to 1.88)
	70-95	0.73	0.44 (-1.00 to 1.89)
	71-90	0.61	0.25 (-0.96 to 1.45)
	71-99	0.61	0.37 (-0.83 to 1.58)
	71-200	0.66	0.41 (-0.88 to 1.71)
	80-200	0	0.00 (-0.04 to 0.04)
	81-99	0	$-3.92e^{-16}$ (-0.04 to 0.03)
	81-200	0	0.00 (-0.04 to 0.04)
	85-200	0	$-4.37e^{-24}$ (-0.04 to 0.04)
	90-99	0	0.00 (-0.03 to 0.03)
	90-200	0	0.00 (-0.03 to 0.03)
35-200	20-200	0.15	1.79 (1.48 to 2.10)
	26-200	0.14	1.02 (0.73 to 1.31)
	26-99	0.14	1.02 (0.73 to 1.31)
	30-200	0.07	0.55 (0.40 to 0.70)
	31-200	0.05	0.43 (0.33 to 0.54)
	31-99	0.04	0.44 (0.34 to 0.54)
	40-200	0.04	-0.49 (-0.58 to -0.39)
	40-99	0.05	-0.48 (-0.59 to -0.38)
	41-200	0.09	-0.59 (-0.78 to -0.39)
	41-99	0.10	-0.58 (-0.78 to -0.39)
95-2000	61-99	0.80	2.42 (0.84 to 4.03)
	71-99	0.90	0.65 (-1.14 to 2.43)
	71-200	0.88	0.60 (-1.13 to 2.33)
	80-200	0.22	0.08 (-0.34 to 0.52)
	81-99	0.21	0.08 (-0.35 to 0.50)
	81-200	0.18	0.05 (-0.30 to 0.41)
	85-200	0	0.00 (-0.04 to 0.04)
	90-99	0	0.00 (-0.02 to 0.02)
	90-200	0	0.00 (-0.02 to 0.02)
	91-99	0	0.00 (-0.03 to 0.02)
	91-200	0	0.00 (-0.02 to 0.02)
	95-99	0	0.00 (-0.02 to 0.02)
	96-99	0	0.00 (-0.02 to 0.02)

Modelling strategy

We modelled the prevalence of hearing loss over five steps. First, we ran three DisMod-MR 2.1 models to estimate the total prevalence of the following levels of hearing by y-a-s-l: normal hearing (0–19dB), mild hearing loss (20–34dB), and moderate hearing loss and above (35+ dB). For normal hearing loss (0-19 dB), Dismod-MR 2.1 had trouble fitting prevalence values close to 100% in very young ages. Initial models attempted to follow lower prevalence data points in teen and middle-aged populations, and resulting, estimates of the prevalence of normal hearing in infants were implausible in the face of the data. As a

solution, we modeled all data adjusted to the normal hearing loss category as 1-prevalence, to accommodate for the fact that Dismod interacts better with data points at lower values. We then took the complement of the fitted model at the draw level to obtain normal hearing prevalence estimates. Next, we rescaled the prevalence estimates from the three models (0-19, 20-34, 35+) to sum to 1 for every year, age, sex, and location. We estimated prevalence of normal hearing for the purpose of correctly scaling the other two models only, and hence it did not form part of further analysis.

These three models used Socio-demographic index as a covariate. SDI was also used as a covariate in GBD 2017. The estimated betas are shown in the table below.

Table 4: Covariates

Model	Covariate name	Measure	Beta value	Exponentiated value
Hearing loss impairment at 0-19 dB	Socio-demographic Index	Prevalence	0.013 (0.00067 to 0.033)	1.01 (1.00 to 1.03)
Hearing loss impairment at 35+ dB	Socio-demographic Index	Prevalence	-1.59 (-1.87 to -1.27)	0.20 (0.15 – 0.28)
Hearing loss impairment at 95+ dB	Socio-demographic Index	Prevalence	-1.22 (-1.84 to -0.56)	0.30 (0.16 to 0.57)

Second, we ran five additional DisMod-MR 2.1 models for each severity level of hearing loss above mild: moderate (35–49dB), moderately severe (50–64dB), severe (65–79dB), profound (80–94dB), and complete (95+). We then rescaled the prevalence estimates from these models to fit within the prevalence estimated for 35+dB in the first step. By the end of the second step, we had estimated prevalence of six severity levels of hearing loss, including mild (20–34dB).

Third, we ran two additional Dismod models. The first is a model to estimate the proportion of the hearing impaired that use a hearing aid, deemed “hearing aid coverage”. The second estimates the proportion of hearing loss across all severities that is attributable to age-related and other factors.

Fourth, we adjusted the prevalence of each of the six hearing loss severity levels estimated in steps one and two to account for hearing aid use. To do this, we made the assumption that the use of a hearing aid reduces the severity of impairment by one category.

The model used to estimate hearing aid coverage represents *all* severity categories. To estimate the proportion of hearing aid coverage for *each* severity category, we used data obtained from the Nord-Trondelag study and NHANES surveys. These two sources provided detailed information on hearing aid coverage among the impaired by age, sex, and most importantly, severity. We ran a logistic regression on age with binary indicators for severity levels and sex. Outputs of this regression were the proportion of individuals at every severity of hearing impairment that used a hearing aid. We assumed that 0% of people in the completely deaf category (95+) used a hearing aid. We then took estimates of hearing aid coverage that were produced in step 3, and scaled the estimate by dividing the value produced in each location by the value produced for Norway. This was to correct for any bias created by using adjustment factors calculated mostly with data from Norway. From there, we multiplied the scaled value of hearing aid coverage for each location by each of the 6 proportions of severity-specific coverage. This gave us the proportion of individuals in each severity category that use a hearing aid. Lastly, we shifted the identified

fraction of people in each severity category that used a hearing aid to the category directly below. This provided the adjusted prevalence of six severity levels of all-cause hearing loss.

Fifth, we estimated the prevalence of hearing loss due to multiple causes: otitis media, congenital, meningitis, and age-related and other causes not classified elsewhere. In GBD 2017, we estimated the prevalence of hearing loss for each subtype of meningitis (pneumococcal, *H influenzae* type B meningitis, meningococcal, and other bacterial), but in GBD 2019, we estimated the prevalence of hearing loss for meningitis as a whole. See the meningitis cause write-up for further details. For congenital hearing loss, we assumed that all hearing loss occurring at the time of birth are of congenital nature. We also assumed that all hearing loss due to otitis media is at the mild or moderate level. Up to the age of 20, we implemented proportional squeezes to scale cause-specific hearing loss prevalence to the total prevalence of each severity level. Above age 20, we subtracted the prevalence of congenital hearing loss, meningitis, and otitis from the total and called any remainder age-related and other hearing loss. Limitations in the model and underlying data for age-related and other hearing loss required such a step. Since we ensured that congenital prevalence was constant in each age group for every location, year, and sex combination after conducting the proportional squeeze, the sum of the prevalence of all hearing loss aetiologies sometimes exceeded the total prevalence of some severity levels.

Finally, we estimated the percent of people experiencing tinnitus. We determined the proportion of people suffering from tinnitus using data from NHANES years that asked about the frequency each survey respondent heard ringing, roaring, and/or buzzing (1999, 2001, 2003, and 2011–2012). We labeled anyone with mild hearing loss and ringing, roaring, or buzzing "at least once a month" as a mild hearing loss with tinnitus case. Anyone with moderate hearing through to severe hearing loss and ringing, roaring, or buzzing "at least once a day" was labelled as a moderate hearing loss with tinnitus case. Anyone with complete hearing loss who responded that they "almost always" had ringing or buzzing was labelled as a complete hearing loss with tinnitus case. Using the data from NHANES, we calculated confidence intervals assuming a binomial distribution. We assumed the same distribution of tinnitus across all aetiologies of hearing loss. This is the same strategy used in previous GBD cycles.

Table 5: Health states and disability weights

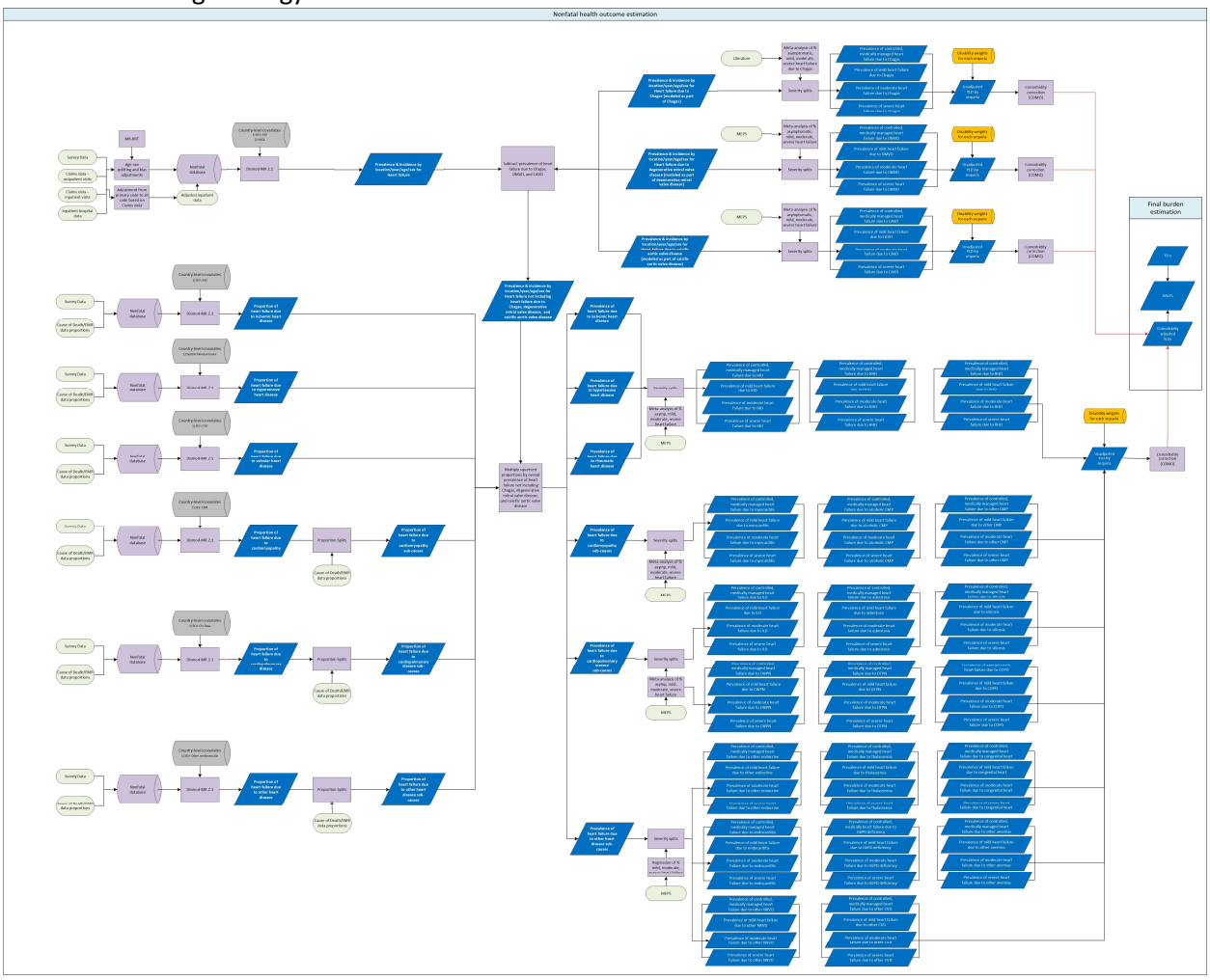
Health state name	Health state description	Disability weight
Hearing loss, mild	has great difficulty hearing and understanding another person talking in a noisy place (for example, on an urban street).	0.01 (0.004–0.019)
Hearing loss, mild, with ringing	has great difficulty hearing and understanding another person talking in a noisy place (for example, on an urban street), and sometimes has annoying ringing in the ears.	0.021 (0.012–0.036)
Hearing loss, moderate	is unable to hear and understand another person talking in a noisy place (for example, on an urban street), and has difficulty hearing another person talking even in a quiet place or on the phone.	0.027 (0.015–0.042)
Hearing loss, moderate, with ringing	is unable to hear and understand another person talking in a noisy place (for example, on an urban street), and has difficulty hearing another person talking even in a quiet place or on the phone, and has annoying ringing in the ears for more than 5 minutes at a time, almost every day.	0.074 (0.048–0.107)
Hearing loss, moderately severe	(custom DW from hearing loss impairment envelope)	0.092 (0.064–0.129)
Hearing loss, moderately severe, with ringing	(custom DW from hearing loss impairment envelope)	0.167 (0.114–0.231)
Hearing loss, severe	is unable to hear and understand another person talking, even in a quiet place, and unable to take part in a phone conversation. Difficulties with communicating and relating to others cause emotional impact at times (for example worry or depression).	0.158 (0.104–0.227)
Hearing loss, severe, with ringing	is unable to hear and understand another person talking, even in a quiet place, and unable to take part in a phone conversation, and has annoying ringing in the ears for more than 5	0.261 (0.174–0.361)

	minutes at a time, almost every day. Difficulties with communicating and relating to others cause emotional impact at times (for example worry or depression).	
Hearing loss, profound	is unable to hear and understand another person talking, even in a quiet place, is unable to take part in a phone conversation, and has great difficulty hearing anything in any other situation. Difficulties with communicating and relating to others often cause worry, depression, and loneliness.	0.204 (0.134–0.288)
Hearing loss, profound, with ringing	is unable to hear and understand another person talking, even in a quiet place, is unable to take part in a phone conversation, has great difficulty hearing anything in any other situation, and has annoying ringing in the ears for more than 5 minutes at a time, several times a day. Difficulties with communicating and relating to others often cause worry, depression, or loneliness.	0.277 (0.182–0.388)
Hearing loss, complete	cannot hear at all in any situation, including even the loudest sounds, and cannot communicate verbally or use a phone. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.215 (0.143–0.307)
Hearing loss, complete, with ringing	cannot hear at all in any situation, including even the loudest sounds, and cannot communicate verbally or use a phone, and has very annoying ringing in the ears for more than half of the day. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.316 (0.211–0.436)

Heart failure impairment

Flowcharts

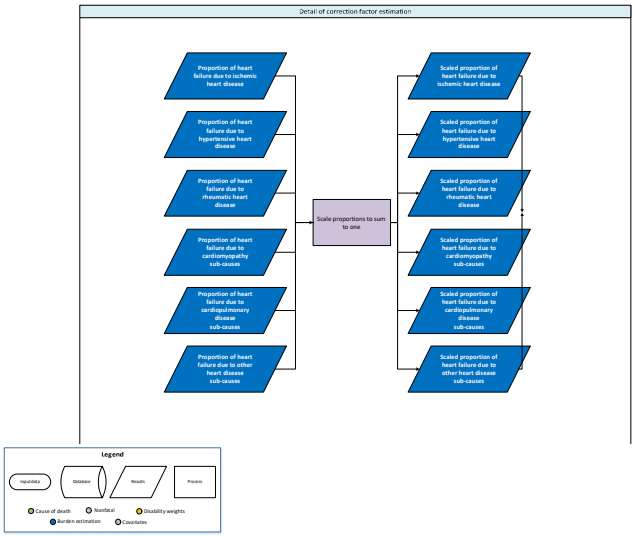
Overall modelling strategy



Abbreviations

DMVD: Degenerative mitral valve disease; CAVD: Calcific aortic valve disease; IHD: Ischaemic heart disease; CMP: Cardiomyopathy and myocarditis; HHD: Hypertensive heart disease; ILD: Interstitial lung disease; CWPN: Coal workers pneumoconiosis; OTPN: Other pneumoconiosis; COPD: Chronic obstructive pulmonary disease; RHD: Rheumatic heart disease; CVD: Cardiovascular disease; NRVD: Non-rheumatic valve disease

Proportion splits and correction factor estimation



Case definition

Heart failure was diagnosed clinically using structured criteria such as the Framingham or European Society of Cardiology criteria. Previous iterations of GBD modelled symptomatic (i.e. NYHA Class II and above) episodes of HF only. Beginning in GBD 2016, we used ACC/AHA Stage C and above to capture both persons who are currently symptomatic and those who have been diagnosed with heart failure but are currently asymptomatic.

Framingham Criteria (1): Must fulfill two major criteria or one major and two minor criteria.
Major criteria: Paroxysmal nocturnal dyspnoea, neck vein distention, rales, radiographic cardiomegaly, acute pulmonary oedema, S3 gallop, increased central venous pressure (>16 cm H_2O at right atrium), hepatojugular reflux; weight loss >4.5 kg in 5 days in response to treatment
Minor criteria: bilateral ankle oedema, nocturnal cough, dyspnoea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one-third from maximum recorded, tachycardia (heart rate>120 beats/min).

European Society of Cardiology (2): Typical signs (elevated jugular venous pressure, pulmonary crackles and peripheral oedema) and symptoms (eg, breathlessness, ankle swelling, and fatigue) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

Input data

A systematic review was performed GBD 2016, and updated with an unstructured review of the data in 2019. In 2016, the search terms used were: "heart failure"[TIAB] AND (epidemiology[MeSH Terms] OR prevalence[TIAB] OR incidence[TIAB] OR mortality[TIAB]) AND ("1990/01/01"[PDAT] : "2016/09/02"[PDAT]) NOT “animal model” NOT rat NOT mice NOT diabetes[TIAB] NOT “renal transplant”[TIAB]. The dates of the search were 01/01/1990 through 09/02/2016. 37,891 initial hits were returned, and 57 sources were added. An unstructured review yielded an additional 30 sources, of which

six were extracted. In 2019, a review of 8 systematic review articles yielded 519 sources to review, of which 14 were extracted.

The final dataset also included inpatient hospital data and claims data from the US and Taiwan. Inpatient hospital data were corrected for readmission, primary diagnosis to any diagnosis ratios, and inpatient to outpatient utilisation ratios using adjustment factors calculated from individual-level claims data. This methodology is detailed elsewhere in the appendix. Inpatient data were excluded if the facilities were not representative of the national population.

Additionally, we used the following data sources to estimate the proportion of heart failure attributable to each aetiology: Vital Registry data from Mexico, Brazil, Taiwan, Colombia, and the US; Inpatient admissions from Friuli Venezia, Italy; and Linked Vital Registry data from Friuli Venezia, Italy.

For GBD 2019, we used the modeling software Meta-Regression, Baysian Regularized Trimming (MR-BRT) to correct for biases in data types, replacing the in-DisMod crosswalks used in GBD 2017 and earlier. We used a network meta-analysis to adjust MarketScan data from 2010-2016 and MarketScan data from 2000, which used a different sampling methodology than other years, to literature and inpatient data. Table 2 shows MR-BRT crosswalk adjustment factors.

MR-BRT was used to split both-sex data points into sex-specific estimates. This methodology is detailed elsewhere in the appendix. We also split data points where the age range was greater than 25 years. Age splitting was based on the global sex-specific age pattern from a Dismod model that only used input data from scientific literature with less than a 25-year age range.

Table 2: MR-BRT Crosswalk Adjustment Factors for Heart Failure prevalence

$$Estimated\ Reference\ Def = invlogit(logit(Alternative\ Def) - Beta_{Alternative\ Def} - Beta_{Sex} * Sex - Beta_{Age_{scaled}} * Age\ Scaled)$$

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)
Inpatient or Literature data	Reference	0.02	---
MarketScan, 2000	Alternate		-0.59 (-0.51, -0.67)
MarketScan, 2010-2016	Alternate		-0.53 (-0.45, -0.61)
Age, scaled			-0.01 (-0.06, 0.03)
Male sex			-0.03 (-0.08, 0.02)

Table 3. Severity distribution, details on the severity levels for Heart Failure in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)
Controlled, medically managed	Has been diagnosed with clinical heart failure, a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049 (0.031-0.072)

Mild	Is short of breath and easily tires with moderate physical activity, such as walking uphill or more than a quarter-mile on level ground. The person feels comfortable at rest or during activities requiring less effort.	0.041 (0.026–0.062)
Moderate	Is short of breath and easily tires with minimal physical activity, such as walking only a short distance. The person feels comfortable at rest but avoids moderate activity.	0.072 (0.047–0.103)
Severe	Is short of breath and feels tired when at rest. The person avoids any physical activity, for fear of worsening the breathing problems.	0.179 (0.122–0.251)

Source counts

Measure	**Total sources**	**Countries with data**
Prevalence	192	38
Incidence	31	14
Standardized mortality ratio	2	2
With-condition mortality rate	56	22
Proportion	68	51

Modelling strategy

To estimate the burden of heart failure due to each of 23 underlying causes, we first estimated the overall prevalence of heart failure and then the proportion of heart failure that could be attributed to each cause. The latter process includes an initial assessment of the fraction of heart failure cases attributable to each of six high-level parent cause groupings, followed by further division into the detailed causes within each of these groupings. The selection for aetiological causes was based on a review of the literature and expert opinion regarding diseases that lead to congestive heart failure.

Prevalence estimation

Overall prevalence of AHA/ACC stage C or D heart failure was estimated in DisMod-MR 2.1 using literature data, hospital data, and claims data. We set a prior of no remission and capped excess mortality at 1. All data adjustments were done outside of DisMod, described above.

Estimates for the prevalence of heart failure due to Chagas, degenerative mitral valve disease, and calcific aortic valve disease were generated separately as part of the modelling strategy for those causes. We subtracted the prevalence of heart failure due to these causes from the overall heart failure estimates to give an adjusted prevalence of heart failure due to all other aetiologies.

Aetiological fraction estimation

To estimate the proportion of heart failure attributable to each cause, we used Equation 1 to calculate the prevalence of heart failure due to each aetiology, which was then scaled into a proportion.

Equation 1:

$$Prevalence_{\,HF\ due\ to\ aetiology} = \frac{Cause\ Specific\ Mortality\ Rate_{\,HF\ due\ to\ aetiology}}{Excess\ Mortality\ Rate_{\,HF\ due\ to\ aetiology}}$$

First, we calculated the Cause Specific Mortality Rate (CSMR) for heart failure due to each aetiology. We used age-, sex-, and location-specific CSMR (post CoDCorrect) for each aetiology, multiplied by the fraction of deaths that also involved heart failure (Equation 2). This fraction was a modeled quantity, informed by person-level vital registry (VR) data from the United States, Mexico, Brazil, Taiwan, and Colombia, data sources which contained the underlying cause of death as well as all codes in the causal chain. From these sources, we calculated the fraction of underlying deaths from each aetiology in which heart failure was coded in the causal chain. These data were modeled in MR-BRT to generate age- and sex-specific estimates of this proportion. For Hypertensive Heart Disease, Alcoholic Cardiomyopathy, and Other Cardiomyopathy, we set the proportion to be 1, as all deaths due to these causes involve heart failure.

Equation 2:

$$CSMR_{\,HF\ due\ to\ aetiology} = CSMR_{\,aetiology} * Proportion\ deaths\ with\ HF_{aetiology}$$

Next, we estimated the Excess Mortality Rate (EMR) for heart failure due to each aetiology. We used uniquely identified person-level hospital discharge data for the entire Italian region of Friuli Venezia Giulia, linked to all death records from the region. Inpatient data contained all primary and non-primary diagnoses associated with the visit, and mortality data contained the underlying cause of death as well as all codes in the causal chain. We identified patients with heart failure due to each aetiology as individuals with hospital coded heart failure concurrent or after a hospital code of the aetiology. Excess Mortality Rate for heart failure due to each aetiology was calculated by subtracting the background mortality rate from the mortality rate of persons with heart failure due to that aetiology. We modelled this quantity in MR-BRT to generate age- and sex-specific estimates of this value. Due to small number of deaths in younger ages, we assumed equal EMR across aetiologies for ages under 45.

We calculated the prevalence of Heart Failure due to each aetiology using Equation 1. These were scaled to sum to one, generating the estimated proportions of Heart Failure due to each aetiology.

These proportions, along with literature data, were used to inform DisMod-MR 2.1 models for the six broadest and mutually exclusive and collectively exhaustive cause groupings: ischaemic heart disease, hypertensive heart disease, cardiomyopathy and myocarditis, rheumatic heart disease, cardiopulmonary disease, and other cardiovascular and circulatory diseases. An exception to this approach was made for sub-Saharan Africa, where we excluded the proportion estimates generated from death data, relying instead on published literature to determine the proportions of heart failure aetiologies. This decision was based on expert opinion that local patterns differed significantly from what would have been determined from death data. The THESUS-HF study, a large-scale, prospective, echocardiographic study of heart failure aetiologies in multiple African countries, provided these proportions (3).

The results of these six proportion models were scaled to sum to one.

For heart failure due to cardiopulmonary disease, heart failure due to cardiomyopathy and myocarditis, and heart failure due to other causes, we calculated the proportion for each sub-cause according to the proportion of that cause within each larger aggregate group.

These estimates were then split into asymptomatic, mild, moderate, and severe heart failure based on an analysis of MEPS data, with the exception of Chagas disease. For that aetiology, we based the severity splits on a meta-analysis of NYHA class among persons diagnosed with heart failure due to Chagas disease in areas where Chagas is endemic.

Models were evaluated based on expert opinion, comparison of results with other rounds of GBD, and model fit.

Limitations

Our estimation of the aetiological causes of heart failure makes several assumptions and has several limitations. First, we assume that each case of heart failure only has one cause. Second, we rely on individually linked inpatient and mortality records from a small region of Italy to calculate aetiology-specific EMR. Third, we rely on multiple cause of death VR data from five countries to inform use the proportion of deaths that contain heart failure in all countries. This approach allows us to produce estimates for all locations and can be updated to include more detailed health record and claims data from additional locations as they become available.

Overall heart failure impairment envelope

Study covariate	Parameter	Beta	Exponentiated beta
Log-transformed age-standardised SEV scalar: Ischemic Heart Disease	Prevalence	0.75 (0.75–0.77)	2.38 (2.21–2.53)
Healthcare access and quality index	Excess mortality rate	-1.05 (-2.00 – -0.12)	0.35 (0.14–0.88)

Six main sub-cause proportion envelopes

Sub-cause	Covariate	Parameter	Beta	Exponentiated beta
Heart failure due to cardiomyopathy impairment envelope	Log-transformed age-standardised SEV scalar: CMP	Proportion	0.75 (0.75–0.75)	2.12 (2.12–2.12)
Heart failure due to cardiopulmonary disease impairment envelope	Log-transformed age-standardised SEV scalar: COPD	Proportion	0.76 (0.75–0.77)	2.13 (2.12–2.15)

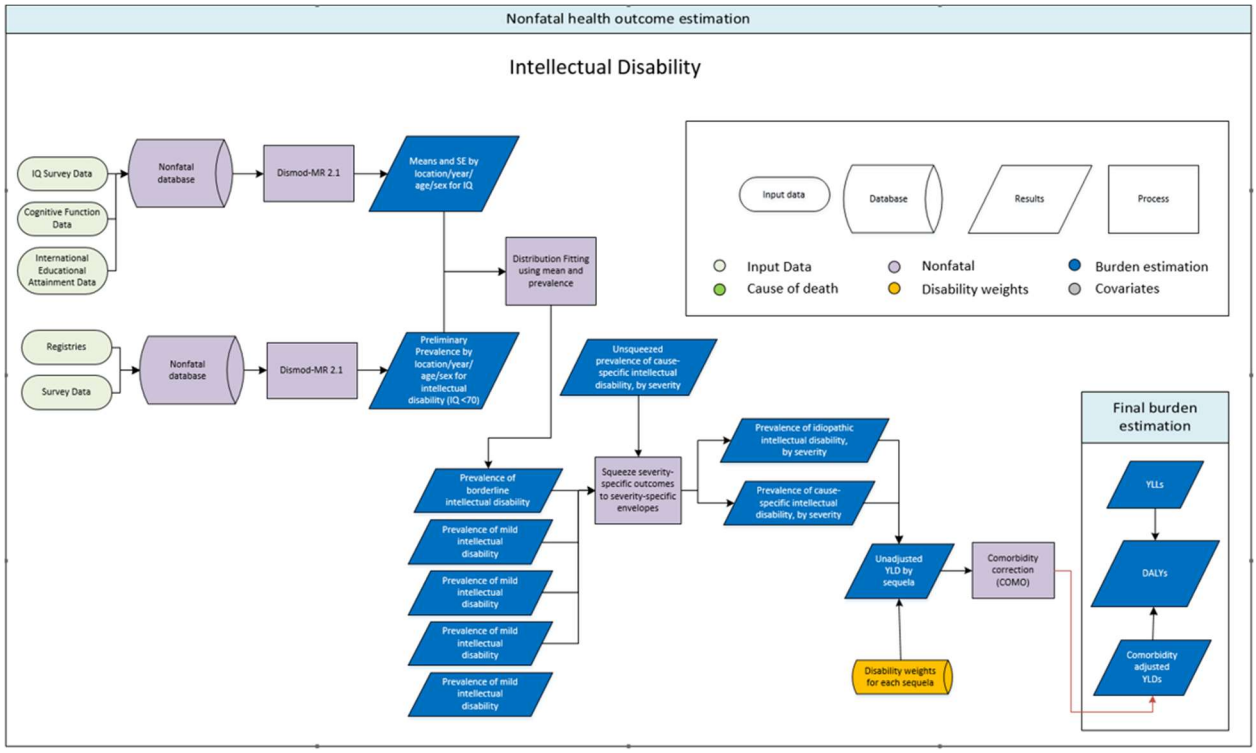
Heart failure due to hypertensive heart disease impairment envelope	Systolic blood pressure (mmHg)	Proportion	8.6E-5 (2.7E-6 to 2.9E-4)	1.00 (1.00–1.00)
Heart failure due to ischaemic heart disease impairment envelope	Log-transformed age-standardised SEV scalar: IHD	Proportion	0.75 (0.75–0.75)	2.12 (2.12–2.13)
Heart failure due to other causes impairment envelope	Log-transformed SEV scalar: Oth Cardio	Proportion	0.75 (0.75–0.76)	2.12 (2.12–2.13)
Heart failure due to valvular heart disease impairment envelope	Log-transformed age-standardised SEV scalar: CVD	Proportion	0.75 (0.75–0.76)	2.12 (2.12–2.13)

References

1) http://www.framinghamheartstudy.org/share/protocols/soe0_03s_protocol.pdf
2) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37 (27): 2129-2200.
3) Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The Causes, Treatment, and Outcome of Acute Heart Failure in 1006 Africans From 9 Countries. Results of the Sub-Saharan Africa Survey of Heart Failure. Arch Intern Med. 2012;172(18):1386-1394.

Developmental intellectual disability

Flowchart



Case definition

Developmental intellectual disability (ID) is a condition of below-average intelligence or mental ability. Consistent with the American Association on Intellectual and Developmental Disabilities, we define developmental intellectual disability as a condition originating before age 18 (as such, it does not include impairment due to stroke, Alzheimer's disease, or other conditions that affect older populations). We model the severities shown in Table 1, as measured by score on intelligence quotient (IQ) tests, which are standardised to have a mean of 100.

Table 1. ID severity definitions

Severity of intellectual disability	IQ score
Profound	0 to 19
Severe	20 to 34
Moderate	35 to 49
Mild	50 to 69
Borderline	70 to 85

Input data

Model inputs

The prevalence of intellectual disability (IQ score <70) came from a systematic review of publications since January 1, 1990, using the following search string: *(((intellectual disability[MeSH Terms]) AND prevalence[Title/Abstract]) AND ('1990'[Date - Publication] : '3000'[Date - Publication]))*. We included studies that estimate the general population prevalence of intellectual disability. We excluded studies that did not use a case definition based on intelligence quotient (IQ) and studies that investigated non-representative groups, such as hospital patients or people of a specific ethnicity. This systematic review was last updated for GBD 2016. Table 2 shows a summary of the input data used.

Table 2. Input data

Measure	Total sources	Countries with data
All measures	58	31
Prevalence	58	31

Data processing

In GBD 2019, we used MR-BRT to split our both-sex data points into sex-specific data. Table 3 has the model coefficient used in sex-splitting.

Table 3. MR-BRT coefficient values (raw and exponentiated)

Sex-split coefficient (95% CI)	Exponentiated sex-split coefficient (95% CI)
-0.10 (-0.14 to -0.07)	0.90 (0.87 to 0.93)

Because we code males as "1" and females as "2", this coefficient means that the observed prevalence of ID is slightly higher in males than in females (i.e., prevalence in females is 0.90 times prevalence in males). To split our both-sex data, we first used the coefficient to get a population-weighted adjustment factor. We then multiplied that adjustment factor by the both-sex data points to get expected prevalence in males, and finally multiplied the coefficient by the expected male prevalence to get expected prevalence in females. In our final modelling dataset, we exclusively used the sex-specific and sex-split data (i.e., no both-sex data were included in the model).

Severity splits – disability weights

Table 4. Intellectual disability severity disability weights

Health state	Description	Disability weight
Borderline intellectual functioning	This person is slow in learning at school. As an adult, the person has some difficulty doing complex or unfamiliar tasks but otherwise functions independently.	0.011 (0.005–0.02)
Intellectual disability/mental retardation, mild	This person has low intelligence and is slow in learning at school. As an adult, the person can live independently, but often needs help to raise children and can only work at simple supervised jobs.	0.043 (0.026–0.064)

Intellectual disability/mental retardation, moderate	This person has low intelligence, and is slow in learning to speak and to do even simple tasks. As an adult, the person requires a lot of support to live independently and raise children. The person can only work at the simplest supervised jobs.	0.1 (0.066–0.142)
Intellectual disability/mental retardation, severe	This person has very low intelligence and cannot speak more than a few words, needs constant supervision and help with most daily activities, and can do only the simplest tasks.	0.16 (0.107–0.226)
Intellectual disability/mental retardation, profound	This person has very low intelligence, has almost no language, and does not understand even the most basic requests or instructions. The person requires constant supervision and help for all activities.	0.2 (0.133–0.283)

Modelling strategy

We modelled the prevalence of ID, both aetiology-specific IDs and idiopathic ID, over multiple steps.

First, we ran a DisMod-MR 2.1 model to estimate the total prevalence of intellectual disability of level IQ <70. We included lagged distributed income and child underweight summary exposure value (SEV) in the model as predictive covariates. Table 5 shows raw and exponentiated model coefficients for the covariates used in the estimation process for the DisMod model. Exponentiated coefficients can be interpreted as odds ratios.

Table 5. Model coefficient values (raw and exponentiated)

Covariate	Parameter	Coefficient (95% CI)	Exponentiated coefficient (95% CI)
Lagged distributed income (LDI) per capita	Prevalence	-0.37 (-0.46 to -0.28)	0.69 (0.63 to 0.76)
Age- and sex-specific SEV for child underweight	Prevalence	1.49 (0.19 to 2.77)	4.42 (1.20 to 15.99)
Sex	Prevalence	0.18 (0.12 to 0.24)	1.19 (1.13 to 1.27)

Second, we split the total prevalence of idiopathic into four severity levels: mild (IQ 50-69), moderate (IQ 35-49), severe (IQ 20-34), and profound (IQ below 20). We pooled a subset of studies that distinguished intellectual disability by these severity levels. We used cumulative severity levels (i.e., IQ <50, IQ <35, and IQ <20) to maximise the number of sources. We estimated these cumulative severities' proportion of the <70 envelope via random effects meta-analyses stratified by two levels of income status (high-income versus low- and middle-income). These proportions were used to estimate discrete severities from the overall intellectual disability (IQ <70) prevalence. We estimated the final severity level, borderline disability (IQ 70-84), via another random-effects meta-analysis of the ratio of IQ 70-84 to IQ <70. The uncertainty of the pooled fractions and ratios were propagated throughout our calculations using 1,000 draws from a normal distribution with mean and standard error estimated by the meta-analysis. The results of the meta-analysis are shown in Table 6.

Table 6. Proportion of intellectual disability cases by severity

Severity	Mean	Standard error
None	0.161	0.034
Borderline	0.161	0.034
Mild	0.375	0.037
Moderate	0.190	0.031
Severe	0.090	0.177
Profound	0.024	0.134

Third, we estimated prevalence of each aetiology-specific intellectual disability using models of the following parent causes. Since we model only developmental intellectual disability, causes that affect older populations such as stroke and Alzheimer's disease are not included in the causal attribution process.

Parent causes included in causal attribution:

- Neonatal preterm birth complications (<28w, 28-32w, 32-36w)
- Neonatal encephalopathy due to birth asphyxia and trauma
- Congenital birth defects (diaphragmatic hernia, cardiovascular anomalies)
- Haemolytic disease and other neonatal jaundice
- Meningitis (pneumococcal, *H influenzae* type B, meningococcal, other bacterial)
- Encephalitis
- Malaria
- Neonatal tetanus
- Neonatal sepsis and other neonatal infections
- Iodine deficiency
- African trypanosomiasis
- Down syndrome
- Klinefelter syndrome
- Chromosomal abnormalities (unbalanced rearrangements, Down syndrome, Edwards syndrome, Patau syndrome, other chromosomal abnormalities)
- Neural tube defects (eg, spina bifida, encephalocele)
- Hypertensive disorders of pregnancy (eclampsia, preeclampsia)
- Autism spectrum disorders (ASD)
- Fetal alcohol syndrome

For autism spectrum disorders (ASD), we identified six studies reporting severity of intellectual disability. We conducted a meta-analysis to produce a severity distribution which we applied to the prevalence of autism to produce severity-specific ID due to autism.[1-6]

[1] Croen LA, Grether JK, Hoogstrate J, Selvin S. The Changing Prevalence of Autism in California. *J Autism Dev Disord*. 2002; 32(3): 207-15.

[2] Fombonne E, du Mazaubrun C. Prevalence of infantile autism in four French regions. *Soc Psychiatry Psychiatr Epidemiol*. 1992; 27(4): 203-10.

We calculated the prevalence of idiopathic ID by subtracting all severity- and aetiology-specific ID from the severity-specific envelope assuming the residuals to represent idiopathic disability. If the residual was less than 5% of the severity-specific envelope, the prevalence of all aetiology-specific ID was proportionally squeezed to fit within 95% of the envelope, leaving 5% for idiopathic ID.

As we estimated the prevalence of individual aetiology-specific ID by models from the respective parent causes, the squeezing may have resulted in a distorted balance of prevalence estimates within their parent causes. With the aim to maintain consistencies of prevalence within each of the parent causes, we added the difference between the original and the squeezed prevalence estimates to the "motor impairment" sequela if the squeezed sequela represented "motor and cognitive impairment." For autism, we obtained the fraction of cases that result in ID from literature (0.29; 95% CI 0.27–0.30) and applied this fraction to the subtraction and squeezing processes. We assumed that all ID cases due to iodine deficiency (cretinism) would result in either severe or profound disability, and that Klinefelter syndrome cases that result in ID would have either borderline or mild severity. Lastly, in GBD 2013, all aetiology-specific models were squeezed into the overall (IQ <70) envelope, while in all subsequent rounds (including GBD 2019), we squeezed each model into its discrete severity envelope.

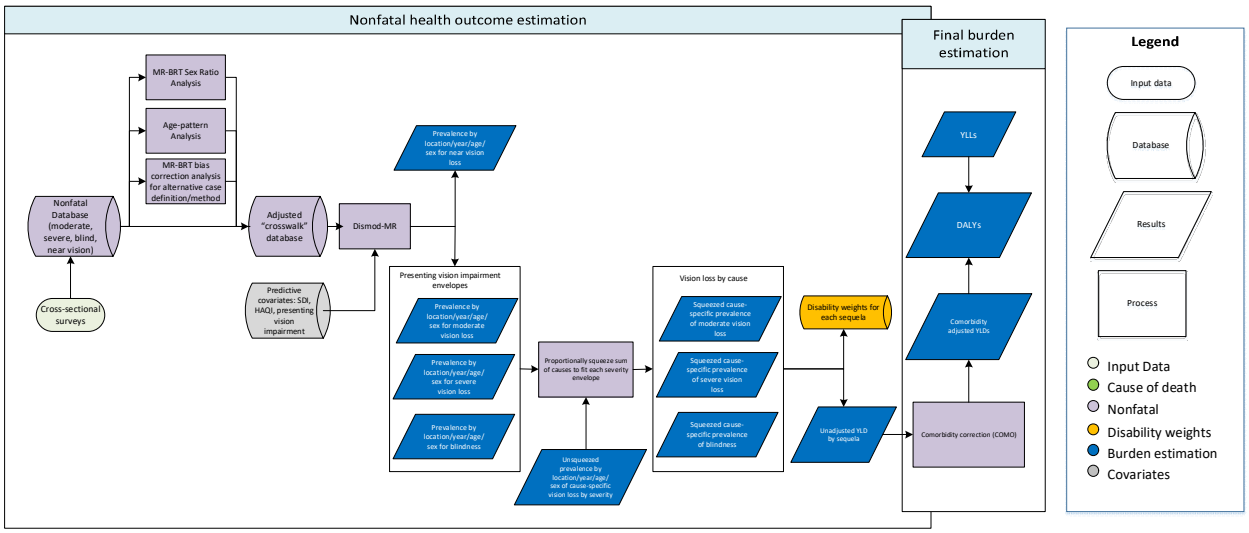
[3] Ritvo ER, Freeman BJ, Pingree C, Mason-Brothers A, Jorde L, Jenson WR, McMahon WM, Petersen PB, Mo A, Ritvo A. The UCLA-University of Utah epidemiologic survey of autism: prevalence. *Am J Psychiatry*. 1989; 146(2): 194-9.
[4] Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA*. 2003; 289(1): 49-55.
[5] Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, Charman T. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet*. 2006; 368(9531): 210-5.
[6] Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of Autism in a United States Population: The Brick Township, New Jersey, Investigation. *Pediatrics*. 2001; 108(5): 1155-61.

Blindness and vision loss

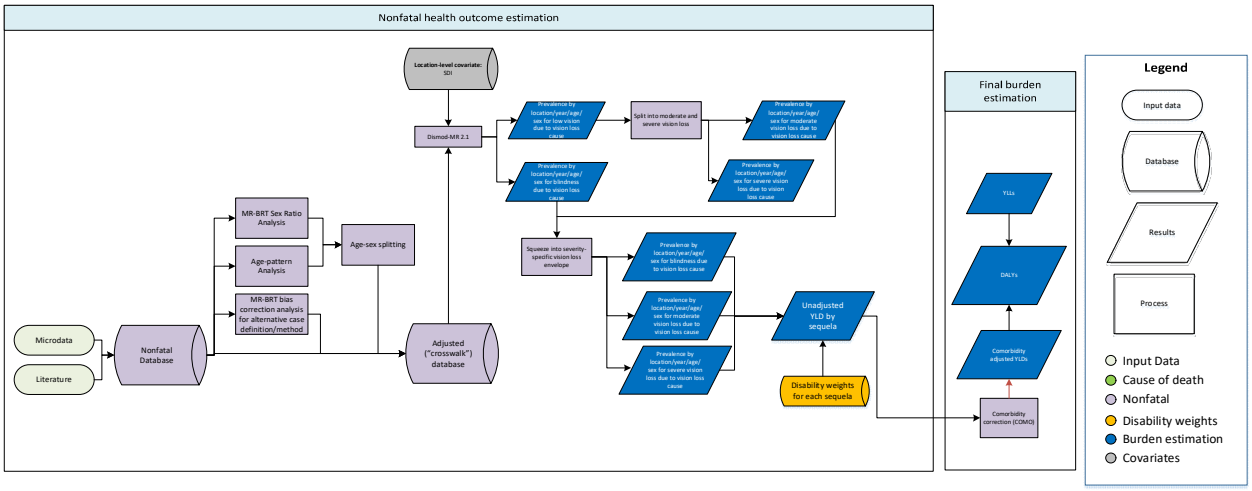
Flowcharts

Vision loss

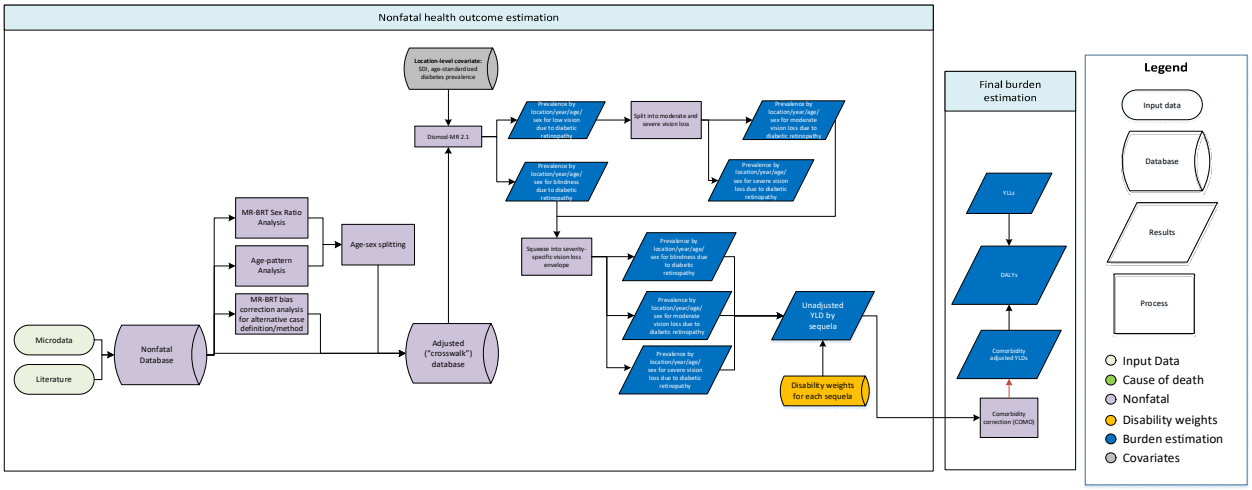
Nonfatal health outcome estimation



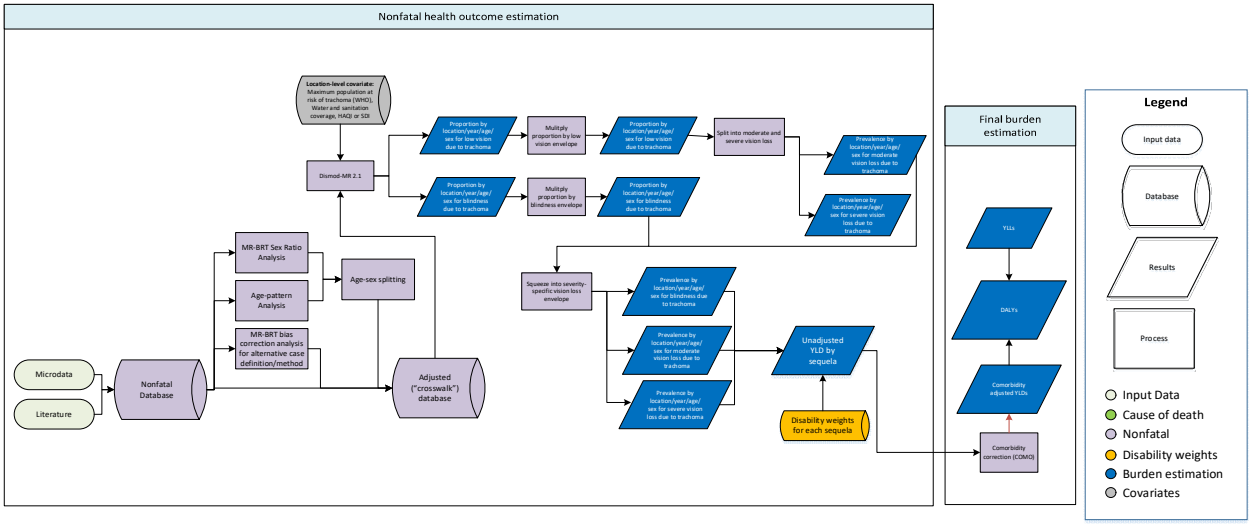
Cause-specific vision loss: Cataract, Glaucoma, Macular Degeneration, Other Vision Loss



Cause-Specific Vision Loss: Diabetic Retinopathy



Cause-Specific Vision Loss: Trachoma



Case definition

We model vision loss with visual acuity <6/18 according to the Snellen chart as our reference case definition. The following levels of severity are modeled:

Condition	Case definition
Blindness	Visual acuity of <3/60 or <10% visual field around central fixation
Severe vision loss	≥3/60 and <6/60

Moderate vision loss	≥6/60 and <6/18
Near vision loss	Near visual acuity of <6/12 distance equivalent

Near vision loss describes the progressive inability to focus on near objects as individuals age (presbyopia). This impairs the ability to read. The majority of presbyopia can be corrected by the use of reading glasses, contact lenses, or refractive surgery.

We model vision loss due to the following causes: uncorrected refractive error, cataract, glaucoma, macular degeneration, diabetic retinopathy, trachoma, vitamin A deficiency, retinopathy of prematurity, meningitis, encephalitis, onchocerciasis, and a residual category of other vision loss. Vision loss due to vitamin A deficiency, retinopathy of prematurity, meningitis, encephalitis, and onchocerciasis are modelled as part of their underlying cause as described in their respective sections.

Refractive error is blurry vision due to the lens's inability to focus. The blurriness caused by refractive error can be addressed through the use of contact lenses, glasses, or refractive surgery. Cataract is clouding of the lens of the eye due to protein buildup that impairs vision. Glaucoma is a condition with increased intraocular pressure which can lead to damage of the optic nerve. Macular degeneration is a deterioration of the macula, leading to central vision loss. Diabetic retinopathy is damage to the retina caused by damaged blood vessels that can leak blood into the retina and cause scarring of the retina. Trachoma results from a conjunctival bacterial infection (*Chlamydia trachomatis*) that produces inflammation and scarring which leads to an inversion of the eyelids and eyelashes scratching the cornea, which, eventually after decades, leads to scarring of the cornea and vision loss or blindness.

Input data

Model inputs

Data on overall vision loss come from surveys measuring visual acuity in representative population-based studies, either from publications in peer-reviewed and grey literature or surveys for which we had the unit record data. Data were excluded if no test was used of visual acuity that can be converted to the Snellen scale, and if a study did not assess "presenting" or "best-corrected" vision. Presenting vision is the visual acuity as measured with the glasses used by an individual. Best corrected vision is with the best possible correction for refractive error, regardless of the strength of glasses used by an individual. A subset of these studies that reported vision loss by cause were used to estimate the prevalence of vision loss due to cataract, glaucoma, macular degeneration, diabetic retinopathy, and other causes.

For GBD 2015, we conducted a systematic review for new sources since GBD 2013 (covering 1/1/2013 – 5/20/2015), using the following search string:

((((glaucoma[Title/Abstract] OR cataract[Title/Abstract] OR macular[Title/Abstract] OR 'refractive error'[Title/Abstract] OR presbyopia[Title/Abstract]) OR (('blindness'[MeSH Terms] OR 'blindness'[All Fields]) OR 'vision, low'[MeSH Terms])) AND ('2013'[PDAT] : '3000'[PDAT])) AND 'humans'[MeSH Terms]) AND (prevalence[Title/Abstract] OR incidence[Title/Abstract] OR epidemiology[Title/Abstract])

This yielded 1,169 results, of which we extracted 20 sources. Furthermore, we extracted from the following nationally representative surveys measuring visual acuity: the WHO Studies on Global Ageing and Adult Health (SAGE) and the United States National Health and Examination Surveys (NHANES).

For GBD 2016 and GBD 2017, we did a comprehensive extraction of the Rapid Assessment of Avoidable Blindness (RAAB) repository (http://raabdata.info/), a database of vision loss studies in developing settings across the world. There are 266 site-years of data, the majority of which have publicly available reports or publications of the data. A standardized methodology was used by all sources in the repository. This allowed us to use all 185 available reports, 70 of which were newly included for GBD 2017. In addition, we extracted two state-level national surveys from India.

For GBD 2019, we added literature sources from a systematic review conducted by collaborators in the Vision Loss Expert Group (VLEG) where all screened abstracts were sent to regional expert groups to assess data quality for inclusion. Many members of VLEG are also GBD collaborators and for GBD2019 estimates VLEG and GBD estimates are the same. This systematic review was conducted using the search engines MEDLINE, Embase, WHOLIS, SciELO, Open Grey and other grey literature searches commissioned by VLEG from York Health Economics Consortium, UK, an organization that has supported the VLEG by independently conducting these searches in the past. These searches covered the time period of 1980-2018. In total, since 2010 VLEG has provided data extracted from 137 studies, of which 67 came from the most recent systematic review update (2014-2018). In GBD 2019, data from 95 of these literature sources that matched GBD inclusion criteria were newly added to vision models. The Vision Loss Expert Group also provided additional data provided by principle investigators for existing studies, 51 new RAAB surveys, and 5-year disaggregated data for 151 RAAB surveys (previously only data for combined ages 50-99 were available), which better informed the age pattern for vision loss in this year's estimates.

In 2017, near-vision acuity included data from the following nationally representative studies measuring self-reported near vision loss: the Surveys of Health, Ageing, and Retirement in Europe (SHARE); the Multi-Country Survey Study on Health and Responsiveness (MCSS); and the World Health Surveys (WHS). In 2019, we transitioned to measured-only data, and added 11 new sources. The reason for this change in approach was that we could not find a plausible adjustment between measured and self-reported data in SAGE and NHANES surveys, which provide both measured and self-report data on vision loss. A crosswalk using NHANES data demonstrated an over-estimation in self-report data compared to measured data, while a crosswalk using SAGE data demonstrated the opposite.

Several adjustments were made to data extracted from the original data sources.

1) Where studies only reported "both" sex data, a meta-regression in MR-BRT was used to split these data points into sex-specific data points.
2) Where studies reported visual acuity spanning multiple thresholds (e.g., <6/60, rather than separate severe and blind estimates), we applied a logit-difference adjustment meta-regression, using data from studies reporting vision loss by both severity levels.
3) Some studies reported best-corrected vision loss, but not presenting vision loss. We crosswalked these data points using a logit difference meta-regression. This gave us predicted presenting vision loss data points for studies not explicitly reporting presenting vision loss.
4) Where data points spanned more than 25 years of age, we age-split using an algorithm that applies the age-pattern of the super-region (from a DisMod-MR model) to split the data to five-year age groups.

Whereas other vision loss aetiologies are modelled based on prevalence data, vision loss due to trachoma is modelled as a proportion of the overall best-corrected vision loss envelope, a strategy that was chosen based on the nature of available data.

The total source count used in GBD 2019 modeling is listed in the table below:

Total vision loss for each severity

Measure	Total sources
All measures	481
Prevalence	481

Vision loss for the modeled causes of vision loss

Measure	Total sources
All measures	387
Prevalence	369
Proportion	25

Modelling strategy

We modelled the prevalence of vision loss in two steps. In the first step, we estimated the total prevalence estimates of presenting vision loss: moderate vision loss, severe vision loss, blindness, and near vision loss (presbyopia). We directly derived prevalence of near vision loss from this step, whereas the remaining three models that reflect different severity levels of distance vision loss continued to the next step.

1) Estimate severity-specific vision loss (the "envelopes")

First, we ran five DisMod-MR 2.1 models to estimate the total prevalence estimates of presenting vision loss: moderate vision loss, severe vision loss, blindness, near vision loss, and presenting vision loss (moderate + severe + blindness). The presenting vision loss model was used as a covariate in the severity-specific models to improve consistency across severities.

Betas and exponentiated values, which can be interpreted as an odds ratio, are shown in the tables below for each adjustment for alternative case definitions. The best-corrected adjustment factor indicates whether the test measured visual acuity with the level of correction the patient presents with or the ophthalmologist provides additional correction via pinhole or lens correction. Rapid-assessment corrects for potential biases in cause-specific vision loss from studies using expedited visual acuity measurement. The severity covariate splits mixed severity data (moderate/severe, severe/blindness) into severity-specific data. Gamma captures the between study heterogeneity, and the adjustment factor is the inverse-logit transformed beta coefficient where <0.5 represents that the alternative case definition is adjusted upward and >0.5 represents that the alternative case definition is adjusted downward.

MR-BRT Crosswalk Adjustment Factors for Moderate Vision Loss Envelope

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
Presenting visual acuity, does not use rapid methodology	Ref	0.59	---	---
Best-corrected visual acuity	Alt		-1.11 (-2.27 – 0.06)	0.25
Uses rapid methodology	Alt		-0.06 (-1.23 – 1.11)	0.48

MR-BRT Crosswalk Adjustment Factors for Severe Vision Loss Envelope

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
Presenting visual acuity, does not use rapid methodology	Ref	0.69	---	---
Best-corrected visual acuity	Alt		-0.94 (-2.30 – 0.42)	0.28
Uses rapid methodology	Alt		0.11 (-1.25 – 1.48)	0.53

MR-BRT Crosswalk Adjustment Factors for Blindness Envelope

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
Presenting visual acuity, does not use rapid methodology	Ref	0.02	---	---
Best-corrected visual acuity	Alt		-0.15 (-0.19 – -0.15)	0.28
Uses rapid methodology	Alt		0.07 (-0.03 – 0.34)	0.53

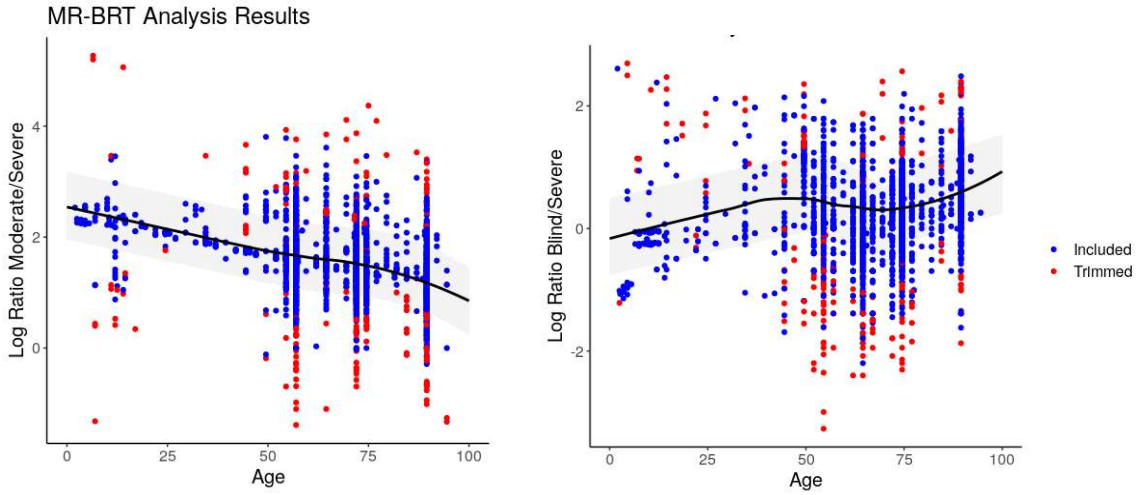
MR-BRT Crosswalk Adjustment Factors for Cause-Specific Low Vision Models

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
Does not use rapid methodology	Ref	0.70	---	---
Uses rapid methodology	Alt		0.12 (-0.03 – 0.34)	0.53

MR-BRT Crosswalk Adjustment Factors for Cause-Specific Blindness Models

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
Does not use rapid methodology	Ref		---	---
Uses rapid methodology	Alt		0.06 (-0.03 – 0.15)	0.51

MR-BRT Crosswalk Adjustment for Mixed Severity Vision Loss Data



Mixed severity data (either mixed moderate and severe vision loss, or mixed severe vision loss and blindness) was split into severity-specific vision loss using a meta-regression in MR-BRT with a cubic spline on age. The above plots show the underlying data input in each regression, and the model fit over age. These plots demonstrate that the ratio of moderate to severe vision loss decreases with age, and the ratio of blindness to severe vision loss increases slightly with age.

Socio-demographic Index (SDI) and healthcare access and quality index (HAQI) were used as location covariates as a proxy measure of access to eye care such as cataract surgery. All predictors are listed below for each vision model. The exponentiated beta can be interpreted as an odds ratio. For example, in row 1 below, an exponentiated beta of 0.44 for socio-demographic index means that for every 1 unit change in socio-demographic index (measured on a scale from 0 to 1), moderate vision loss is lower by a factor of 0.44.

Summary of predictive covariates used in vision DisMod-MR meta-regression models

Cause	Covariate	Type	Parameter	Exponentiated beta (95% Uncertainty Interval)
Moderate vision loss envelope	Socio-demographic index	Prevalence	-0.83	0.44 (0.37 – 0.53)
Severe vision loss envelope	Socio-demographic index	Prevalence	-1.3	0.27 (0.22 – 0.35)
Blindness loss envelope	Socio-demographic index	Prevalence	-1.51	0.22 (0.18 – 0.28)

Blindness loss envelope	Healthcare access and quality index	Prevalence	-0.01	0.99 (0.99 – 0.99)
Blindness loss envelope	Presenting vision loss	Prevalence	1.20	3.31 (3.01 – 3.61)
Moderate vision loss due to uncorrected refractive error	Socio-demographic index	Prevalence	-1.46	0.23 (0.22 – 0.25)
Severe vision loss due to uncorrected refractive error	Socio-demographic index	Prevalence	-1.94	0.14 (0.14 – 0.16)
Blindness due to uncorrected refractive error	Socio-demographic index	Prevalence	-1.98	0.14 (0.14 – 0.14)
Vision loss due to other vision loss	Socio-demographic index	Prevalence	-1.00	0.37 (0.37-0.37)
Blindness due to other vision loss	Socio-demographic index	Prevalence	-1.00	0.37 (0.37-0.37)
Vision loss due to macular degeneration	Socio-demographic index	Prevalence	-0.94	0.39 (0.37 – 0.45)
Blindness due to macular degeneration	Socio-demographic index	Prevalence	-0.91	0.40 (0.37 – 0.48)
Vision loss due to glaucoma	Socio-demographic index	Prevalence	-0.99	0.37 (0.37 – 0.38)
Blindness due to glaucoma	Socio-demographic index	Prevalence	-1.97	0.14 (0.14 – 0.15)
Vision loss due to cataract	Socio-demographic index	Prevalence	-0.66	0.52 (0.40 – 0.66)
Blindness due to cataract	Socio-demographic index	Prevalence	-2.96	0.052 (0.05 – 0.05)
Vision loss due to diabetes mellitus	Socio-demographic index	Prevalence	-1.7	0.18 (0.14 – 0.29)
Vision loss due to diabetes mellitus	Diabetes age-standard prevalence (proportion)	Prevalence	0.72	2.05 (1.56 – 2.70)
Blindness due to diabetes mellitus	Socio-demographic index	Prevalence	-1.77	0.17 (0.14 – 0.24)
Blindness due to diabetes mellitus	Diabetes age- standard prevalence (proportion)	Prevalence	3.95	52.12 (48.23 – 54.49)
Vision loss due to trachoma	Socio-demographic index	Proportion	-5.99	0.003 (0.003 – 0.003)
Blindness due to trachoma	Healthcare access and quality index	Proportion	-1.98	0.14 (0.11 – 0.17)
Blindness due to trachoma	Max trachoma population at risk	Proportion	-0.66	0.51 (0.30 – 0.82)
Blindness due to trachoma	Improved water source (proportion access)	Proportion	-2.19	0.11 (0.07 – 0.18)

2) Estimate cause-specific vision loss

In the second step, we estimated the prevalence of vision loss due to multiple causes: refractive error, cataract, glaucoma, macular degeneration, diabetic retinopathy, retinopathy due to prematurity, trachoma, vitamin A deficiency, onchocerciasis, meningitis, and other causes not classified elsewhere. The vision loss due to retinopathy of prematurity, vitamin A deficiency, onchocerciasis, meningitis, tetanus, and neonatal conditions was modeled as part of these underlying causes. Vision loss due to trachoma was modelled as a proportion of the envelope, with separate proportion models for (sever and moderate) vision loss and blindness. For each of cataract, glaucoma, macular degeneration, diabetic retinopathy,

and other vision loss, we ran two DisMod-MR 2.1 models: one for the combined category of moderate and severe vision loss due to the cause, and one for blindness due to the cause. Moderate and severe vision loss were modelled together because input data were mostly available for the aggregate. Refractive error was modelled in three models, one for each severity. We used the following age restrictions:

Cause	Minimum age
Cataracts	20
Glaucoma	45
Macular degeneration	45
Diabetic retinopathy	20
Trachoma	15
Other vision loss	0

We estimated the proportions of low vision and blindness due to trachoma using Dismod-MR 2.1 models. Our model included fixed effects on the maximum population at risk for trachoma (proportion) reported by WHO, the proportion of the population with access to sanitation, and HAQI. Finally, we applied geographic and age restrictions to ensure that we estimate zero proportions in non-endemic locations and among those younger than 15 year of age (as scarring of the cornea due to trachoma takes decades to develop). The prevalence of trachoma at each severity level was calculated by multiplying the proportion of vision loss due to trachoma by the corresponding corrected vision loss envelope. For lack of data by level of severity of vision loss this assumes a similar distribution as for all causes of vision loss combined.

We split the moderate plus severe vision loss estimates for each cause into moderate and severe using the ratio of presenting moderate and severe vision loss envelopes. As exceptions, onchocerciasis and retinopathy of prematurity were modelled for moderate and severe vision loss as part of the estimation process of these causes.

We scaled the cause-specific vision loss prevalence to the total prevalence of the vision loss envelopes for each of the three severity levels. The final result is prevalence of vision loss due to each cause by severity.

Health states and disability weights

Health state name	Health state description	Disability weight
Distance vision, severe loss	This person has severe vision loss, which causes difficulty in daily activities, some emotional impact (for example, worry), and some difficulty going outside the home without assistance.	0.184 (0.125–0.259)
Distance vision, moderate loss	This person has vision problems that make it difficult to recognize faces or objects across a room.	0.031 (0.019–0.049)
Distance vision blindness	This person is completely blind, which causes great difficulty in some daily activities, worry and anxiety, and great difficulty going outside the home without assistance.	0.187 (0.124–0.26)

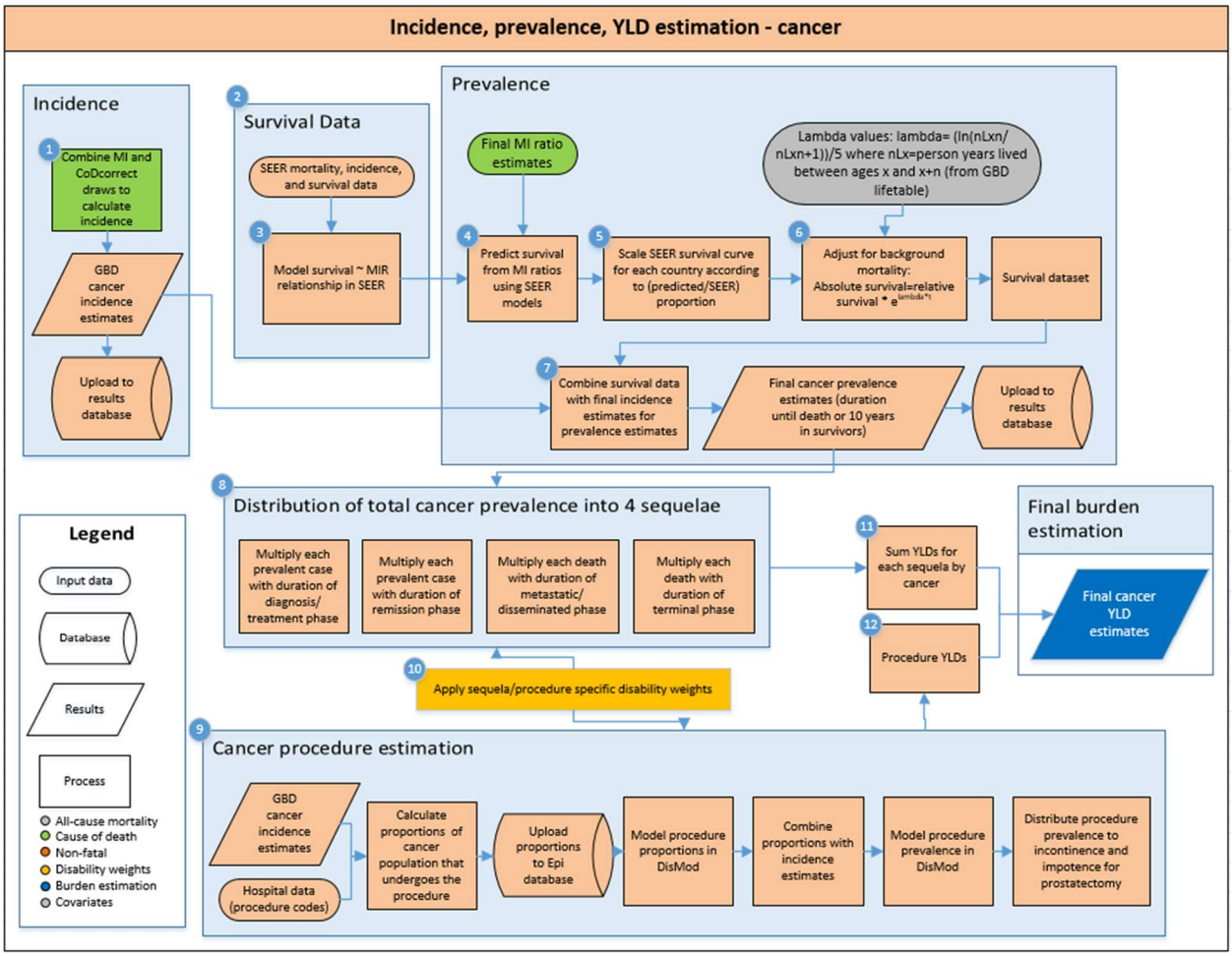
Near Vision Loss	This person has difficulty seeing things that are nearer than 3 feet if uncorrected by reading glasses, but has no difficulty with seeing things at a distance.	0.011 (0.005–0.02)

The following changes have been implemented for GBD 2019:

- We incorporated 151 age-disaggregated RAAB surveys, of which 51 RAAB surveys were newly added this year
- We added new data from 84 literature studies for distance vision and 11 literature studies for near vision loss
- Evaluated alternative case definitions (best-corrected data, studies using Rapid Assessment of Avoidable Blindness methodology, mixed severity data) using new logit difference meta-regression method to determine adjustment factors
- Used new MR-BRT methods to assess sex differences in prevalence for each vision loss cause and the vision loss envelopes, and apply this to "both" sex data points
- Transitioned to only using measured data for near vision loss estimates, and accepted case definition of near vision loss of 6/12 or worse.

Neoplasms

The general framework for the GBD 2019 cancer estimation applies to all malignant neoplasms (i.e. cancers) except for: non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma); benign and in situ neoplasms (which include intestinal, cervical and uterine, and other benign neoplasms); and myelodysplastic, myeloproliferative, and other hematopoietic neoplasms.



Input data and methodological appendix

Case definition

For GBD 2019, incidence, prevalence, and disability are estimated for all cancers and benign neoplasms as defined in ICD-10 (C00-D49). The associated ICD codes for neoplasms estimated for GBD 2019 are listed in Appendix Table 4. Prevalence for all cancers is estimated for a maximum of 10 years after incidence, as in GBD 2013, GBD 2015, GBD 2016, and GBD 2017. Prevalence extending beyond the 10year period is only estimated for permanent sequelae resulting from five treatment-related surgical procedures (cystectomy, laryngectomy, mastectomy, prostatectomy, and stoma).

To estimate disability for each cancer, total prevalence is split into four sequelae: 1. diagnosis and primary therapy; 2. controlled phase; 3. metastatic phase; and 4. terminal phase. The diagnosis and primary therapy phase is defined as the time from the onset of symptoms to the end of treatment. The controlled phase is defined as the time between finishing primary treatment and the earliest of either: cure (defined as recurrence- and progression-free survival after 10 years); death from another cause; or progression to the metastatic phase. The metastatic phase is defined as the time period of intensive treatment for metastatic disease, as determined for each cancer by SEER (Surveillance, Epidemiology, and End Results Program) averages (Table 1). The terminal phase is defined as the one-month period prior to death. Each of these four sequelae has a separate disability weight, which are the same across cancer types (Error! Reference source not found.). Because of long-term disability associated with treatment-related procedures, additional disability beyond these four sequelae is estimated for five cancers: breast cancer (disability due to mastectomy), larynx cancer (disability due to laryngectomy), colon and rectum cancer (disability due to stoma), bladder cancer (disability due to incontinence from cystectomy), and prostate cancer (disability due to either incontinence or impotence from prostatectomy).

Input data

Cancer incidence is directly estimated from cancer mortality using mortality to incidence ratios (MIRs). Data sources for cancer mortality are described in detail elsewhere.[1] To estimate the proportion of cancer patients undergoing surgical procedures we used SEER data form 1983 to 2008[2] and Mexico Hospital Data from 2001 to 2009[3]. Data sources used to adjust procedure sequelae will be listed below.

Table 1a. Data Inputs for neoplasms morbidity modelling by parameter.

Cause	Prevalence		Incidence		Deaths		All measures	
	Sources	Countries with data	Sources	Countries with data	Sources	Countries with data	Sources	Countries with data
Neoplasms	299	45	4329	107	1621	42	5212	121
Esophageal cancer	3	1	3305	102	1519	41	3646	102
Stomach cancer	3	1	3316	102	1532	41	3659	102
Liver cancer	3	1	3361	106	1522	41	3974	117
Larynx cancer	3	1	3311	101	1561	40	3653	101
Tracheal, bronchus, and lung cancer	3	1	3341	106	1562	41	3689	106
Breast cancer	3	1	3365	106	1533	41	3713	106

Cervical cancer	3	1	3303	106	1514	41	3636	106
Uterine cancer	3	1	3311	102	1492	40	3617	102
Prostate cancer	3	1	3293	102	1531	41	3635	102
Colon and rectum cancer	3	1	3357	106	1533	41	3705	106
Lip and oral cavity cancer	3	1	2909	103	1059	35	3192	103
Nasopharynx cancer	3	1	3314	106	1488	41	3631	106
Other pharynx cancer	3	1	3221	102	1419	41	3536	102
Gallbladder and biliary tract cancer	3	1	3283	100	1514	40	3600	100
Pancreatic cancer	3	1	3359	106	1532	41	3707	106
Malignant skin melanoma	3	1	3245	105	1458	41	3593	105
Non-melanoma skin cancer	0	0	1434	91	0	0	1434	91
Ovarian cancer	3	1	3325	106	1509	41	3652	106
Testicular cancer	3	1	3215	105	1444	40	3563	105
Kidney cancer	3	1	3209	103	1447	40	3544	103
Bladder cancer	3	1	2997	105	1048	34	3258	105
Brain and central nervous system cancer	3	1	3339	105	1522	42	3686	105
Thyroid cancer	3	1	3355	106	1534	41	3703	106
Mesothelioma	3	1	1329	94	180	19	1389	95
Hodgkin lymphoma	3	1	3318	104	1524	41	3666	104
Non-Hodgkin lymphoma	3	1	3537	105	752	28	3646	105
Multiple myeloma	3	1	3265	100	1506	39	3593	100
Leukemia	3	1	3539	104	1389	38	3816	104
Other malignant neoplasms (internal)	3	1	3263	105	1425	41	3584	105
Other neoplasms	296	45	0	0	0	0	296	45

Table 1b. Data Inputs for liver cancer subtypes morbidity modelling by parameter.

Cause	Proportion	
	Sources	Countries with data
Neoplasms	267	53
Liver cancer due to hepatitis B	267	53
Liver cancer due to alcohol use	96	25
Liver cancer due to other causes (internal)	55	18

Modelling strategy

Estimation of cancer mortality and MIR estimation has been described in the GBD 2019 Mortality and Causes of Death capstone paper. The final GBD cancer mortality estimates are transformed to incidence estimates by using MIRs (which are modeled separately). To summarize the MIR estimation process: incidence and mortality data from cancer registries were matched by cancer, age, sex, year, and location to generate M/I ratios. These MIR data were used to fit cause-specific fixed effect logistic regression models with covariates for sex, categorical age, and the Healthcare-access and quality index (HAQ index) [4]:

$$\text{logit}\left(MI\ ratio_{c,a,s,t}\right) = \alpha + \beta_1 HAQI_{c,t} + \sum_{a}^{A} \beta_2 I_a + \beta_3 I_s + \epsilon_{c,a,s,t}$$

c: country, a: age group, t: time (years); s: sex
HAQI: Healthcare access and quality index
I: indicator variable
$\epsilon_{c,a,s,t}$: error term

These models were then used to obtain MIR estimates for all combinations of GBD age, sex, year, cause, and location. Data points were outliered manually if they clearly influenced the model in an unrealistic way. For example, a data point was marked as an outlier if it created a single-year, single age group spike in model predictions that was inconsistent with the trend suggested by surrounding data points. Results from the final linear model were used as input for space-time smoothing and a Gaussian Process Regression (ST-GPR). The ST-GPR process has been updated for GBD 2019 to utilize more MIR input data (by lessening the inclusion criteria for MIR data from 25 incident cases to 15) and to perform more smoothing across age and time (by adjusting modeling hyperparameters that control the weighting of adjacent data values).

Final MIR estimates at the 1000-draw level were combined with final mortality estimates (also at the 1000-draw level) to generate 1000 draws of incidence estimates (which provides an estimated mean incidence with 95% uncertainty interval). It was assumed that uncertainty in the MIR is independent of uncertainty in the estimated mortality.

After transforming the final GBD cancer mortality estimates to incidence estimates (step 1 in the general cancer flowchart), incidence was combined with annual relative survival estimates from 1 to 10 years

(step 7 in the flowchart). Our survival estimation methods were first implemented in GBD 2017 to more directly utilize MIRs to generate yearly cancer relative survival estimates; for GBD 2019 we updated these methods to utilize age-specific rather than all-ages survival curves. Previous reports suggest that the value of (1 – MIR) may serve as a proxy for 5-year relative survival, with the exact correlation varying slightly by cancer type.[5] We used SEER*Stat[6] to obtain mortality, incidence, and relative survival statistics from the 9 SEER registries[7] reporting from 1980-2014 (step 2), by cancer type, sex, 5-year blocks (i.e., 1980-84, 1985-1989, etc.), and 5-year age groups (except combining 80+). For each cancer, we modelled 5-year relative survival with the SEER MIRs. For GBD 2019 we updated this model from the Poisson regression used in GBD 2017 to using a generalized linear model with a quasibinomial family and logit link, weighted by the number of index cases (step 3). To reduce variability due to small samples, we only included MIRs based on at least 25 incident cases (except for the rarer cancers mesothelioma, nasopharyngeal cancer, and acute myeloid leukemia, where MIRs based on at least 10 cases were included). These models were then applied to the GBD MIR estimates to predict an estimated 5-year survival for each age/sex/year/location (step 4). To prevent unrealistic values, predicted 5-year survival values were winsorized to be between 0% and 100% survival. Unlike GBD 2017, we did not require the estimated survival to be greater than the all-ages worst-case survival scenario from SurvCan and US 1950 survival data[8,9], since age-specific survival could be plausibly lower than for these all-ages scenarios.). To generate yearly survival estimates up to 10 years, for GBD 2019 we downloaded SEER sex- and age-specific annual 1- through 10-year relative survival data from patients diagnosed between 2001 and 2010 (compared to GBD 2017 where we downloaded all-ages survival data from 2004).[10] The proportion of the predicted GBD 5-year survival estimate to the SEER 5-year survival statistic was calculated as a scalar, and then used to generate yearly survival estimates by scaling the 1-10 year SEER curve to the GBD survival predictions under the proportional hazard assumption (step 5). This change from GBD 2017 (where we used SEER all-ages data from 2004 as the scalar and survival curve) impacts prevalence and YLD estimation, generally leading to survival estimates that are higher for younger ages and lower for older ages compared to estimates using the all-ages curve.

To transform relative to absolute survival (adjusting for background mortality), GBD 2019 lifetables were used (step 6 and 7 in the flowchart) to calculate lambda values: lambda= (ln(nLxn/nLxn+1))/5, where nLx=person years lived between ages x and x+n (from GBD lifetable). Absolute survival was then calculated using an exponential survival function (absolute survival = relative survival * $e^{lambda*t}$). Absolute survival is combined with incidence to estimate the prevalence at each year after diagnosis, which is then split into the four sequelae (step 8 in the flowchart).

For the purposes of calculating disability due to cancer, survivors beyond 10 years were considered cured. For this group, the survivor population prevalence was divided into two sequelae (1. diagnosis and primary therapy; 2. controlled phase). For the population that did not survive beyond 10 years, the yearly prevalence was divided into the four sequelae by assigning the fixed durations for each of the diagnosis and primary therapy phase, metastatic phase, and terminal phase, and assigning the remaining prevalence to the controlled phase (step 8 in the flowchart). Duration of these four sequelae remained the same as for GBD 2013, GBD 2015, GBD 2016, and GBD 2017.[11] Table 1 lists the duration of each, along with the sources used to determine their length.

Table 2. Duration of four prevalence sequelae by cancer

	Diagnosis/ Treatment (months)	Remission	Disseminated/metastatic (months)	Note	Terminal (months)
Esophageal cancer	5[12]	Calculated based on remainder of time after attributing other sequelae.	4.6[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	1 months
Stomach cancer	5.2[12]		3.88[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Liver cancer	4		2.51[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Larynx cancer	5.3[12]		8.84[10]	SEER Stage IVc	
Lung cancer	3.3[13]		4.51[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Breast cancer	3[13]		17.7[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Cervical cancer	4.8[12]		9.21[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Uterine cancer	4.6[12]		11.6[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Prostate cancer	4[13]		30.35[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Colorectal cancer	4[13]		9.69[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Oral cancer	5.3[12]		9.33[10]	SEER Stage IVc	
Nasopharyngeal cancer	5.3[12]		13.19[10]	SEER Stage IVc	
Cancer of other part of pharynx	5.3[12]		7.91[10]	SEER Stage IVc	
Gallbladder cancer	4		3.47[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Pancreas cancer	4.1[12]		2.54[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	
Melanoma	2.9[14]		7.18[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000	

Ovarian cancer	3.2[13]	25.6[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000
Testicular cancer	3.7[12]	19.47[10]	SEER Stage III
Kidney cancer	5.3[12]	5.38[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000
Bladder cancer	5.1[12]	5.8[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000
Brain cancer	5	6.93[10]	SEER Median age standardized survival all patients, all years
Thyroid cancer	3	19.39[10]	SEER Stage IVc
Mesothelioma	4	7.75[10]	SEER Summary Stage 1997 (Distant site/node involved) 1995-2000
Hodgkin lymphoma	3.7[13]	26[15]	
Non Hodgkin lymphoma	3.7[13]	7.7[15]	
Multiple myeloma	7[12]	36.82[10]	SEER Median age standardized survival all patients, all years
Leukemia[12]	5	43.67[10]	SEER Median age standardized survival all patients, all years
ALL	12	7.02[10]	SEER Median age standardized survival all patients, all years
AML	6	4.6[10]	SEER Median age standardized survival all patients, all years
CLL	6	48[16]	SEER Median age standardized survival all patients, all years
CML	6	4.6[10]	SEER Median age standardized survival for AML (patients with CML die in blast crisis, which is treated like AML) all patients, all years
Leukemia other	6	48[16]	SEER Median age standardized survival all patients, all years

Other	4.4 (mean of other cancer durations)		15.81[10]	SEER Median age standardized survival all patients, all years	

For cancer-specific procedure sequelae, hospital data were used to estimate the number of cancer patients undergoing mastectomy, laryngectomy, stoma, prostatectomy, and cystectomy (step 9 in the flowchart). These proportions remained the same as in GBD 2013, GBD 2015 GBD 2016, and GBD 2017.[11] Proportions were generated by dividing the rate of procedures generated from the diagnostic codes in the hospital dataset and the coverage population by the GBD age-, and sex-specific disease incidence rates for that country. Diagnostic codes used are listed in Table 2:

Table 3. Procedure codes used to estimate cancer procedure proportions

Procedure	Cancer	Procedure code (ICD-9_CM)
Mastectomy	Breast cancer	854, 8541, 8542, 8543, 8544, 8545, 8546, 8547, 8548
Laryngectomy	Larynx cancer	301, 303, 304, 3029
Stoma	Colon and rectum cancer	461, 4610, 4611, 4613, 4862
Cystectomy	Bladder cancer	5771, 5779
Prostatectomy	Prostate	603, 604, 605, 606, 6062

To estimate procedure-related disability for each of these five cancers, the procedure proportions (proportion of each cancer population that undergo these procedures) from hospital data were used as input for a proportion model in Dismod-MR 2.1 to estimate the proportions for all locations, by age, year, and by sex.

Since colostomy or ileostomy procedures are done for reasons other than cancer, a literature review was conducted to determine the proportion of ostomies due to colorectal cancer. Based on the results of the literature review that an average of 58% of ostomies are done for colorectal cancer, the “all cause” colostomy proportions were multiplied by 0.58.[17–19]

The final procedure proportions were applied to the incidence cases of the respective cancers and multiplied with the proportion of the incidence population surviving for 10 years to determine the incident cases of the cancer population that underwent procedures and that survived beyond 10 years. These incident cases were used again as an input for DisMod-MR 2.1, with a remission specification of zero and an excess mortality rate prior of 0 to 0.1, as well as with increasing the age of the population and the year by 10 years to reflect prevalence after that population has survived 10 years. The results from this model are incidence and lifetime prevalent cases of persons with these cancer-related sequelae who have survived beyond 10 years.

Since disability associated with prostatectomy comes from impotence and incontinence, and not from the prostatectomy itself, 18% of the prostatectomy prevalence was assumed to have incontinence and 55% was assumed to have impotence, based on a literature review done for GBD 2013.[20–27] Cases were assigned disability for either impotence or incontinence, but no cases were assigned disability from both.

We assumed that for the population surviving up to 10 years, only the prevalence population being in remission experiences additional disability due to procedures (e.g. a women suffering from metastatic

breast cancer do not experience additional disability due to a mastectomy during this phase). To estimate the prevalence of the cancer population in remission during the first 10 years after diagnosis with and without procedure-related disability, we multiplied the prevalence of the population in the remission phase with the proportion of the population undergoing a procedure. This step allowed us to estimate disability during the remission phase for both the population experiencing disability due to the remission phase alone, as well as the population experiencing disability from the remission phase and the additional procedure-related disability.

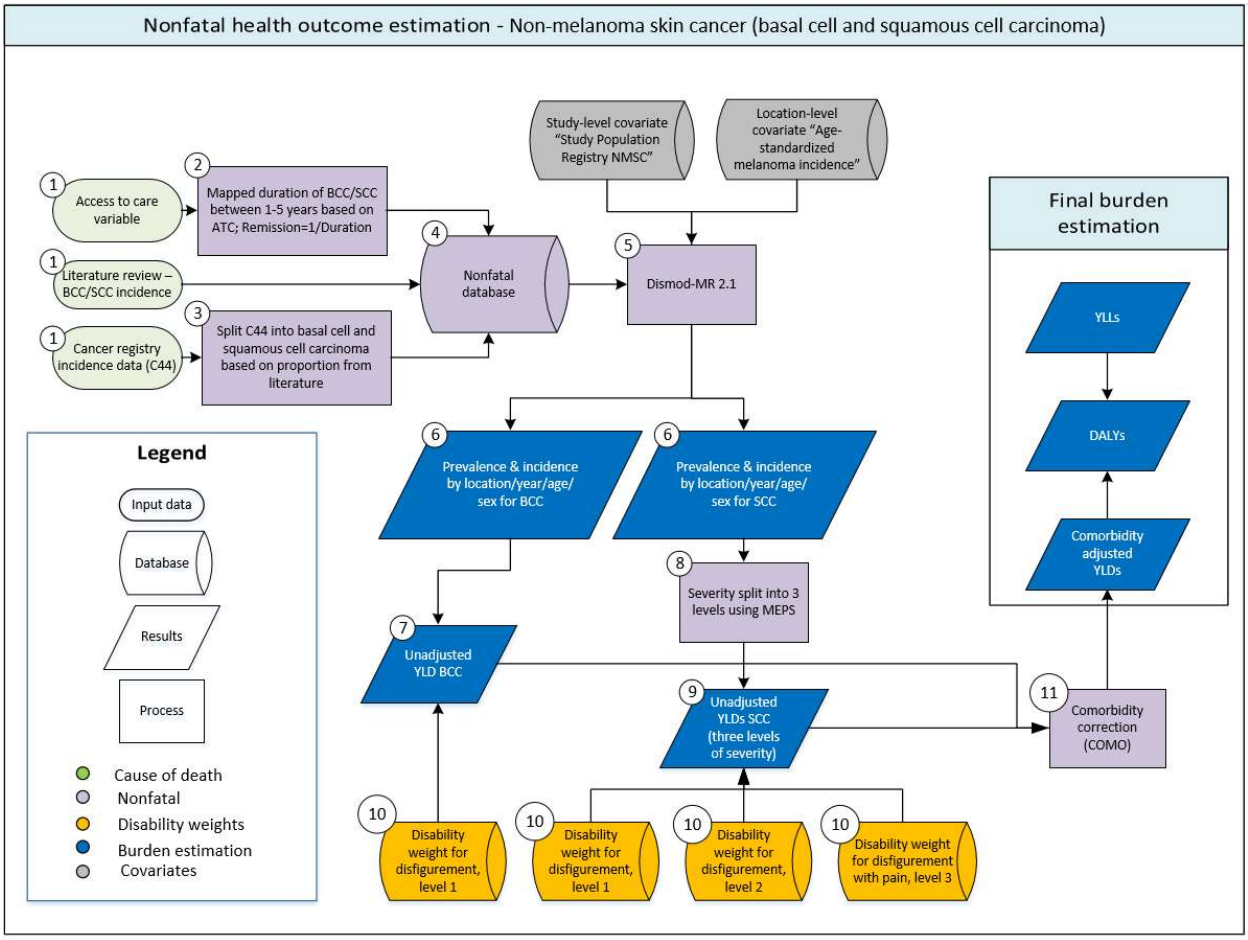
Lastly, the procedure sequelae prevalence and general sequelae prevalence were multiplied with their respective disability weights (Table 3) to obtain the number of YLDs (steps 11 and 12 in the flowchart). The sum of these YLDs is the final YLD estimate associated with each cancer.

Table 4. Lay description and disability weights

Health state	Lay description	Estimate	Uncertainty interval	
Cancer, diagnosis and primary therapy (cancer_diagnosis)	This person has pain, nausea, fatigue, weight loss and high anxiety.	0.288	0.193	0.399
Cancer, controlled phase (generic_medication)	This person has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0.049	0.031	0.072
Cancer, metastatic (cancer_metastatic)	This person has severe pain, extreme fatigue, weight loss and high anxiety.	0.451	0.307	0.600
Terminal phase, with medication (cancer_terminal_treat)	This person has lost a lot of weight and regularly uses strong medication to avoid constant pain. The person has no appetite, feels nauseous, and needs to spend most of the day in bed.	0.540	0.377	0.687
Mastectomy (cancer_mastectomy)	This person had one of her breasts removed and sometimes has pain or swelling in the arms.	0.036	0.020	0.057
Stoma (cancer_stoma)	This person has a pouch attached to an opening in the belly to collect and empty stools.	0.095	0.063	0.131
Laryngectomy (speech_problems)	This person has difficulty speaking, and others find it difficult to understand.	0.051	0.032	0.078
Urinary incontinence (incontinence)	This person cannot control urinating.	0.139	0.094	0.198

Impotence (impotence)	This person has difficulty in obtaining or maintaining an erection.	0.017	0.009	0.030

Non-melanoma skin cancer (squamous and basal cell carcinoma)



Case definition

Non-melanoma skin cancer (NMSC) is defined as basal cell carcinoma and squamous cell carcinoma. NMSC does not include other types of skin cancer (e.g. melanoma, Merkel cell carcinoma).

Input data

We estimated squamous cell and basal cell skin cancer incidence by using cancer registry as well as primary literature, and clinical informatics data (such as Marketscan) for incidence. Only cancer registries that were listed in CI5 VIII as registering squamous cell carcinoma or basal cell carcinoma, respectively, were included in the analysis. For 2019, the clinical data were adjusted for the healthcare access and quality index of the country, and accounts for outpatient encounters. This is a change from GBD 2017, where these data only included non-primary diagnoses in inpatient admissions. This change led to higher values in the input clinical informatics data compared to last year, as it now includes diagnoses from outpatient procedures that did not require hospital admission (whereas previously these data approximated the rate of inpatient admissions for cases with benign neoplasms who had access to hospitals).

Modelling strategy

For cancer registry data reported at the three digit level (i.e., C44: Other and unspecified malignant neoplasm of skin), proportions from Karagas et al were used to split C44 into squamous cell carcinoma and basal cell carcinoma.[28] The only new data we added compared to GBD 2017 was additional data from hospital and outpatient sources. DisMod-MR 2.1 was used to model incidence and prevalence. Prevalence was calculated as a function of two extreme scenarios (duration 1 versus 5 years). Country, age, sex and year-specific duration was estimated using a country-age-sex-year specific relative access-to-care-score.

The access to care score was based on the melanoma mortality to incidence ratio:

$$Access\ to\ care = 1 - \frac{Age\ standardized\ MIR_{cys} - Age\ standardized\ MIR_{min}}{Age\ standardized\ MIR_{ma} - Age\ standardized\ MIR_{min}}$$

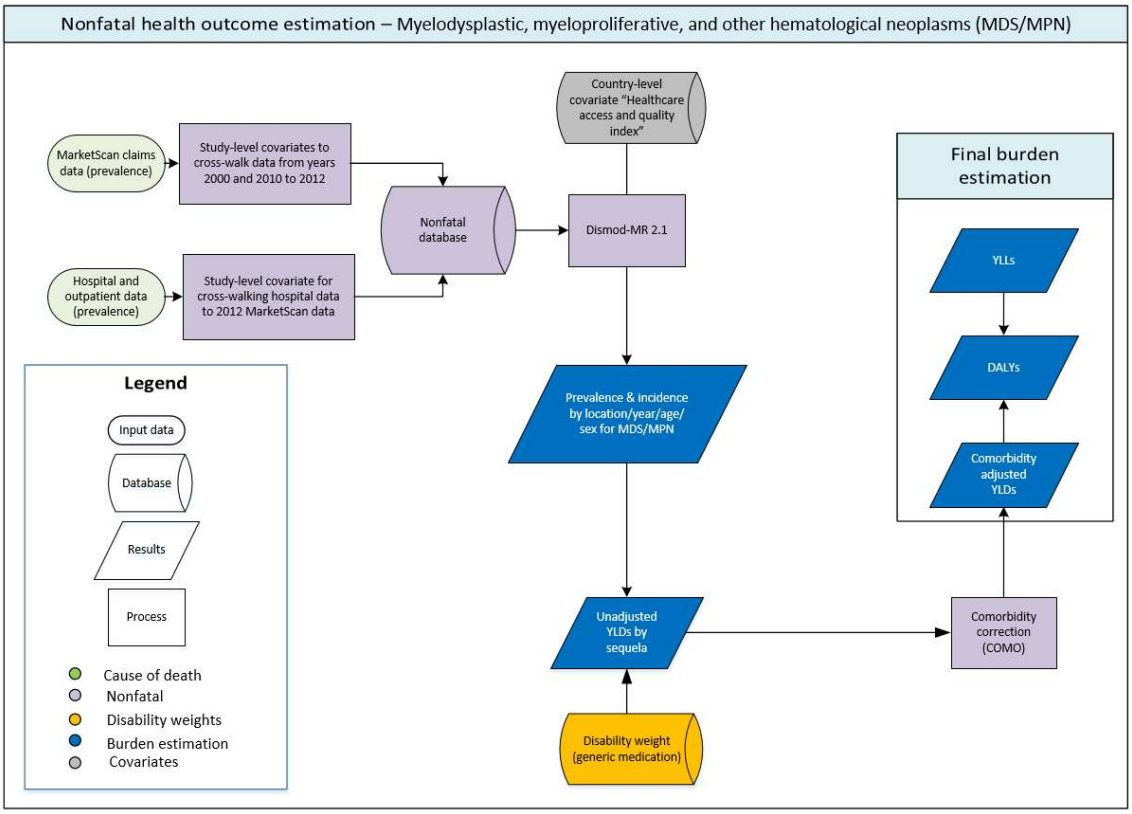
c=country; y=year; s=sex; Age-standardized MI ratio$_{min}$=lowest MIR for all countries and years; Age standardized MIR$_{max}$=highest MIR for all countries and years

Remission was calculated as the inverse of the duration estimates and used as additional input for DisMod-MR 2.1.

To reflect differing degrees of disability due to squamous cell carcinoma we used three levels of severity that were derived from MEPS (Medical Expenditure Panel Survey), resulting in proportions of 80% mild, 15% moderate, and 5% severe disfigurement. For basal cell carcinoma, disability severity was split into 60% asymptomatic (without disability) and 40% with mild disfigurement. Prevalence was multiplied by distinct disability weights (Table 4) to generate YLDs.

Table 5. Lay description and disability weights			
Cause	Health state		Estimate (95% Uncertainty Interval)
Cutaneous squamous cell carcinoma, mild	Disfigurement, level 1	has a slight, visible physical deformity that others notice, which causes some worry and discomfort.	0.011 (0.005-0.021)
Cutaneous squamous cell carcinoma, moderate	Disfigurement, level 2	has a visible physical deformity that causes others to stare and comment. As a result, the person is worried and has trouble sleeping and concentrating.	0.067 (0.044-0.096)
Cutaneous squamous cell carcinoma, severe	Disfigurement, level 3, with itch/pain	has an obvious physical deformity that is very painful and itchy. The physical deformity makes others uncomfortable, which causes the person to avoid social contact, feel worried, sleep poorly, and think about suicide.	0.576 (0.401-0.731)
Disfigurement due to basal cell carcinoma	Disfigurement, level 1	has a slight, visible physical deformity that others notice, which causes some worry and discomfort.	0.011 (0.005-0.021)

Myelodysplastic, myeloproliferative, and other hematopoieticneoplasms



Case definition

Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms (MDS/MPN) comprise a wide variety of diseases and outcomes. These were modelled together as a single group for GBD 2019 (the same as for GBD 2017).

Input data

We estimated MDS/MPN deaths using vital registration data (as outlined above). We did not use cancer registry data for these neoplasms, as it has only been reported within some cancer registries since 2001 and is recognized to be underreported.[29] We estimated MDS/MPN prevalence using MarketScan claims data from the United States in the years 2000, 2010, and 2012, as well as hospital and outpatient data from other health systems worldwide. For 2019, these prevalence data were adjusted for the healthcare access and quality index of the country, and accounts for outpatient encounters. This is a change from GBD 2017, where prevalence only included non-primary diagnoses in inpatient admissions. This change led to a large increase in incidence and prevalence compared to last year, as it now includes diagnoses from outpatient procedures that did not require hospital admission (whereas previously these data approximated the rate of inpatient admissions for cases with benign neoplasms who had access to hospitals).

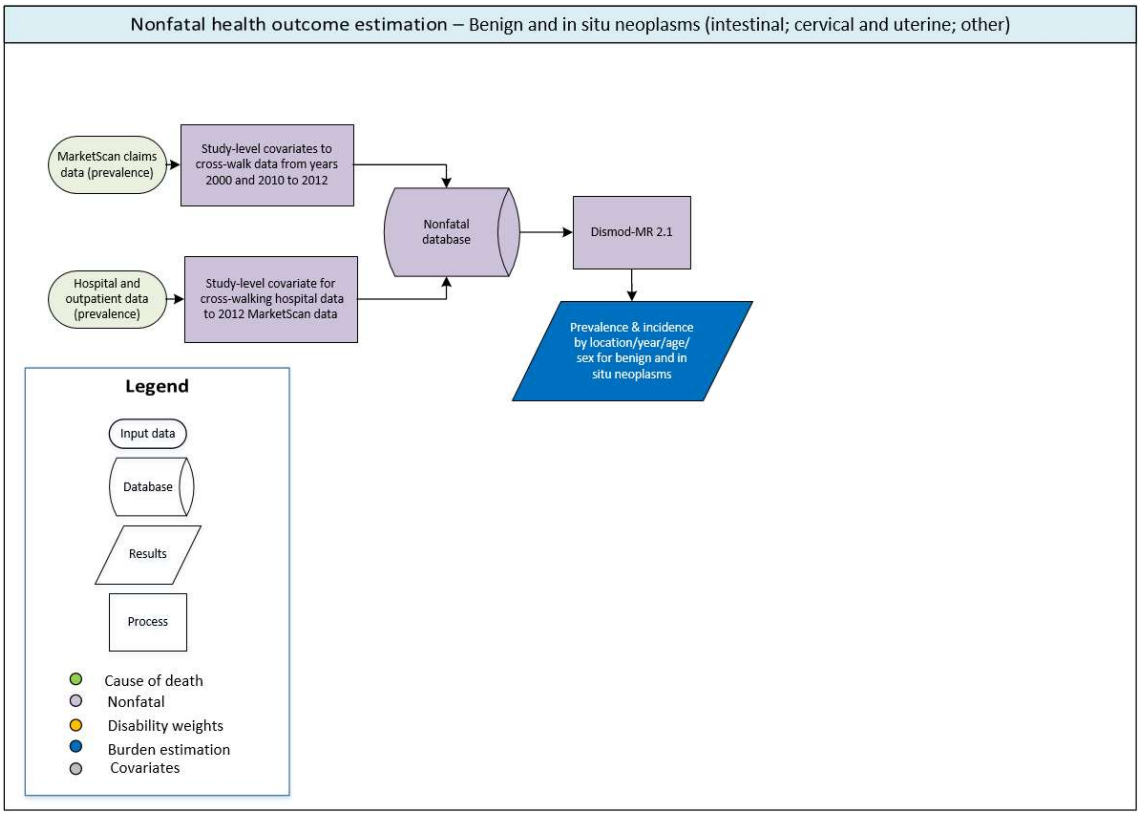
Modelling strategy

We modelled deaths for all locations and years, by age and by sex, using CODEm. As MDS/MPN can be a precursor to leukemia, our MDS/MPN CODEm model used the same covariate priors as the CODEm model for acute myeloid leukemia.

We modelled the prevalence of these diseases for all combinations of location, age, year, and sex using a prevalence model in Dismod-MR 2.1. For Dismod model specifications, cause-specific mortality rates came from the CODEm model, remission was specified to be zero, and the excess mortality rate was set to be inversely related to the healthcare access and quality index covariate.

While this broad category of hematological neoplasms is heterogeneous in its components' severity or propensity for transformation to leukemia, modelling these components separately was not feasible for 2019. This is an admitted limitation, and an area of desired future improvement as data availability improves. For GBD 2019, the "generic medication" disability weight was assigned for all MDS/MPN cases (see Table 3).

Benign and in situ intestinal neoplasms; Benign and in situ cervical and uterine neoplasms; Other benign and in situ neoplasms



Case definition

For GBD 2019 we estimated three categories of benign and in-situ neoplasms: intestinal neoplasms; cervical and uterine neoplasms; and other benign and in situ neoplasms. Benign and in situ intestinal neoplasms were defined as any non-invasive intestinal growth. Benign and in situ cervical and uterine neoplasms were defined as any non-invasive cervical and uterine growth, except for uterine fibroids. Other benign and in situ neoplasms were defined as any non-invasive neoplasms not covered by other GBD causes.

Input data

To estimate the prevalence of each of these categories for all locations, by age, year, and sex, the prevalence of these neoplasms from hospital data was used as input for a prevalence model in Dismod-MR 2.1. These inputs included MarketScan claims data from the United States in the years 2000, 2010, and 2012, as well as hospital and outpatient data from other health systems worldwide. For GBD 2019, these prevalence data were adjusted for the healthcare access and quality index of the country, and accounts for outpatient encounters. This is a change from GBD 2017, where prevalence only included non-primary diagnoses in inpatient admissions. This change led to a large increase in incidence and prevalence compared to last year, as it now includes diagnoses from outpatient procedures that did not require hospital admission (whereas previously these data approximated the rate of inpatient admissions for cases with benign neoplasms who had access to hospitals).

Modelling strategy

In the Dismod model for benign and in situ intestinal neoplasms, excess mortality rate was specified to be zero, and remission was allowed to vary from 0 to 1. In the Dismod model for benign and in situ cervical and uterine neoplasms, excess mortality rate was specified to be zero, and remission was allowed to vary from 0 to 0.75. In the Dismod model for other benign and in situ neoplasms, excess mortality rate was specified to be zero, and remission was allowed to vary from 0 to 1.

All three of these benign and in-situ neoplasms are by definition benign and localized. As such, no deaths or disability were attributed to their occurrence in GBD 2017.

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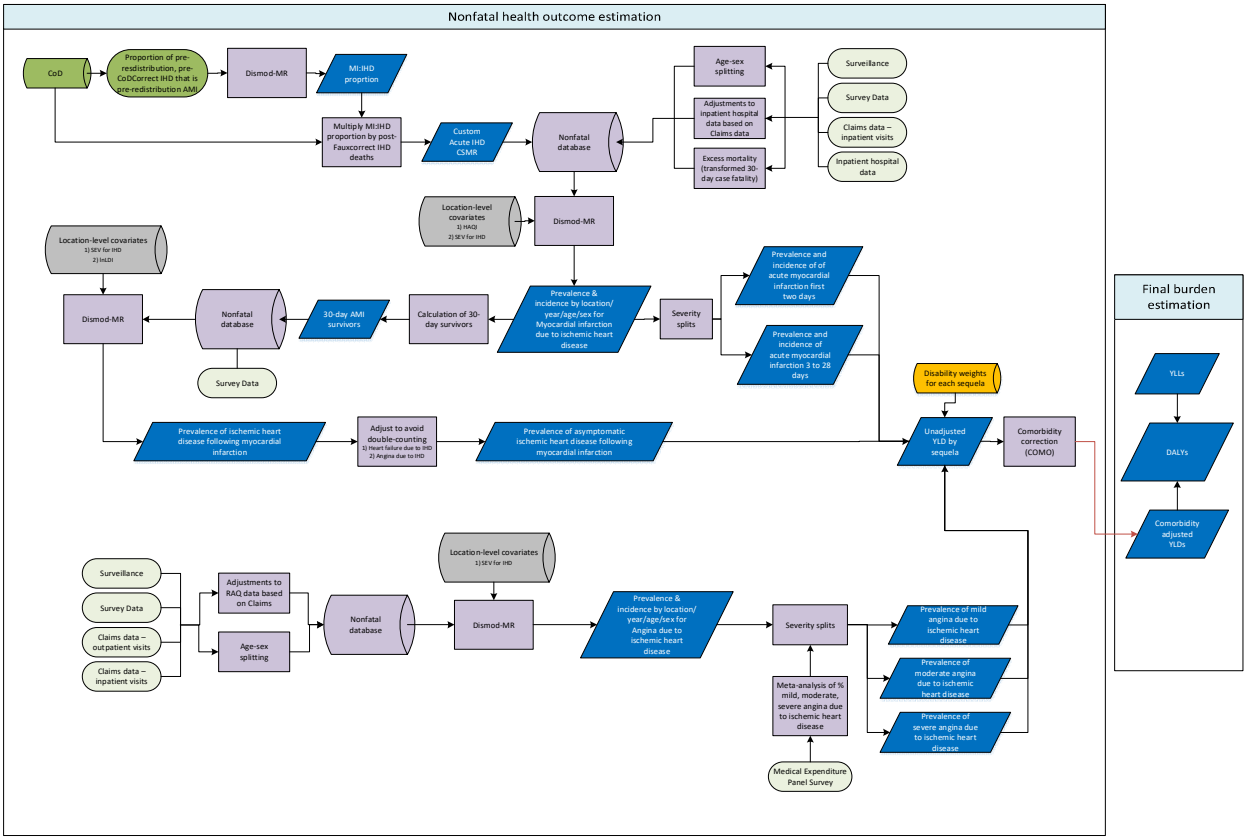
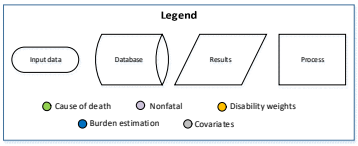
Ischaemic heart disease

Flowchart





Input data and methodological summary

Case definition

Case definitions:

1) Acute myocardial infarction (MI): Definite and possible MI according to the third universal definition of myocardial infarction:
    a. When there is clinical evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia or
    b. Detection of a rise and/or fall of cardiac biomarker values and with at least one of the following: i) symptoms of ischaemia, ii) new or presumed new ST-segment-T wave changes or new left bundle branch block, iii) development of pathological Q waves in the ECG, iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or v) identification of an intracoronary thrombus by angiography or autopsy.
    c. Sudden (abrupt) unexplained cardiac death, involving cardiac arrest or no evidence of a non-coronary cause of death
    d. Prevalent MI is considered to last from the onset of the event to 28 days after the event and is divided into an acute phase (0–2 days) and subacute (3–28 days).

2) Chronic IHD
    a. Angina; clinically diagnosed stable exertional angina pectoris or definite angina pectoris according to the Rose Angina Questionnaire, physician diagnosis, or taking nitrate medication for the relief of chest pain.
    b. Asymptomatic ischaemic heart disease following myocardial infarction; survival to 28 days following incident MI. The GBD study does not use estimates based on ECG evidence for prior MI, due to its limited specificity and sensitivity (1).

ICD codes used for inclusion of hospital and claims data for MI and angina can be found elsewhere in the appendix.

Input data

The total source counts for non-fatal ischaemic heart disease are shown in the table below by measure.

Table 1: Source counts for all non-fatal ischaemic heart disease models.

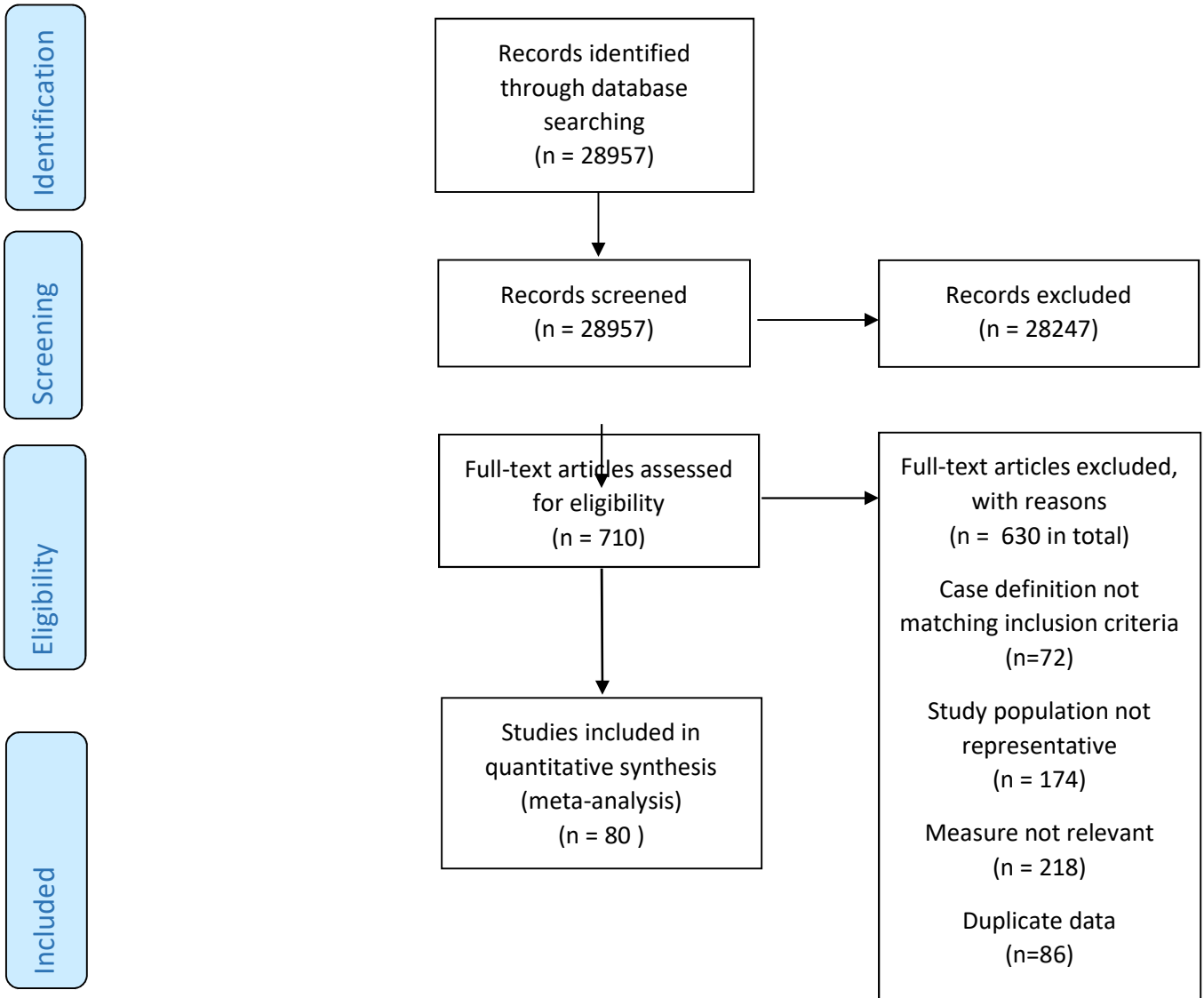
Measure	Total sources	Countries with data
All measures	442	84
Prevalence	88	61
Incidence	296	44
Excess mortality rate	90	21
Relative risk	1	1
Standardized mortality ratio	1	1
With-condition mortality rate	4	4
Proportion	16	1

Myocardial infarction

A systematic review was done for myocardial infarction for GBD 2019 in order to update our current database. The search strings used were ((“myocardial infarction”[tiab] AND (incidence OR “case fatality” OR “excess mortality”)) OR (“acute coronary syndrome”[tiab] AND (incidence OR “case fatality” OR “excess mortality”)) OR (angina[tiab] AND (incidence OR prevalence OR “case fatality” OR “excess mortality”))) AND ("2019/01/01"[PDAT] : "2019/12/31"[PDAT]) NOT rat[tiab] NOT mice[tiab] NOT monkey[tiab] NOT pig[tiab] NOT animals[tiab].

The dates of the search were 1/1/2019 – 12/31/2019. 28957 studies were returned, 80 were extracted. The PRISMA diagram for the systematic review is given below. In the diagram, screening refers to reviewing of the title and abstract of an article for relevant information, not screening of the entire article.

PRISMA Diagram



The last systematic review for myocardial infarction was done for GBD 2015. The dates of the search were 1/1/2009 – 2/3/2015. 38,522 studies were returned; 194 were extracted (this number includes extractions that were done for STEMI/NSTEMI models and revascularisation models that are not currently part of the MI modelling process but may be in the future).

A systematic review for myocardial infarction was also done for GBD 2013. The extensive search terms for that review will be provided on request.

Apart from inpatient hospital and inpatient claims data, we did not include any data from sources other than the literature for myocardial infarction. We also split excess mortality data points where the age range was greater than 25 years. Age splitting was based on the global sex-specific age pattern from a Dismod model that only used excess mortality input data from scientific literature with less than a 25-year age range. We excluded incidence data with broad age ranges where it was impossible to obtain more granular data, as these data caused the known age pattern for increased risk of myocardial infarction to be masked in the estimates generated from DisMod.

We crosswalked incidence measurements for myocardial infarction literature data with alternative definitions to agree with our case reference definition using MR-BRT (Meta Regression – Bayesian, Regularized, Trimmed) modeling tool. MR-BRT and the process of data adjustment are discussed elsewhere in the appendix. For myocardial infarction we crosswalked using multiple different covariates: a covariate to capture only first-ever MI, using studies where all events were included as the reference; a covariate to adjust estimates from studies that only included non-fatal cases, using sources that included fatal and non-fatal cases as reference; and a covariate to adjust for studies that did not use troponin measurements in their case diagnosis, using sources that did include troponin measurements in their diagnostic method. The coefficients in Table 2 below can be used to calculate adjustment factors for alternative definitions. The formula for computing adjustment factors is given in equation 1 below. We also included a standardized age variable (age scaled) and a sex variable to the regression to adjust for the possibly of bias.

Equation 1: Calculation of adjustment factors:

$$Estimated\ Reference\ Def = invlogit(logit(Alternative\ Def) - Beta_{Alternative\ Def} - Beta_{Sex} * Sex - Beta_{Age_{scaled}} * Age\ Scaled)$$

Table 2a: MR-BRT Crosswalk Adjustment Factors for Myocardial Infarction

Data input	Measure	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)
Any event, fatal and nonfatal events, used troponin	Incidence	Ref	0.27	---
Troponin not used as part of definition	Incidence	Alt		-0.55 (-1.08 - -0.01)
First-ever	Incidence	Alt		-0.59 (-1.21 – 0.03)
Non-fatal	Incidence	Alt		-0.35 (-0.98 – 0.29)
Age scaled	Incidence	Alt		-0.05 (-0.59 – 0.49)
Sex (male)	Incidence	Alt		-0.001 (-0.54 – 0.54)

Asymptomatic ischaemic heart disease following myocardial infarction

No systematic review was performed for Asymptomatic ischaemic heart disease following myocardial infarction in GBD 2019. The primary input for this model are 28-day survivors calculated from the excess mortality estimates for the myocardial infarction model. We included data for excess mortality and standardised mortality ratio to inform the estimates of survival after myocardial infarction.

Angina

A systematic review was not performed for GBD 2019. Updates to systematic reviews are performed on an ongoing schedule across all GBD causes; an update for angina will be performed in the next one to two iterations.

A systematic review for angina was last performed for GBD 2013. The search terms for that are: (Angina Pectoris/epidemiology[Mesh] OR Angina Pectoris/mortality[Mesh]) AND (prevalence[Title/Abstract] OR incidence[Title/Abstract]) AND ("2010"[Date - Publication] : "3000"[Date - Publication])

We included survey data (including NHANES and World Health Study questionnaires) which included the RAQ items. Prevalence of angina was calculated using the standard algorithm to determine whether the RAQ was positive or negative.

We excluded data with broad age ranges where it was impossible to obtain more granular data, as these data caused the known age pattern for increased risk of angina to be masked in the estimates generated from DisMod.

We also included US claims data, but did not include inpatient hospital data from any locations. Stable angina (unstable angina is modeled as part of MI) is expected to be rare in inpatient but common in outpatient data as it is a condition usually managed on an outpatient basis, except for specific surgical interventions. This discrepancy leads to implausible correction factors based on inpatient/outpatient information from claims data (~150X); thus adjusted data cannot be used. Including uncorrected data in the model is likely to lead to incorrect estimates as hospitalisation and procedure rates are likely to vary between geographies based on access to and patterns of care. All outpatient data were excluded as they were implausibly low for all locations when compared with literature and claims data.

We crosswalked prevalence data obtained from survey data using the RAQ using claims data as a reference since the RAQ has been shown to be neither sensitive nor specific. Specifics on the crosswalking process are discussed elsewhere in the appendix. Table 2b shows the coefficients adjustments made to the alternative definition.

Table 2b: MR-BRT Crosswalk Adjustment Factors for Angina

Data input	Measure	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)
United States Claims Data	Prevalence	Ref	0.11	---
Rose Angina Questionnaire	Prevalence	Alt		2.21 (1.97 to 2.44)
Age (scaled)	Prevalence	Alt		-0.97 (-1.20 to -0.74)
Sex (male)	Prevalence	Alt		-0.62 (-0.86 to -0.38)

Severity split inputs

Acute myocardial infarction was split into two severity levels by length of time since the event – days 1 and 2 versus days 3 through 28. Disability weights were established for these two severities using the standard approach for GBD 2019.

Asymptomatic ischaemic heart disease following myocardial infarction was all assigned to the asymptomatic severity level. No disability weight is assigned to this level.

Angina was split into asymptomatic, mild, moderate, and severe groups using information from MEPS. Disability weights were established for these severities using the standard approach for GBD 2019.

Acute myocardial infarction

Table 3a. Severity distribution, details on the severity levels for Myocardial Infarction in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)
Acute myocardial infarction, days 1-2	Has severe chest pain that becomes worse with any physical activity. The person feels nauseated, short of breath, and very anxious.	0.432 (0.288–0.579)
Acute myocardial infarction, days 3-28	Gets short of breath after heavy physical activity, and tires easily, but has no problems when at rest. The person has to take medication every day and has some anxiety.	0.074 (0.049–0.105)

Asymptomatic ischaemic heart disease following myocardial infarction

Table 3b. Severity distribution, details on the severity levels for Asymptomatic ischaemic heart disease following myocardial infarction in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)
Asymptomatic ischaemic heart disease		N/A

Angina pectoris

Table 3c. Severity distribution, details on the severity levels for Angina pectoris in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	DW (95% CI)
Asymptomatic angina		N/A
Mild angina	Has chest pain that occurs with strenuous physical activity, such as running or lifting heavy objects. After a brief rest, the pain goes away.	0.033 (0.02–0.052)
Moderate angina	Has chest pain that occurs with moderate physical activity, such as walking uphill or more than half a kilometer (around a quarter-mile) on level ground. After a brief rest, the pain goes away.	0.08 (0.052–0.113)
Severe angina	Has chest pain that occurs with minimal physical activity, such as walking only a short distance. After a brief rest, the pain goes away. The person avoids most physical activities because of the pain.	0.167 (0.11–0.24)

Modelling strategy

Myocardial infarction

- We first calculated custom cause-specific mortality estimates using cause of death data prior to garbage code redistribution, generating age-sex-country-specific proportions of IHD deaths that were due to MI (acute IHD) versus those due to other causes of IHD (chronic IHD). Estimates of this proportion for all locations were then generated using a DisMod proportion-only model. Due to a high degree of variability in pre-redistribution coding practices by location, we used the global age-, sex-, and year-specific proportions of acute deaths in subsequent calculations. The global proportions were multiplied by post-Fauxcorrect (final GBD 2019 CoD estimates with GBD 2017 scalers) IHD deaths by location to generate CSMR estimates for MI. These data, along with incidence and excess mortality data, informed a DisMod model to estimate the prevalence and incidence of myocardial infarction due to ischaemic heart disease.
- These estimates were split into estimates for days 1-2 and days 3-28 post-event. Disability weights were assigned to each of these two groupings.
- We set a value prior of one month for remission (11/13) from the MI model. We also set a value prior for the maximum excess mortality rate of 10 for all ages. We included the Healthcare Access and Quality (HAQ) Index as a fixed-effect country-level covariate on excess mortality, forcing an inverse relationship.

Table 4a. Covariates. Summary of covariates used in the Myocardial Infarction DisMod-MR meta-regression model

Covariate	Parameter	Beta	Exponentiated beta
Healthcare Access and Quality (HAQ) Index	Excess mortality rate	-0.01 (-0.01 to -0.01)	0.99 (0.99 to 0.99)
Log-transformed age-standardised SEV scalar: IHD	Incidence	0.75 (0.75 to 0.76)	2.12 (2.12 to 2.13)

Asymptomatic ischaemic heart disease

- Excess mortality estimates from the myocardial infarction model were used to generate data of the incidence of surviving 28 days post-event.
- We used these data, along with the estimates of CSMR due to chronic IHD (the other part of the proportion described in step 1) and excess mortality data in a DisMod model to estimate the prevalence of persons with IHD following myocardial infarction. This estimate included subjects with angina and heart failure; a proportion of this prevalence was removed in order to avoid double-counting based on evidence from the literature (2). The result of this step generates estimates of asymptomatic ischaemic heart disease following myocardial infarction.
- We set a value prior of 0 for remission for all ages.
- We also included the log-transformed, age-standardised SEV scalar for IHD as a fixed effect, country-level covariate on prevalence and LDI (I$ per capita) as a fixed-effect country-level covariate on excess mortality, forcing an inverse relationship for LDI.

Table 4b. Covariates. Summary of covariates used in Asymptomatic Ischaemic Heart Disease DisMod-MR meta-regression model

Covariate	Parameter	Beta	Exponentiated beta
LDI (I$ per capita)	Excess mortality rate	-0.28 (-0.45 to -0.13)	0.76 (0.63 to 0.88)
Log-transformed age-standardised SEV scalar: IHD	Incidence	1.00 (0.77 to 1.24)	2.72 (2.15 to 3.47)

Angina

- We used prevalence data from the literature and USA claims databases, along with data on mortality risk to estimate the prevalence and incidence of angina for all locations. Data which used the Rose Angina Questionnaire to determine prevalence of angina was adjusted using MR-BRT as described above.
- The proportion of mild, moderate, and severe angina was determined by the standard approach for severity splitting for GBD 2019.
- We included a value prior of 0 for remission for all ages. We also included a value prior of 1 for excess mortality for all ages.
- We also included the log-transformed, age-standardised SEV scalar for IHD as a fixed effect, country-level covariate on prevalence and LDI (I$ per capita) as a fixed effect, country-level covariate on excess mortality, forcing an inverse relationship LDI.

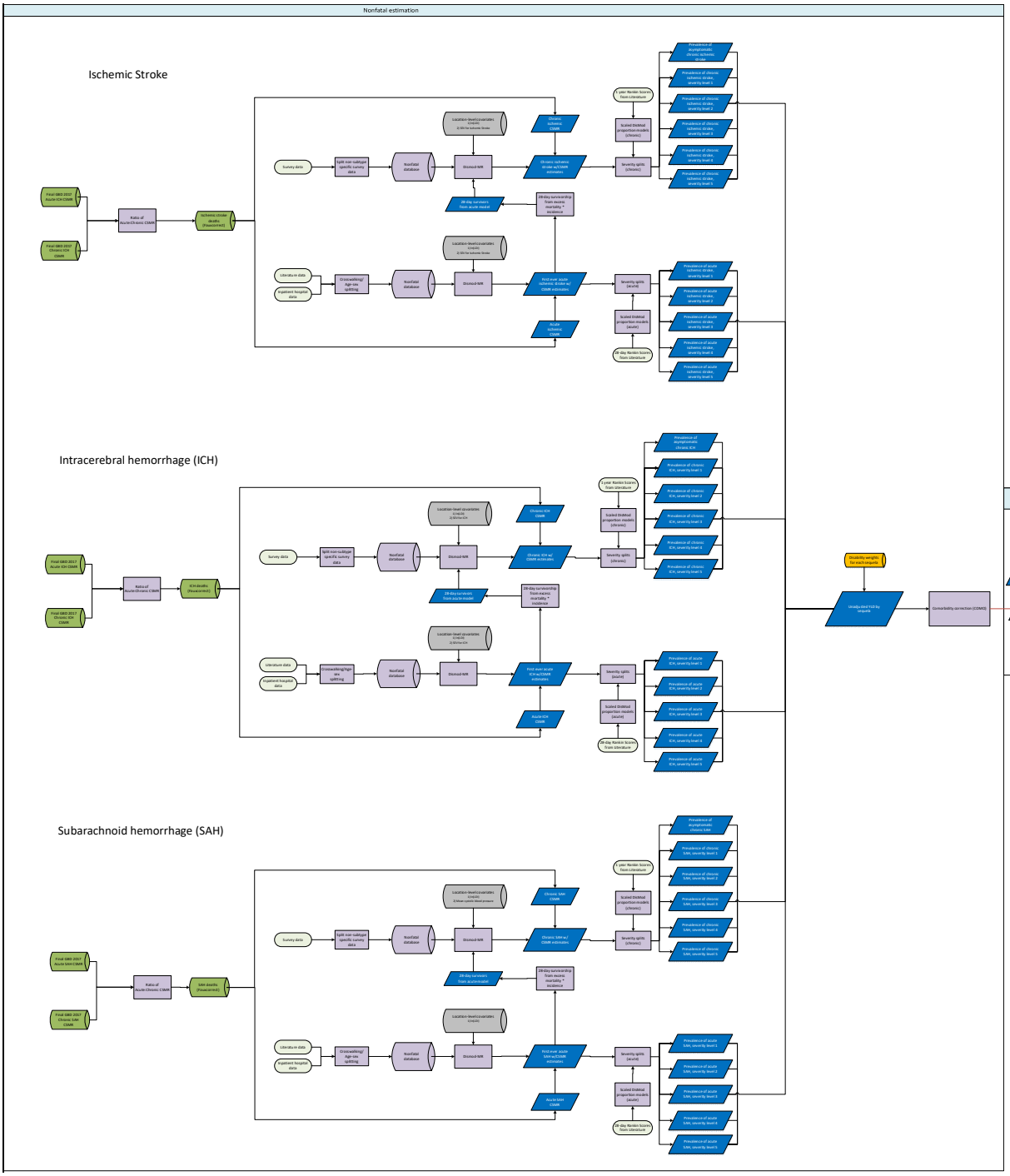
Table 4c. Covariates. Summary of covariates used in the Angina DisMod-MR meta-regression model

Covariate	Parameter	Beta	Exponentiated beta
Log-transformed age-standardised SEV scalar: IHD	Prevalence	1.09 (1.01 to 1.18)	2.99 (2.74 to 3.27)
LDI (I$ per capita)	Excess mortality rate	-0.54 (-0.99 to -.10)	0.58 (0.37 to 0.90)

There have been no substantive changes in the modelling strategy for myocardial infarction, asymptomatic ischaemic heart disease following myocardial infarction, and angina from GBD 2017.

Ischaemic Stroke, Intracerebral Haemorrhage, and Subarachnoid Haemorrhage

Flowchart



Input data and methodological summary

Case definition

Stroke was defined according to WHO criteria – rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin (1). Data on transient ischaemic attack (TIA) were not included.

Acute stroke: Stroke cases are considered acute from the day of incidence of a first-ever stroke through day 28 following the event.

Chronic stroke: Stroke cases are considered chronic beginning 28 days following the occurrence of an event. Chronic stroke includes the sequelae of an acute stroke AND all recurrent stroke events. GBD 2015 adopts this broader definition of chronic stroke than was used in prior iterations in order to model acute strokes using only first-ever incident events.

Ischaemic stroke: an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction

Intracerebral haemorrhage: a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma

Subarachnoid haemorrhage: bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord)

ICD codes used for inclusion of hospital and claims data can be found elsewhere in the appendix.

Input data

Tables 1a, 1b, and 1c display source count information for non-fatal ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage respectively.

Table 1a: Source counts for ischaemic stroke models.

Measure	Total sources	Countries with data
All measures	523	76
Prevalence	117	24
Incidence	332	62
Excess mortality rate	141	47
Case fatality rate	50	22

Table 1b: Source counts for intracerebral haemorrhage models.

Measure	Total sources	Countries with data
All measures	502	74
Prevalence	117	24
Incidence	322	61
Excess mortality rate	125	41
Case fatality rate	40	18

Table 1c: Source counts for subarachnoid haemorrhage models.

Measure	Total sources	Countries with data
All measures	435	63
Prevalence	117	24
Incidence	260	47
Excess mortality rate	88	28

A systematic review was not performed for GBD 2019. However, a systematic review was performed for GBD 2017. Search terms, dates of search, and databases queried follow:

1) Ischaemic stroke
    a. Google scholar: ("ischemic stroke" OR “cerebral infarction” OR “ischaemic stroke”) AND (incidence OR prevalence OR mortality OR epidemiology). Reviewed first 1000 hits, sorted by relevance
    b. Global Index Medicus search: (tw:("ischemic stroke") OR tw:(“cerebral infarction” OR tw:(“ischaemic stroke”)) AND (tw:(incidence) OR tw:(prevalence) OR tw:(mortality) OR tw:(epidemiology)) AND NOT (tw:(rats) OR tw:(mice) OR tw:(dogs) OR tw:(apes) OR tw:(monkeys)). Dates of search: 01Jan2010 – 31Aug2017
2) Intracerebral haemorrhage
    a. Google scholar: ("hemorrhagic stroke" OR “intracerebral hemorrhage” OR “haemorrhagic stroke” OR “intracerebral haemorrhage”) AND (incidence OR prevalence OR mortality OR epidemiology). Reviewed first 1000 hits, sorted by relevance
    b. GIM search: (tw:("intracerebral hemorrhage") OR tw:(“intracerebral haemorrhage”) OR tw:(“hemorrhagic stroke”) OR tw:(“haemorrhagic stroke”)) AND (tw:(incidence) OR tw:(prevalence) OR tw:(mortality) OR tw:(epidemiology)) AND NOT (tw:(rats) OR tw:(mice) OR tw:(dogs) OR tw:(apes) OR tw:(monkeys)). Dates of search: 01Jan2010 – 31Aug2017
3) Subarachnoid haemorrhage
    a. Google scholar search: ("subarachnoid hemorrhage" OR “subarachnoid haemorrhage”) AND (incidence OR prevalence OR mortality OR epidemiology). Reviewed first 1000 hits, sorted by relevance.
    b. GIM search: (tw:("subarachnoid hemorrhage") OR tw:(“subarachnoid haemorrhage”)) AND (tw:(incidence) OR tw:(prevalence) OR tw:(mortality) OR tw:(epidemiology)) AND NOT (tw:(rats) OR tw:(mice) OR tw:(dogs) OR tw:(apes) OR tw:(monkeys)). Dates of search: 01Jan2010 – 31Aug2017

We included inpatient hospital data, adjusted for readmission and primary to any diagnosis using correction factors estimated from US claims data. We excluded data for locations where the data points were implausibly low (Vietnam, Philippines, India). In addition, we included unpublished stroke registry data for acute ischaemic stroke, acute intracerebral haemorrhage, and acute subarachnoid haemorrhage. We also included survey data for chronic stroke. These surveys were identified based on expert opinion and review of major survey series focused on world health that included questions regarding self-reported history of stroke. For GBD 2019, we split unspecified strokes (ICD-10 I64) into ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage according to the proportions of subtype-specific coded strokes in the original data. We also split ICD-10 I62 into intracerebral haemorrhage, and subarachnoid haemorrhage using the same approach.

As with many models in GBD, the diversity of data sources available means that we needed to adjust available data to our reference case definition. We thus crosswalked incidence and excess mortality data that did not meet our reference case definitions using MR- BRT, a Bayesian meta-regression tool develop for the GBD. More information on MR-BRT can be found elsewhere in the appendix.

We adjusted data points for first and recurrent strokes combined, using data for first strokes only as reference. For ischaemic stroke and intracerebral haemorrhage, we also adjusted data points that reported all stroke subtypes combined, using as reference studies with subtype-specific information. We also adjusted data which included only persons who survived to hospital admission, using as reference data on both fatal and nonfatal strokes. In addition, we adjusted subtype-specific, inpatient clinical informatics data using subtype-specific literature estimates as a reference. These adjustments can be examined more closely in Table 2. The coefficients in Tables 2a, 2b, and 2c below can be used to calculate adjustment factors for alternative definitions. The formula for computing adjustment factors is given in equation 1 below. We also included a standardized age variable (age scaled) and a sex variable to the crosswalking procedure to adjust for the possibly of bias.

Equation 1: Calculation of adjustment factors:

$$Estimated\ Reference\ Def = invlogit(logit(Alternative\ Def) - Beta_{Alternative\ Def} - Beta_{Sex} * Sex - Beta_{Age_{scaled}} * Age\ Scaled)$$

No data adjustments were necessary for the chronic stroke models.

Table 2a: MR-BRT Crosswalk Adjustment Factors for Ischaemic stroke

	Data input	Measure	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)
Ischaemic stroke	First-ever, subtype-specific, fatal and nonfatal events	Incidence	Ref	---	---
Ischaemic stroke	Hospital data	Incidence	Alt	0.97	-0.26 (-2.22 to 1.70)
Ischaemic stroke	Any stroke	Incidence	Alt		0.02 (-1.94 to 1.98)
Ischaemic stroke	Acute first-ever stroke	Incidence	Alt		0.22 (-1.67 to 2.12)
Ischaemic stroke	Inpatient clinical informatics	Incidence	Alt		0.70 (-1.26 to 2.66)
Ischaemic stroke	Sex (male)	Incidence	Alt		0.07 (-1.82 to 1.96)
Ischaemic stroke	Age scaled	Incidence	Alt		0.28 (-1.61 to 2.17)

Table 2b: MR-BRT Crosswalk Adjustment Factors for Intracerebral Haemorrhage

	Data input	Measure	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)
Intracerebral Haemorrhage	First-ever, subtype-specific, fatal and nonfatal events	Incidence	Ref	---	---
Intracerebral Haemorrhage	Hospital data	Incidence	Alt	0.50	0.04 (-0.93 to 1.02)
Intracerebral Haemorrhage	Any stroke	Incidence	Alt		1.78 (0.80 to 2.76)
Intracerebral Haemorrhage	Acute first-ever stroke	Incidence	Alt		0.15 (-0.83 to 1.13)
Intracerebral Haemorrhage	Inpatient clinical informatics	Incidence	Alt		1.40 (0.41 to 2.38)
Intracerebral Haemorrhage	Age scaled	Incidence	Alt		0.09 (-0.88 to 1.07)
Intracerebral Haemorrhage	Sex (male)	Incidence	Alt		0.10 (-0.88 to 1.06)

Table 2c: MR-BRT Crosswalk Adjustment Factors for Subarachnoid Haemorrhage

	Data input	Measure	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)
Subarachnoid Haemorrhage	First-ever, subtype-specific, fatal and nonfatal events	Incidence	Ref	---	---
Subarachnoid Haemorrhage	Aneurysmal subarachnoid haemorrhage only	Incidence	Alt	0.76	-0.79 (-2.28 to 0.70)
Subarachnoid Haemorrhage	Age scaled	Incidence	Alt		-0.11 (-1.59 to 1.38)
Subarachnoid Haemorrhage	Sex (male)	Incidence	Alt		-0.07 (-1.56 to 1.42)

Severity split inputs

The table below illustrates the severity level, lay description, and disability weights for GBD 2019. In previous iterations of GBD, severity splits for stroke were based on the standard approach described elsewhere (3). For GBD 2016, we undertook a review to identify epidemiologic literature which reported the degree of disability at 28 days (for acute stroke) or one year (for chronic stroke) using the modified Rankin scale (mRS) and the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). The mRS assesses functional capabilities, while the MMSE and MoCA tests provide evaluations of cognitive functioning. We then mapped these measures to the existing GBD categories as indicated below. This approach allowed us to include location-specific information and can be updated as more data on functional or cognitive status become available.

Acute stroke severity splits

Table 3a. Severity distribution, details on the severity levels for Acute Stroke in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	Modified Rankin score	Cognitive status	DW (95% CI)
Stroke, mild	Has some difficulty in moving around and some weakness in one hand, but is able to walk without help.	1	N/A	0.019 (0.01–0.032)
Stroke, moderate	Has some difficulty in moving around, and in using the hands for lifting and holding things, dressing, and grooming.	2, 3	MoCA>=24 or MMSE>=26	0.07 (0.046–0.099)
Stroke, moderate plus cognition problems	Has some difficulty in moving around, in using the hands for lifting and holding things, dressing and grooming, and in speaking. The person is often forgetful and confused.	2, 3	MoCA<24 or MMSE<26	0.316 (0.206–0.437)

Stroke, severe	Is confined to bed or a wheelchair, has difficulty speaking, and depends on others for feeding, toileting, and dressing.	4, 5	MoCA>=24 or MMSE>=26	0.552 (0.377–0.707)
Stroke, severe plus cognition problems	Is confined to bed or a wheelchair, depends on others for feeding, toileting, and dressing, and has difficulty speaking, thinking clearly, and remembering things.		MoCA<24 or MMSE<26	0.588 (0.411–0.744)

Chronic stroke severity splits

Table 3b. Severity distribution, details on the severity levels for Chronic Stroke in GBD 2019 and the associated disability weight (DW) with that severity.

Severity level	Lay description	Modified Rankin score	Cognitive status	DW (95% CI)
Stroke, asymptomatic		0	N/A	N/A
Stroke, long-term consequences, mild	Has some difficulty in moving around and some weakness in one hand, but is able to walk without help.	1	N/A	0.019 (0.01–0.032)
Stroke, long-term consequences, moderate	Has some difficulty in moving around, and in using the hands for lifting and holding things, dressing, and grooming.	2, 3	MoCA>=24 or MMSE>=26	0.07 (0.046–0.099)
Stroke, long-term consequences, moderate plus cognition problems	Has some difficulty in moving around, in using the hands for lifting and holding things, dressing and grooming, and in speaking. The person is often forgetful and confused.	2, 3	MoCA<24 or MMSE<26	0.316 (0.206–0.437)
Stroke, long-term consequences, severe	Is confined to bed or a wheelchair, has difficulty speaking, and depends on others for feeding, toileting, and dressing.	4, 5	MoCA>=24 or MMSE>=26	0.552 (0.377–0.707)
Stroke, long-term consequences, severe plus cognition problems	Is confined to bed or a wheelchair, depends on others for feeding, toileting, and dressing, and has difficulty speaking, thinking clearly, and remembering things.	4, 5	MoCA<24 or MMSE<26	0.588 (0.411–0.744)

Table 4: Data input counts for the estimation process for the custom severity splits.

	Acute proportion	Chronic proportion
Site-years (total)	9	16
Number of countries with data	6	13
Number of GBD regions with data (out of 21 regions)	6	7
Number of GBD super-regions with data (out of 7 super-regions)	4	5

We used DisMod-MR, a Bayesian meta-regression tool, to model the six severity levels, with an independent proportion model for each. Reports which grouped mRS scores differently than our mapping (eg, 0-2) were adjusted in DisMod by estimating the association between these alternate groupings and our preferred mappings. These statistical associations were used to adjust data points to the referent category as necessary. The six models were scaled such that the sum of the proportions for all levels equaled 1.

Modelling strategy

The general approach employed for all of the components of the stroke modelling process is detailed in the table below.

- Data points were adjusted from alternative to reference case definitions using estimates from statistical models generated by MR-BRT (discussed elsewhere in the appendix) for the acute models. Coefficients for these crosswalks can be found in Table 2a, 2b, and 2c.

- The GBD summary exposure values (SEV), which are the relative risk-weighted prevalence of exposure, were included as covariates for the ischaemic stroke or intracerebral haemorrhage models as appropriate, and a covariate for country income was used as a country-level covariate for both models (4). Subarachnoid haemorrhage did not included an SEV covariate, but did include a covariate for country income for excess mortality. Coefficients for these covariates can be found in Table 5a, 5b, 5c for fixed effects located below.

- We used the ratio of acute:chronic cause-specific mortality estimated by the final GBD 2017 dismod model estimates to divide GBD 2019 stroke deaths into acute and chronic stroke deaths, using the global average for the proportion of acute:chronic stroke mortality. The acute and chronic models were then run using the same incidence, prevalence, and case fatality data as well as the custom cause-specific mortality rates as input data.

- We ran the first-ever acute subtype-specific models with CSMR as derived from FauxCorrect and epidemiological data as described above using Dismod-MR.

- We then calculated the rate of surviving until 28 days after an acute event for all three subtypes using the modelled estimates of excess mortality and incidence from the acute stroke models.

- Twenty-eight-day survivorship data was uploaded into the chronic subtype-specific with CSMR models. These chronic models also use CSMR as derived from FauxCorrect and epidemiological data as described above. Models were evaluated based on expert opinion, comparison with previous iterations, and model fit.

Table 5a, 5b, 5c below indicate the covariates used by cause in the estimation process, as well as the beta and exponentiated beta values.

Table 5a: Coefficients for covariates used in the acute and chronic ischemic stroke DisMod-MR models

Model	Variable name	Measure	beta	Exponentiated beta
First-ever acute ischaemic stroke with CSMR	Log-transformed age-standardised SEV scalar: Ischaemic stroke	Incidence	0.90 (0.85 to 0.95)	2.46 (2.34 to 2.58)
First-ever acute ischaemic stroke with CSMR	Healthcare access and quality index	Excess mortality rate	-0.035 (-0.035 to -0.035)	0.97 (0.97 to 0.97)
Chronic ischaemic stroke with CSMR	Log-transformed SEV scalar: Ischaemic stroke	Prevalence	0.85 (0.78 to 0.92)	2.34 (2.18 to 2.51)
Chronic ischaemic stroke with CSMR	LDI (I$ per capita)	Excess mortality rate	-0.41 (-0.46 to -0.36)	0.67 (0.63 to 0.70)

Table 5b: Coefficients for covariates used in the acute and chronic intracerebral haemorrhage DisMod-MR models

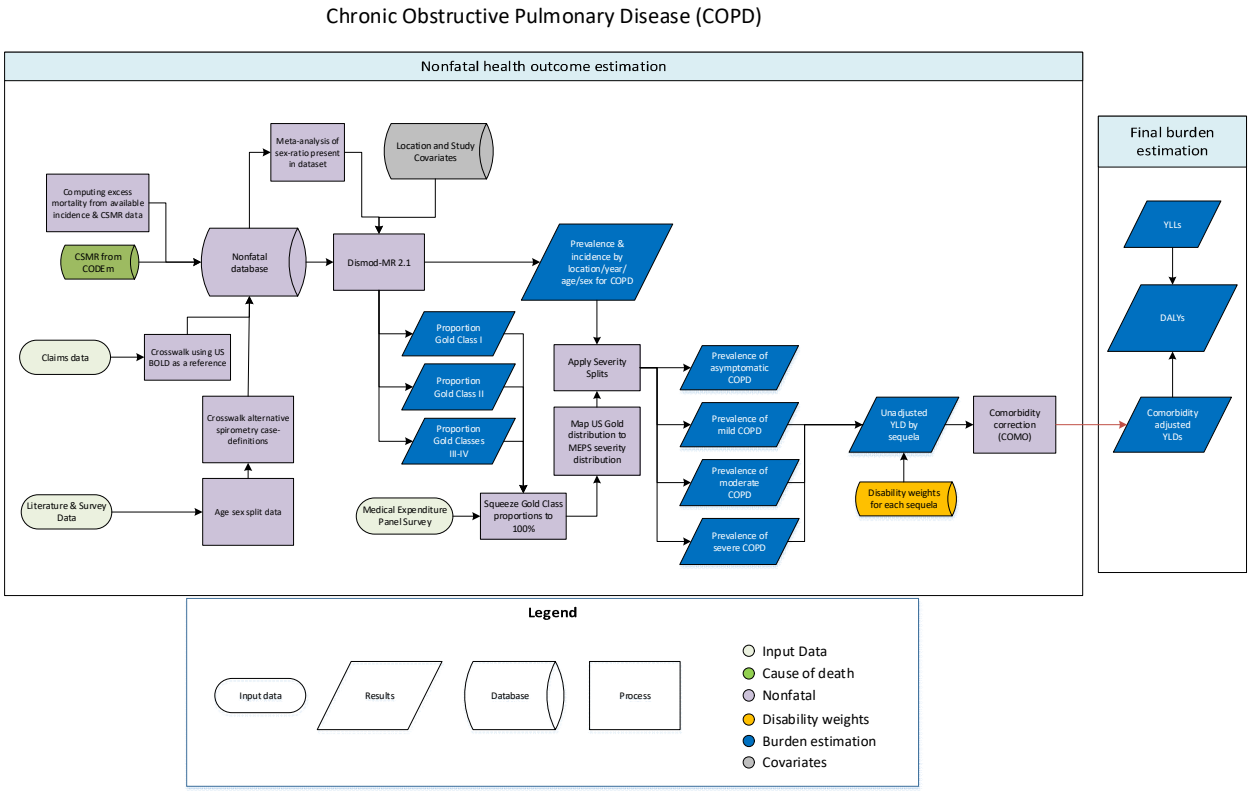
Model	Variable name	Measure	beta	Exponentiated beta
First-ever acute intracerebral haemorrhage with CSMR	Log-transformed SEV scalar: Intracerebral Haemorrhage	Incidence	0.76 (0.75 to 0.77)	2.13 (2.12 to 2.15)
First-ever acute intracerebral haemorrhage with CSMR	Healthcare access and quality index	Excess mortality rate	-0.07 (-0.07 to -0.069)	0.93 (0.93 to 0.93)
Chronic intracerebral haemorrhage with CSMR	Log-transformed SEV scalar: Intracerebral haemorrhage	Prevalence	0.75 (0.75 to 0.76)	2.12 (2.12 to 2.14)
Chronic intracerebral haemorrhage with CSMR	LDI (I$ per capita)	Excess mortality rate	-0.5 (-0.5 to -0.5)	0.61 (0.61 to 0.61)

Table 5a: Coefficients for covariates used in the acute and chronic subarachnoid DisMod-MR models

Model	Variable name	Measure	beta	Exponentiated beta
First-ever acute subarachnoid haemorrhage with CSMR	LDI (I$ per capita)	Excess mortality rate	-0.3 (-0.49 to -0.11)	0.74 (0.61 to 0.90)

Chronic obstructive pulmonary disease (COPD)

Flowchart



Case definition

COPD is defined as in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification: a measurement of <0.7 FEV_1/FVC (one second of forceful exhalation/total forced expiration) on spirometry after bronchodilation. The severity grading of COPD follows this GOLD class definition.

GOLD CLASS	FEV_1 Score
I: Mild	>=80% of normal
II: Moderate	50-79% of normal
IV: Severe	<50% of normal

ICD-10 codes associated with COPD include J41, J42, J43, J44, and J47. The corresponding ICD-9 codes are 491-492, and 496. J40 & 490 (Bronchitis, not specified as acute or chronic) and J47 & 494 (Bronchiectasis) were removed from COPD mapping in GBD 2017.

Alternative case definitions that differ from the GOLD Post-bronchodilation definition are as follows: GOLD Pre-bronchodilation, Lower Limit of Normal (LLN) Post-bronchodilation, LLN Pre-bronchodilation, and European Respiratory Society (ERS) guidelines. These are all different methods of evaluating whether an individual has COPD.

Input data

No systematic review of the literature was completed for GBD 2019; however, for GBD 2016, we updated the systematic review from previous iterations. The full search term was:

(chronic obstructive pulmonary disease[Title/Abstract] AND (prevalence[Title/Abstract] or incidence [Title/Abstract] or mortality [Title/Abstract] or death [Title/Abstract]) AND "Cross-Sectional Studies"[MeSH Terms]) Filters: Publication date from 04/01/2015 to 11/01/2016; Humans

COPD has the following data sources

- Prevalence, incidence, and remission data from literature
- Hospital claims data
- Proportion data of GOLD class severities
- Burden of Obstructive Lung Disease (BOLD) Study data

Prevalence, incidence, and remission data relating to COPD are extracted from literature provided by collaborators or found with a systematic review. All data include spirometry-based measures. Other data come from hospital claims data for nonfatal estimation and vital registrations for cause of death.

GOLD class proportions are extracted from literature when the severity is available. Our models estimate three separate severities:

- Mild COPD: GOLD class I
- Moderate COPD: Gold class II
- Severe COPD: Gold class III & IV

These severities are used in the modelling process to split COPD by severities.

The Burden of Obstructive Lung Disease (BOLD) data is specifically notable because of its use in bias adjustments described in the data processing section.

New data this year include the English Longitudinal Study of Aging (ELSA), and claims data for the United States. Additional information on the claims data collection and pre-corrections are provided elsewhere. Briefly, we determined USA national and state-level estimates of COPD prevalence from a database of individual-level ICD-coded health service encounters. Persons with any inpatient claim or at least two outpatient claims associated with COPD were marked as a prevalent case for that year.

Data Inputs for Chronic Obstructive Pulmonary Disease

Measure	Total sources	Countries with data
All measures	166	57
Prevalence	142	54
Incidence	6	6
Relative risk	2	2
Proportion	36	32

Data Processing

Age-Sex and Sex Split

In some cases, data are reported by only age or only sex, but not both. For example, a study may have included the prevalence of males and females with COPD and then separately reported the prevalence for both sexes in smaller age bins (e.g. age 40-45, 46-50, etc.) that have COPD. In these cases, we perform an age-sex split by utilizing proportions within the study to disaggregate the data.

When data are not disaggregated into male and female categories for a given data source, we instead perform a sex-split on the data by applying sex proportions from other studies that do have male and female specific data. When data are aggregated into age categories larger than 25 years, we split into smaller age bins based on super-regional age patterns in the 2017 COPD model.

Modeled excess mortality data

For GBD 2019, we implemented a new method of modeling excess mortality rate (EMR).

In previous rounds, priors on EMR were estimated in DisMod by matching prevalence data points with their corresponding CSMR values within the same age, sex, year, location (by dividing CSMR by prevalence).

However, for many causes, DisMod estimated a rather unrealistic pattern of EMR compared to an expected pattern of decreasing EMR with greater access to quality health care. Such unexpected patterns often signal inconsistencies between CSMR estimates and the measures of prevalence and/or incidence.

In an effort to provide greater guidance to DisMod on the expected pattern of EMR, EMR data generated in the previous round were used as inputs for modeling in MR-BRT with age, sex, and healthcare access and quality index (HAQi) included as covariates. Results from MR-BRT were then predicted for each location year, sex and for ages 0, 10, 20 ….100.

This method led to improvements in the consistency of EMR relative to health care access. We also included HAQi as a country-level covariate in Dismod to inform EMR with the mean and standard deviation produced from MR-BRT analysis.

Bias Adjustments

In GBD 2019, we improved the bias adjustment methods by utilizing a MR-BRT model outside of DisMod to allow a more direct comparison between different case definitions and/or study designs. In GBD 2017, these adjustments were performed within DisMod.

We made a series of adjustments to data that do not completely match our case definition. Different diagnosis often leads to different estimates of COPD. Similarly, claims data is subject to biases. Claims data are often systemically lower than survey data, probably due to selection bias with regard to socioeconomic status. Adjustments are made to these data to correct these biases.

The adjustment is a logit-transformation method in MR-BRT. The general process is described below:

1. Identify data points with overlapping year, age, sex, and location between reference and alternative definitions.
2. Logit transform overlapping data points of alternative and reference case definitions
3. Convert overlapping data points into a difference in logit space using the following equation:
   $logit(altnerative) - logit(reference)$
4. Use the delta method to compute standard errors of overlapping data points in logit space, then calculate standard error of logit difference using the following equation:
   $\sqrt{(variance\ of\ alternative) + (variance\ of\ reference)}$
5. Using MR-BRT, conduct a random effects meta-regression to obtain the pooled logit difference of alternative to reference
6. Apply the pooled logit difference to all data points of alternative case definitions using the following equation:
   $new_{estimate} = inverse.logit((logit(alternative)) - (pooled\ logit\ difference))$
7. Calculate new standard errors using the delta method, accounting for gamma (between-study heterogeneity)

Data derived from claims from commercial health insurance in the United States were also adjusted using a factor estimated in MR-BRT. Claims data, notably US Marketscan was adjusted in relation to the BOLD study data. In this case, the BOLD data serves as the reference definition while the marketscan data are the alternative definition.

MR-BRT Crosswalk Adjustment Factors

Data input	Status	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
GOLD Post	Ref	0.25	---	---
GOLD Pre	Alt		0.50 (-0.02 - 1.07)	0.62 (0.49 - 0.74)
ERS	Alt		0.70 (0.11 - 1.31)	0.67 (0.53 - 0.79)
LLN Pre	Alt	0.08	0.10 (0.01 - 0.19)	0.52 (0.50 - 0.55)
LLN Post			-0.34 (-0.50 - -0.19)	0.42 (0.38 -0.45)
BOLD	Ref	.19	---	---
Marketscan	Alt		-1.93 (-2.35 - -1.50)	0.13 (0.08 - 0.18)

**Adjustment factor is the inverse-logit transformed Beta coefficient; <0.5 represents that alternative is adjusted upward; >0.5 represents alternative is adjusted downward*

Modelling strategy

The estimation of COPD burden has two distinct steps.

1. Estimate prevalence and incidence using a DisMod-MR 2.1 model
2. Estimate proportion of COPD severities using GOLD class groupings in DisMod-MR 2.1

After these two steps, the COPD prevalence and incidence is split by age, sex, location for each severity level.

Step 1: Main COPD model – Estimate prevalence and incidence using DisMod-MR 2.1

Model Settings

We set remission to 0 because individuals do not recover once they have COPD. The symptoms are only managed. Incidence ceiling is set at .0002 before age 15 and a ceiling at .0005 before age 30 to avoid a kick-up of estimates in age ranges with few or no primary data.

Each model includes a series of country-level covariates that describe spatiotemporal patterns.

- COPD standardised exposure variables (SEV) aggregates multiple risk factors into a single variable.
- Healthcare Access and Quality (HAQi) index on EMR to capture country-level variation of EMR, assuming a negative coefficient (ie, lower mortality with rising GDP and HAQ). The priors of HAQi came from the EMR MRBRT prediction.
- The proportion of elevation over 1500m was included as a country-level covariate on EMR because of its significance in COPD cause of death models.

Model coefficients for COPD

Model	Variable name	Measure	Beta	Exponentiated
COPD	Elevation over 1500m (proportion)	excess mortality rate	0.60 (0.14 — 0.95)	1.81 (1.15 — 2.58)
COPD	Healthcare access and quality index	excess mortality rate	-0.022 (-0.023 — -0.022)	0.98 (0.98 — 0.98)
COPD	Log age-standardised SEV scalar: COPD	prevalence	0.91 (0.90 — 0.92)	2.47 (2.46 — 2.50)

Step 2: GOLD class models to estimate proportions of severities

The GOLD class models use data from surveys that specified prevalence by GOLD class after expressing the values as a proportion of all COPD cases. For GBD 2016 we used fixed effects from the SEV scalar and the log of lag-distributed income (LDI) per capita to assist estimation. For GBD 2017, we dropped these covariates because they did not produce significant coefficients and also did not use them for GBD 2019. We also restricted random effects to +/-0.5 to control implausible geographical variation.

Severity Splits

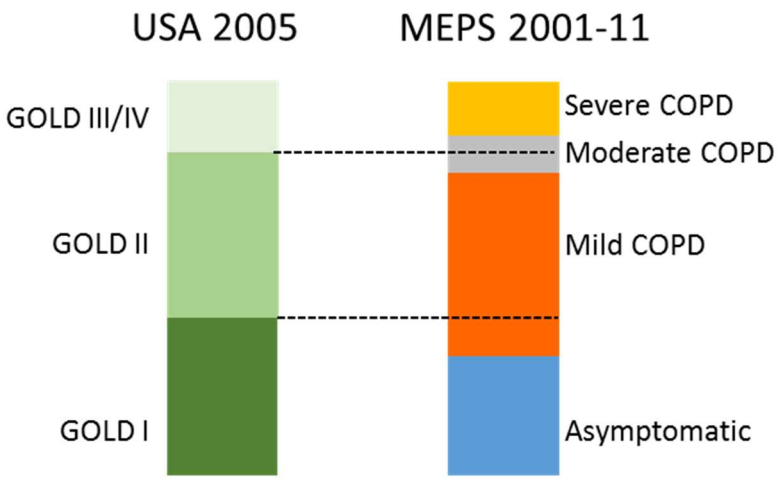
The three GOLD class groupings reflect a grading based on a physiological measurement rather than a direct measurement of disease severity. In order to map the epidemiological findings by GOLD class into

the three COPD health states for which we have disability weights (DW), we used the 2001–2011 Medical Expenditure Panel Survey (MEPS) data from the United States. Specifically, we convert the GOLD class designations estimated for the USA in 2005 (the midpoint of MEPS years of analyses) into GBD classifications of asymptomatic, mild, moderate, and severe COPD.

The table below shows the three health states of COPD and the corresponding lay descriptions and disability weights. The graph shows the average proportion by GOLD class (after scaling to 100%) across all ages for USA in 2005. We also show the proportion of MEPS respondents reporting any health service contact in the past year for COPD with a DW value attributable to COPD of 0, mild range (0 to midpoint between DWs for mild and moderate), moderate range (midpoint of DW values mild and moderate to midpoint of DW values for moderate and severe) and severe range (midpoint between DW values moderate and severe or higher). The DW value for COPD was derived from a regression with indicator variables for all health states reported by MEPS respondents and their reported overall level of disability derived from a conversion of 12-Item Short Form Surveys (SF-12) answers to GBD DW values. This analysis gave the severity distribution for each GBD cause reported in MEPS after correcting for any comorbid causes individual respondents reported during a year.

Description of Health States

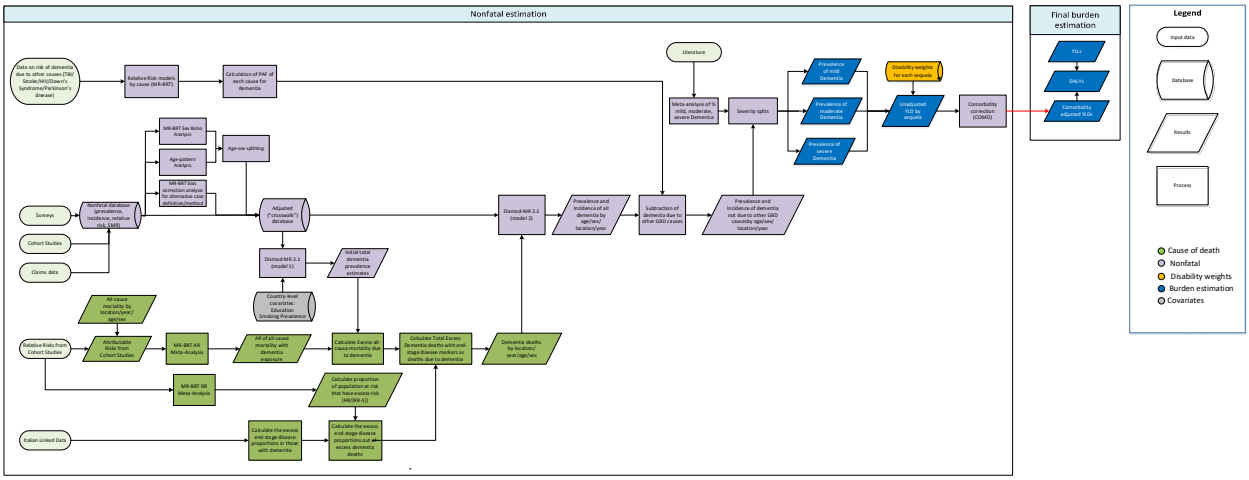
Health state	Lay description	DW (95% CI)
Mild COPD	This person has cough and shortness of breath after heavy physical activity, but is able to walk long distances and climb stairs.	0.019 (0.011–0.033)
Moderate COPD	This person has cough, wheezing, and shortness of breath, even after light physical activity. The person feels tired and can walk only short distances or climb only a few stairs.	0.225 (0.153–0.31)
Severe COPD	This person has cough, wheezing, and shortness of breath all the time. The person has great difficulty walking even short distances or climbing any stairs, feels tired when at rest, and is anxious.	0.408 (0.273–0.556)



The algorithm to translate GOLD class to COPD DW categories first assigns GOLD III&IV to severe COPD and what remains to moderate. Next, GOLD class I is assigned to the asymptomatic category first and what remains goes to mild COPD. This algorithm is repeated for each age and sex category and for all 1,000 draws from the DisMod models of GOLD classes and the MEPS analyses. We end up with proportions of each of the GOLD class categories that map onto GBD COPD health states with uncertainty bounds determined by the 25^{th} and 975^{th} values of the 1,000 draws. These values are then applied to the estimates of the proportion of cases by GOLD class category, after scaling to 100%, by location, year, age, and sex. This assumes that the relationship between GOLD class and GBD COPD health states in the United States applies everywhere.

Alzheimer's disease and other dementias

Flowchart



Input data and methodological summary

Case definition

Dementia is a progressive, degenerative, and chronic neurological disorder typified by memory impairment and other neurological dysfunctions. For the purposes of GBD 2019, we use the Diagnostic and Statistical Manual of Mental Disorders III, IV or V, or ICD case definitions as the reference. The DSM-IV definition is:

- Multiple cognitive deficits manifested by both memory impairment and one of the following: aphasia, apraxia, agnosia, disturbance in executive functioning
- Must cause significant impairment in occupational functioning and represent a significant decline.
- Course is characterized by gradual onset and continuing cognitive decline
- Cognitive deficits are not due to other psychiatric conditions
- Deficits do not occur exclusively during the course of a delirium

A wide array of diagnostic and screening instruments exists, including Clinical Dementia Rating scale (CDR), Mini Mental State Examination (MMSE), and the Geriatric Mental State (GMS). For severity rating purposes we use the CDR as the reference. The relevant ICD-10 codes for dementia are F00, F01, F02, F03, G30, and G31. The ICD-9 codes are 290, 291.2, 291.8, 294 and 331.

Unlike most causes in the Global Burden of Disease project, dementia mortality and morbidity estimates are modelled jointly. This is because of marked discrepancies between prevalence data and cause of death data. Specifically, prevalence data suggest little to no variation over time (eg, 1990–2019), whereas age-standardised mortality rates in vital registrations in high-income countries have increased multiple times over this same period. Additionally, prevalence variation between countries is much smaller than the variation in death rates assigned to dementia in vital registration. We attribute these discrepancies to changing coding practices rather than epidemiological change.

Because of this joint procedure, descriptions of the mortality estimation process are included where relevant.

Input data

Model inputs

To inform our estimates of burden due to dementia, we use mortality data from relative risk studies and linked hospital to mortality data, as well as prevalence data from surveys and administrative data such as claims sources.

Item Response Theory for prevalence prediction

The prevalence models for dementia are data sparse, and there are not many surveys done in low income settings. However, there are a larger body of surveys that collect data on cognitive tests and functional limitations which are the two main components of a DSM or ICD diagnosis. Predictions of dementia prevalence using information from these questions would allow for expanded data coverage and additional information in locations where there are currently no data guiding estimates.

Generating these predictions requires calibrating a model to samples that have information about both functional limitations, cognition and adjudicated dementia diagnoses. However, making comparisons across surveys can be difficult, as each survey asks a different set of questions about cognition and limitations, although there is some overlap. This overlap allows for the use of item response theory methods for the harmonization of these scales. Once the scales are harmonized the subsamples can be utilized to create a model for the prediction of prevalence.

In GBD 2019, data from the ADAMS and HRS surveys were extracted and used for Item Response Theory modeling to estimate prevalence. HRS is a nationally representative survey in the US, which has data on cognition and functional limitations. ADAMS is a subsample of HRS that includes much more detailed neuropsychological testing and adjudicated dementia diagnoses. ADAMS includes almost all questions in HRS plus additional questions as well.

Excluding incidence

Since 2016, we have made the decision to exclude incidence data, because in locations with high quality cohort data on prevalence and incidence, the two are not compatible (incidence data implies a higher prevalence than what is reported). Because dementia has a slow, insidious onset and prevalence is easier to measure, we trust prevalence data more and rely on this, excluding incidence data from DisMod.

Severity splits

Methods to determine severity splits for dementia were redesigned in GBD 2019. A new systematic review was conducted to collect information on the proportion of individuals in each dementia severity class out of the population of all individuals with dementia. There are a variety of commonly-used methods for severity rating; for the purposes of GBD 2019, we took the Clinical Dementia Rating (CDR) scale as our reference definition for severity classification, along with a doctor-given diagnosis according to DSM III, IV, V or ICD case definitions as our reference definition for dementia.

However, as a neurodegenerative disorder with a wide range of categories in which symptoms manifest, there are an abundance of classification tools which discern between severity levels along different criteria. We accepted severities classified by:

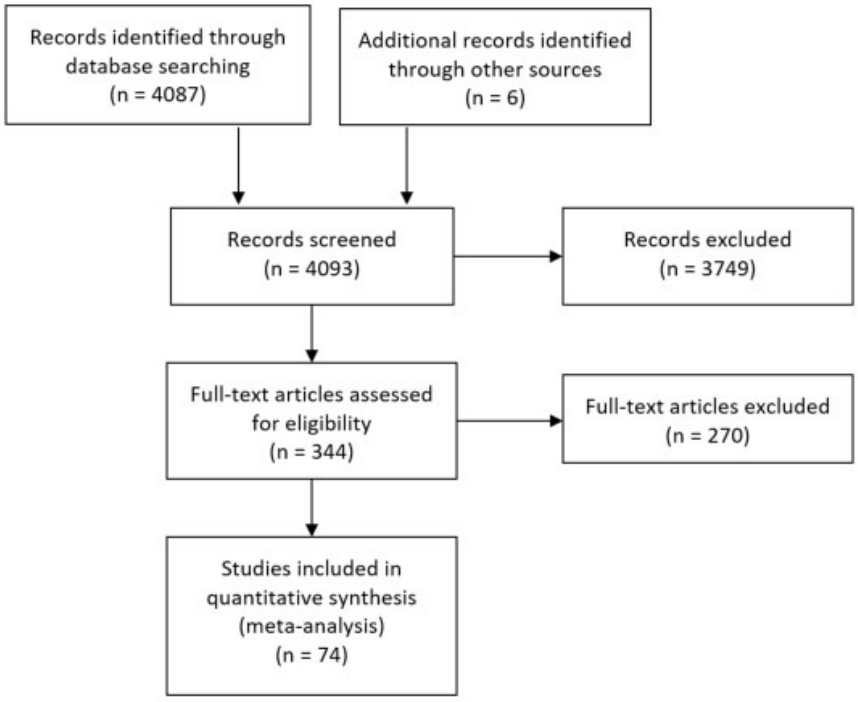
- Clinical dementia rating sum-of-boxes (CSR-SB)
- Blessed test of information, memory, and concentration (BIMC)
- Global deterioration scale (GDS)
- Geriatric Mental State Examination (GMS)
- CAMDEX
- DSM-III-R
- Karasawa's

We excluded any studies which classified dementia severity according to scales that only evaluated cognitive function and memory, excluding activities of daily living (ADLs). The most prominent such scale is MMSE.

The following search string was used:

((dementia[MeSH Terms] OR dementia[Title] OR Alzheimer disease[Title]) AND (severity[Title/Abstract] OR CDR[Title/Abstract] OR Clinical Dementia Rating Scale[Title/Abstract]) AND (Severity of illness index[MeSH] OR diagnosis[sh] OR Cross-Sectional Studies[MeSH])) AND ("1950/01/01"[Date - Publication] : "2100/02/25"[Date - Publication]) NOT (animals[MeSH] NOT humans[MeSH]))

Prisma diagram of dementia severity split systematic review



This yielded 4087 total hits, of which 338 passed initial title/abstract screening. After full-text screening, 68 sources met screening criteria and were extracted, along with one source identified through the bibliographies of other sources, and five additional sources used in GBD 2017 for other purposes. A total of 74 sources were extracted and informed the severity split, as compared to the 11 sources used in GBD 2017.

The severity split analysis was conducted using a MR-BRT meta-regression instead of being analyzed as binned meta-analyses as in GBD 2017.
We multiplied estimations of prevalence (country-year-sex-age-specific) by the fractions of mild, moderate, and severe dementia and estimated 95% uncertainty intervals at the 1,000-draw level. The severity distributions over age for each sex are visualized below, followed by a table describing each severity.

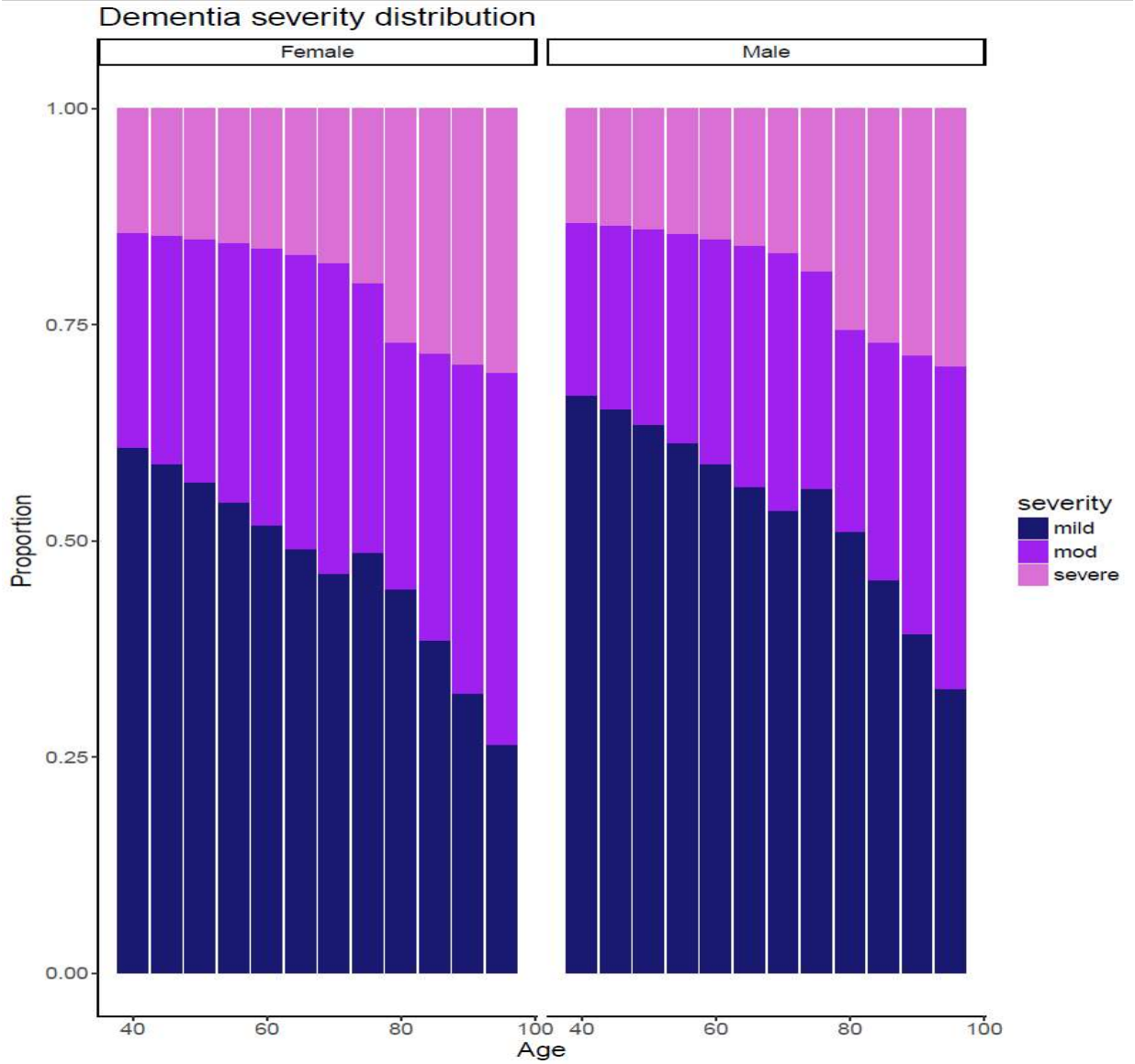


Figure 1 Severity ratios for each 5-year age bin, by sex.

Table of dementia severity levels.

Severity level	Lay description
Mild	The person has some trouble remembering recent events and finds it hard to concentrate and make decisions and plans. They may have slight to moderate difficulty engaging in community affairs, complicated hobbies, and intellectual interests.
Moderate	The person retains highly learned material, but has severe memory problems, is disoriented with respect to time and sometimes place. They are severely impaired in their ability to handle problems and make social judgements. They require assistance with daily activities, and only retain simple chores and hobbies.
Severe	The person has complete memory loss, no longer recognizes close family members, and requires help with all daily activities, including personal care.

Relative risk due to other causes

While the DSM definition excludes dementia cases, where the syndrome is caused by other psychiatric disorders, it does not exclude dementia cases caused by other diseases, not included in DSM. This includes, stroke, Parkinson's disease, Down's syndrome and traumatic brain injury (TBI), which are found elsewhere in the GBD cause list. To prevent double counting of prevalent cases, both under dementia and each of these other causes, we adjusted our dementia prevalence to exclude cases caused by these other conditions. To do so, in GBD 2019 we used data from the Aging, Demographics and Memory study (ADAMS), to estimate the relative risk of getting dementia for each condition included in the ADAMS dataset (stroke, Parkinson's disease, TBI). We then conducted more extensive systematic reviews on all five of these conditions to model each separately. Relative risk models were run using MR-BRT, and population attributable fractions (PAF) for each condition were calculated with the following equation, where exposure is defined as the prevalence of condition:

$$PAF = \frac{exposure * (RR - 1)}{[exposure * (RR - 1)] + 1}$$

Finally, attributable burden was calculated as the PAF multiplied by total burden (i.e. dementia incidence/prevalence).

A summary of each systematic review is displayed in the table below.

	Stroke	**Parkinson's disease**	**Down's Syndrome**	**TBI**
	Recent meta-analysis (2018) [46 sources], plus PubMed review for more recent articles			Three recent systematic reviews (2016, 2016, 2019), cross checked and collated all sources [71 total]
Data Type	Relative Risks	Proportions and Relative Risks	Proportions	Relative Risks

Review Hits	504	1475	355	
Accepted During Title/Abstract Screening	79	135	102	
Accepted During Full Text	35 (33 from systematic review and 2 from PubMed search)	56	26	45

The total source count used in GBD 2019 modeling is listed in the table below:

Measure	Total sources	Countries with data
All measures	529	56
Prevalence	262	48
Incidence	80	24
Relative risk	83	17
Proportion	97	34
Other	34	17

Modelling strategy

First, prevalence data was sex split, crosswalked and age split. Studies with age and sex detail separately were split into age- and sex-specific data points. Data specified as "both" sex data were split into male- and female-specific data points using MR-BRT to get a model ratio of female/male prevalence and then using the following equations:
Male prevalence:

$$prev_{male} = prev_{both} * \frac{pop_{both}}{(pop_{male} + ratio * pop_{female})}$$

Female prevalence:

$$prev_{female} = ratio * prev_{male}$$

We also split data points where the age range was greater than 25 years using the global age pattern.

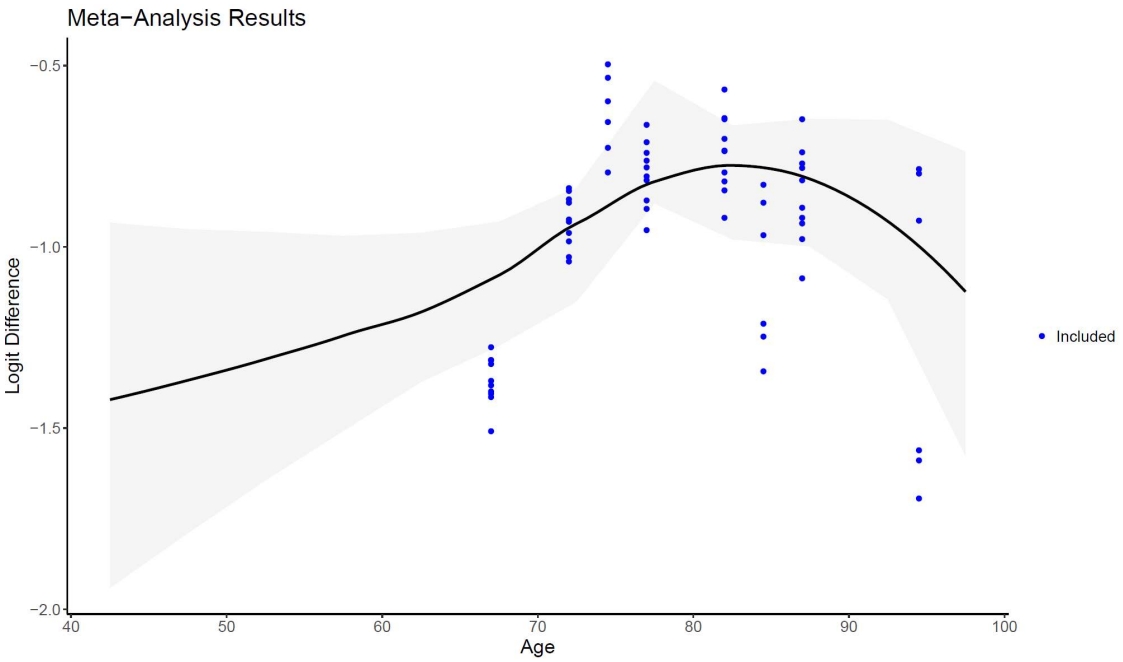
Dementia studies are heterogeneous. Even with a smaller number of definitions (DSM/ICD), there are a large number of different ways to diagnose dementia. For example, out of 272 sources used in GBD 2017, there were 263 different methods of diagnosing dementia (overlap was among those who used 10/66 protocol or AGECAT algorithm). Most use a two-step procedure, where you screen using a cognitive test and then only fully evaluate those that fall below a certain pre-defined threshold. We

controlled for methods differences by crosswalking alternative case definitions to reference. Study covariates are based on broad categories determined after going through the diagnostic heterogeneity and there are some added for specific criteria that we know are biased. The same study-level covariates were used in 2019 as in 2017 with the addition of Item Response Theory HRS predictions. Crosswalking was carried out using a logit difference network meta-regression analysis. U.S. Marketscan were separately crosswalked to standardize the claims data relative to existing literature data.

MR-BRT Crosswalk Adjustment Factors for Dementia (Network Analysis)

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
DSM or ICD case definition	Ref	0.34	---	---
Clinical records diagnosis criteria	Alt		-0.05 (-0.72 – 0.61)	0.51
Algorithm diagnosis criteria (AGECAT)	Alt		0.08 (-0.59 – 0.74)	0.50
U.S. Marketscan	Alt		-0.95 (-1.61 – -0.28)	0.50
NIA-AA diagnosis criteria	Alt		0.51 (-0.16 – 1.17)	0.53
10/66 algorithm diagnosis criteria	Alt		0.97 (0.30 – 1.64)	0.50
GP records used for diagnosis	Alt		-1.21 (-1.88 – -0.54)	

A separate analysis was conducted to crosswalk Marketscan claims data (excluding Marketscan year 2000) to non-claims data using a spline on age. The plot below shows the model fit over different ages (gamma = 0.07).



Two country-level covariates were included in the initial Dismod model. Age-standardised education was used as a proxy for general brain health/use that may be protective of dementia – specifically Alzheimer's disease. Smoking prevalence (age-standardised, both sexes) was also used as a covariate to guide estimates, as the literature has shown a positive relationship between smoking and dementia.

Note that two Dismod models were run with prevalence inputs – the first uses adjusted prevalence data (Dismod Model 1 in flowchart), which accounts for dementia caused by other diseases. The second uses unadjusted dementia (Dismod Model 2 in flowchart) which accounts for all dementia regardless of cause (this is the dementia impairment envelope). The tables below summarize country-level covariates used in each of these Dismod model.

Covariates. Summary of covariates used in the Parkinson's Disease DisMod-MR meta-regression model (adjusted prevalence, Model 1)

Covariate	Type	Parameter	Exponentiated beta (95% Uncertainty Interval)
Smoking prevalence (age-standardized)	Prevalence	TBD – asking Emma	
Healthcare access and quality index	Excess mortality rate		

Covariates. Summary of covariates used in the Parkinson's Disease DisMod-MR meta-regression model (unadjusted prevalence, Model 2)

Covariate	Type	Parameter	Exponentiated beta (95% Uncertainty Interval)

Smoking prevalence (age-standardized)	Prevalence	0.005	1.00 (1.00-1.01)
Healthcare access and quality index	Excess mortality rate	-0.08	0.92 (0.92 – 0.92)

As mentioned previously, the estimation of morbidity due to dementia occurs in conjunction with the mortality estimation. Additional details on this process can be found in the COD capstone appendix.

We pull the cause-specific mortality results from final fatal estimates into a final DisMod model (Model 2), with the same settings as the models previous. To prevent double counting of prevalent cases, both under dementia and under other causes that can lead to dementia, we adjusted our dementia prevalence to exclude cases caused by these other conditions, which include stroke, Parkinson's disease, traumatic brain injury and Down's Syndrome. To do so, we used data from the Aging, Demographics and Memory study (ADAMS) and new systematic reviews, to estimate the relative risk of getting dementia for each condition included in the ADAMS dataset (stroke, Parkinson's disease, TBI). We first fit logistic regression models predicting the outcome of dementia given each exposure, with an additional covariate on age.

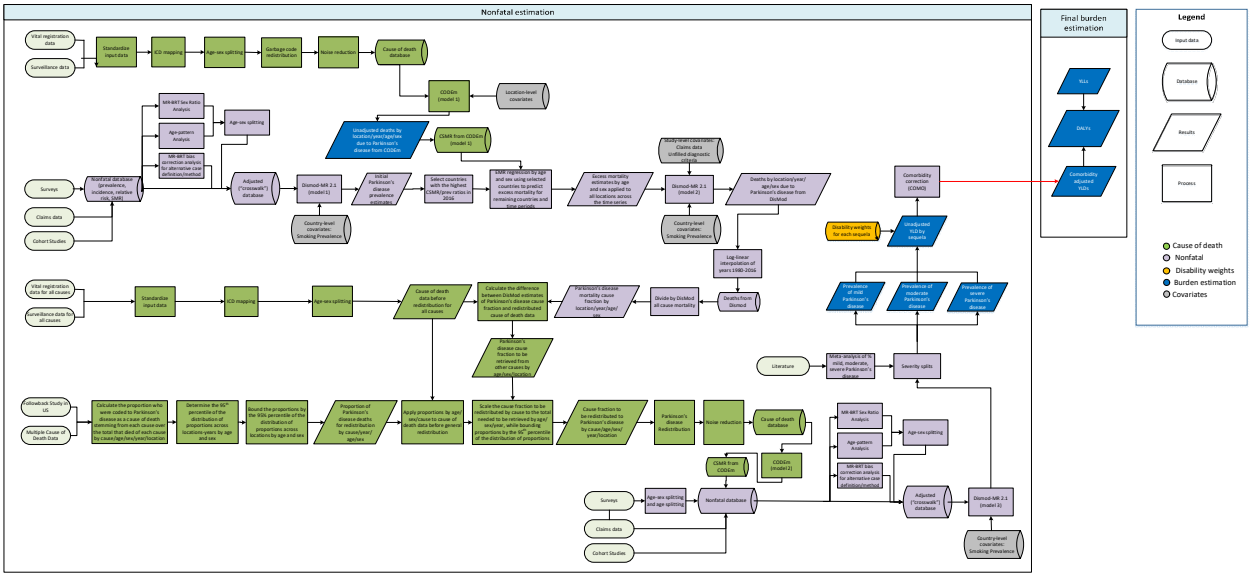
We then used these models to predict the probability of dementia given each exposure at various ages and divided the probability of having dementia by the probability of not having dementia at each age to calculate relative risks. After calculating age specific relative risks, we used these data and estimates of dementia prevalence from our DisMod-MR 2.1 model to calculate the population attributable fractions (PAFs) for each cause and age using the formula:

$$PAF = \frac{prevalence * (RR - 1)}{prevalence * (RR - 1) + 1}$$

Finally, we multiplied the PAF by the total prevalence to get the amount of dementia prevalence that can be attributed to each cause and subtracted this from the total prevalence to get the prevalence of dementia that is not due to other GBD causes.

Parkinson's Disease

Flowchart



Case definition

Parkinson's disease is a chronic, degenerative, and progressive neurological condition typified by the loss of motor mobility and control – most notably tremors. The corresponding ICD-10 codes are G20, G21, and G22. Our case definition for GBD is the presence of at least two of the four primary symptoms: (1) tremors/trembling, (2) bradykinesia, (3) stiffness of limbs and torso, and (4) posture instability.

Unlike most causes in the Global Burden of Disease project, Parkinson's disease mortality and morbidity estimates are modelled jointly. This is because of marked discrepancies between prevalence data and cause of death data. Specifically, prevalence data suggest little to no variation over time (eg, 1990–2017) whereas age-standardised mortality rates in vital registrations in high-income countries have increased multiple times over this same period. Additionally, prevalence variation between countries is much smaller than the variation in death rates assigned to Parkinson's disease in vital registration. We attribute these discrepancies to changing coding practices rather than epidemiological change.

Because of this joint procedure, descriptions of the mortality estimation process are included where relevant, but see the Parkinson's disease fatal write up for more details.

Input data

Model inputs

To inform our estimates of burden due to Parkinson's disease, we use mortality data from vital registration systems, as well as prevalence data from surveys and administrative data such as claims sources.

An updated systematic review was conducted from September 2015 to August 2017, and the search terms were set to capture studies for Parkinson's disease.[1] This search term resulted in 660 initial hits with 20 sources marked for extraction. Studies with no clearly defined sample or that drew from specific clinic/patient organizations were excluded.

Studies using non-representative populations are excluded from modeling. Certain studies have been outliered on a case-by-case basis due to subsequent review and exclusion due to inappropriateness of the study design, or case ascertainment that conflict with existing gold-standard data – where possible. We exclude claims data from the year 2000 because these data are systematically lower than other years. As of GBD 2017, a prevalent case is identified from claims data where an individual has one inpatient visit, two outpatient visits, or one outpatient and one inpatient visit (arguing that a single mention of a code for PD in an individual could be a provisional diagnosis prior to confirmation). This decreased prevalence estimates for the United States because previously an individual with any inpatient or outpatient visit in a given year counted as a case.

The total source count used for modeling in GBD 2019 is listed in the table below:

Measure	Total sources	Countries with data
All measures	186	45
Prevalence	120	42
Incidence	45	22
Relative risk	1	1
Standardized mortality ratio	6	6
With-condition mortality rate	1	1
Proportion	34	14

Modelling strategy

Studies with age and sex detail separately were split into age- and sex-specific data points. Standard GBD sex splitting methods were used for studies with only "both" sex data points: we modeled the ratio of female/male prevalence in MR-BRT and then calculated male prevalence:

$$prev_{male} = prev_{both} * \frac{pop_{both}}{(pop_{male} + ratio * pop_{female})}$$

And then calculated female prevalence:

$$prev_{female} = ratio * prev_{male}$$

We also split data points where the age range was greater than 25 years. In GBD 2017, age splitting was based on the age pattern from the United States, where we had the most detail by age. In GBD 2019, age splitting was based on the global age pattern from a Dismod model that only used input data with less

[1] (Parkinson disease[Title/Abstract] OR Parkinson's disease[Title/Abstract]) AND (epidemiology[Title/Abstract] OR prevalence[Title/Abstract] OR incidence[Title/Abstract]) AND ("2015/09/31"[PDAT] : "2017/08/23"[PDAT])

than a 25-year age range. Data are location split if they are at country level and cover a number of subnationals (or are UK data).

For GBD 2019, adjustment factors for all study-level covariates were determined using matched data (by year, age, sex, location) for reference and alternative case definitions in a logit difference network meta-regression. Study-level covariates included studies that were not population representative, excluded nursing homes from their estimates, followed UKPD Brain Bank diagnosis criteria, followed MDS diagnosis criteria, or did not explicitly define diagnosis criteria. Country covariates are used to inform global patterns. Cause-specific mortality results from the final fatal Parkinson's disease model is pulled into the final non-fatal DisMod model. The following tables provide an overview of the study-level and country covariates used in the Parkinson's disease DisMod MR-2.1 model.

MR-BRT Crosswalk Adjustment Factors for Parkinson's Disease

Data input	Reference or alternative case definition	Gamma	Beta Coefficient, Logit (95% CI)	Adjustment factor*
2 of 4 diagnostic criteria	Ref	0.48	---	---
Not population representative	Alt		0.03 (-0.95 – 1.04)	0.51
Excluded nursing homes	Alt		0.01 (-0.95 – 0.95)	0.50
UKPD Brain Bank criteria	Alt		0.01 (-1.46 – 0.47)	0.50
MDS criteria	Alt		0.14 (-0.83 – 1.54)	0.53
No explicit criteria	Alt		0.01 (=0.56 – 1.37)	0.50

Covariates. Summary of covariates used in the Parkinson's Disease DisMod-MR meta-regression model

Covariate	Type	Parameter	Exponentiated beta (95% Uncertainty Interval)
Smoking prevalence (age-standardized)	Prevalence	-1.15	0.32 (0.28 – 0.36)
Healthcare access and quality index	Excess mortality rate	-0.025	0.98 (0.97 – 0.98)

Severity splits

As in GBD 2013, we use Hoehn and Yahr stages to determine severity. However, for GBD 2017 onward, the cutpoints were updated in order to more accurately correspond with the lay descriptions of severities. Specifically, a Hoehn and Yahr stage 4 now corresponds to a designation of severe, where before it was classified as moderate.

Severity	Stage

Mild	≤2.0
Moderate	2.5-3.5
Severe	≥4

The following figures show the results of the meta-analysis on Hoehn and Yahr stages.

Figure 1. Percentage of mild cases of Parkinson's disease in population-based studies

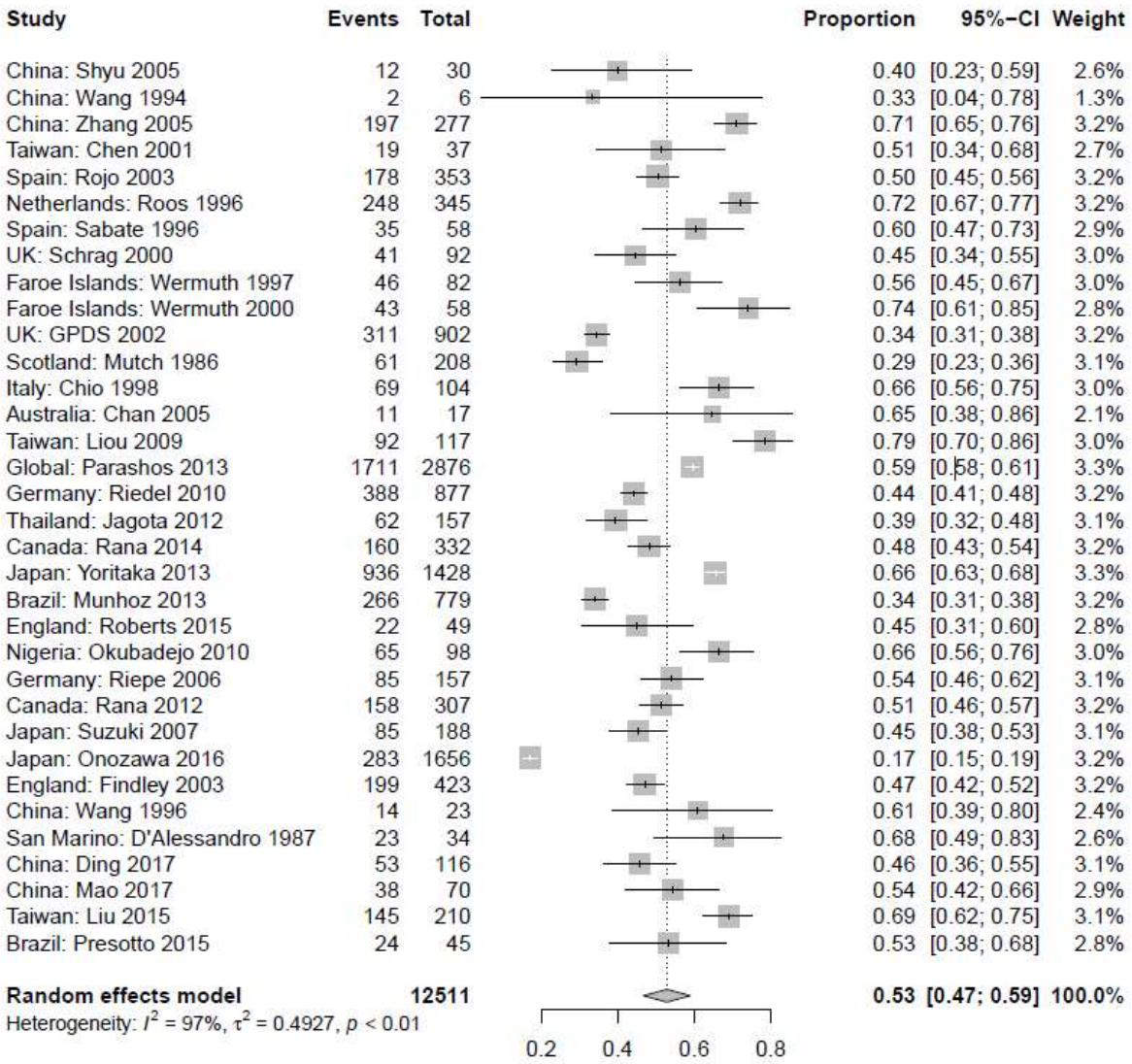


Figure 2. Percentage of moderate cases of Parkinson's disease in population-based studies

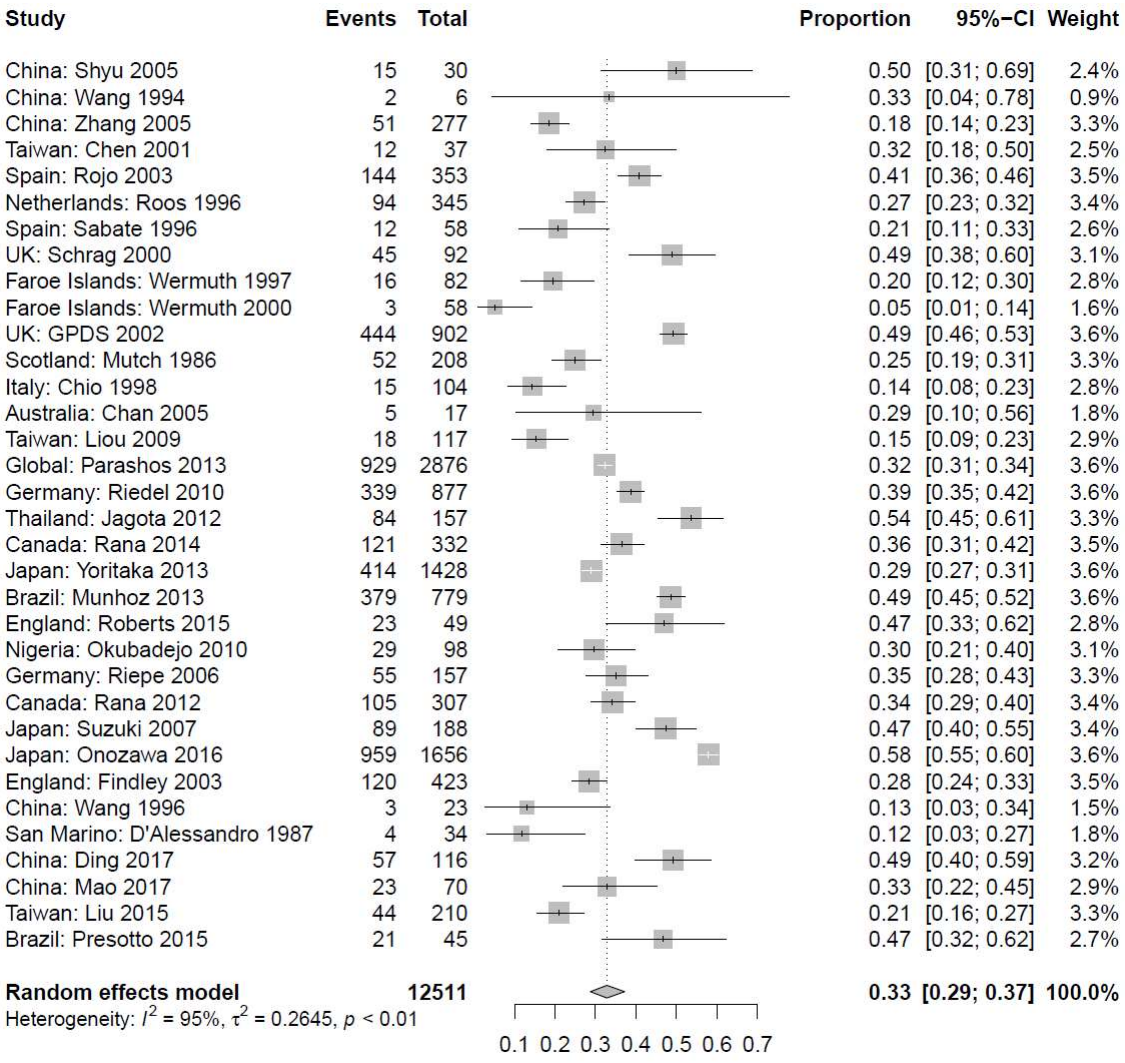
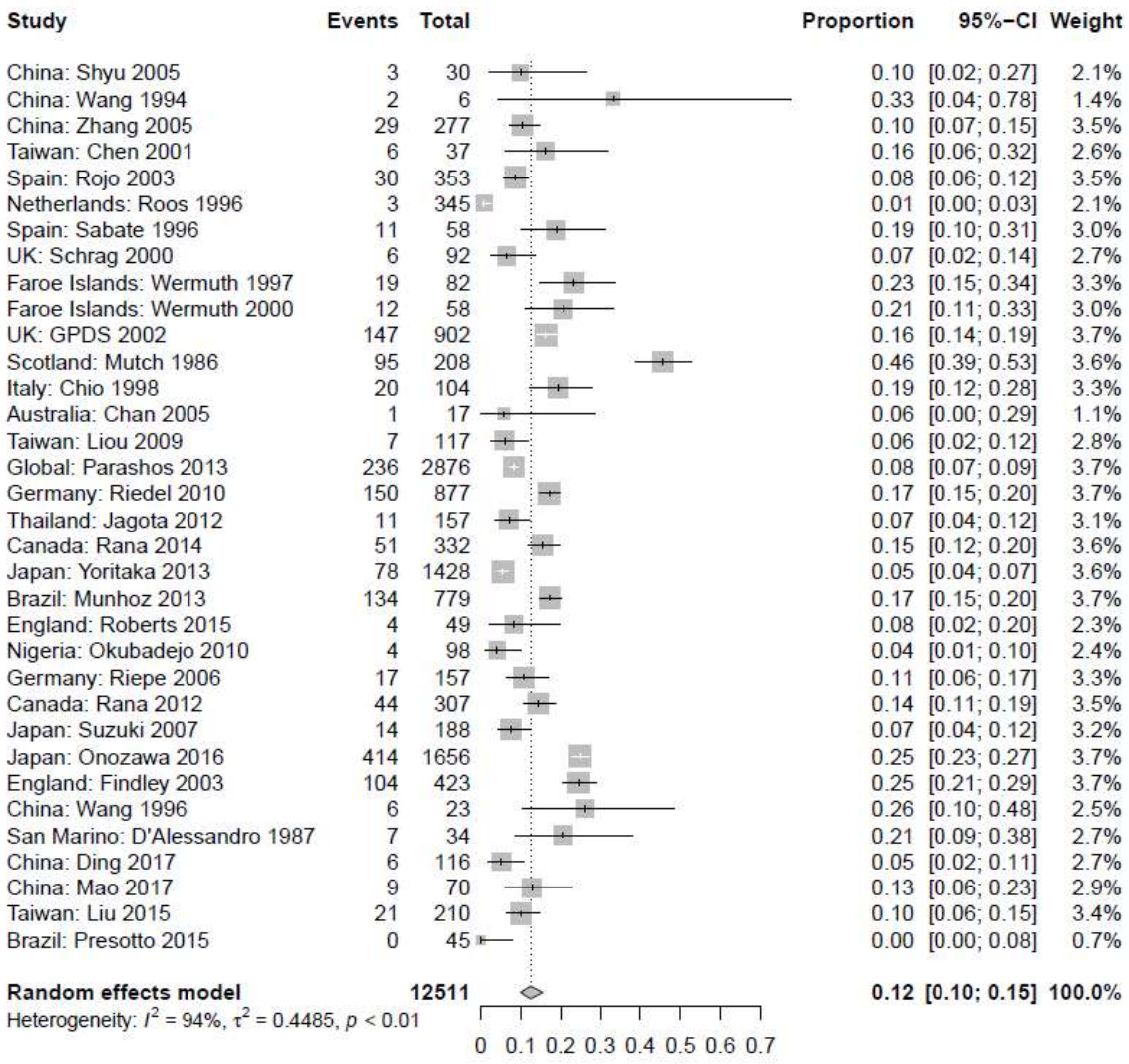


Figure 3. Percentage of severe cases of Parkinson's disease in population-based studies



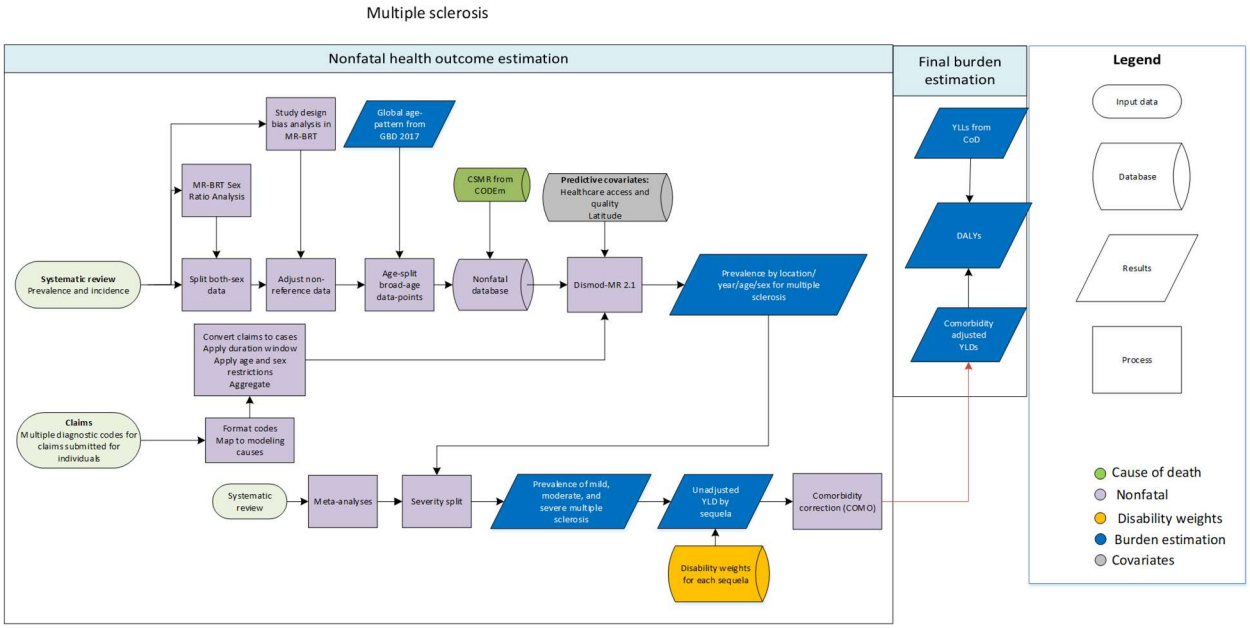
Severity estimates were generated by multiplying estimates of prevalence (country-year-sex-age-specific) by the fractions of mild, moderate, and severe PD, and 95% confidence intervals were estimated by taking 1,000 draws.

The following table provides the lay description and disability weights associated with Parkinson's disease.

Severity level	Lay description	DW (95% CI)
Mild	Has mild tremors and moves a little slowly, but is able to walk and do daily activities without assistance.	0.01 (0.005–0.019)
Moderate	Has moderate tremors and moves slowly, which causes some difficulty in walking and daily activities. The person has some trouble swallowing, talking, sleeping, and remembering things.	0.267 (0.181–0.372)
Severe	Has severe tremors and moves very slowly, which causes great difficulty in walking and daily activities. The person falls easily and has a lot of difficulty talking, swallowing, sleeping, and remembering things.	0.575 (0.396–0.73)

Multiple sclerosis (MS)

Flowchart



Input data and methodological summary

Case definition

Multiple sclerosis is a chronic, degenerative, and progressive neurological condition typified by the damaging of the myelin sheaths. McDonald's criteria for diagnosis are considered the contemporary gold standard. For GBD 2019, as for previous rounds, diagnosis by McDonald's criteria, other published criteria (such as Poser, Schumacher, or McAllen criteria), and clinical neurological exam are all treated as reference. The ICD-10 code for MS is G35.

Input data and processing

The data underpinning estimates of burden due to MS are generally of two types. The first are representative, population-based, cross-sectional or longitudinal studies reported in peer-reviewed journals and identified via a search-string-based review, last updated for GBD 2017 and described in previous reports. Estimates of epidemiologic measures (prevalence, incidence, *etcetera*) were manually extracted from these publications. The second type are claims data as obtained and processed by the GBD Clinical Informatics team and described in a separate section of this Appendix. New data added in GBD 2019 included Polish claims, additional years of USA claims (years 2015-2016). These data link claims for all inpatient and outpatient encounters for a single individual, and provide primary and secondary diagnoses for all encounters. An individual was extracted from claims data as a prevalent case if they had any peptic ulcer disease code as any diagnosis in one or more inpatient encounters or two or more outpatient encounters.

The total number of sources used for modeling in GBD 2019 are listed in the table below:

Measure	Total sources	Countries with data
All measures	251	53
Prevalence	208	46
Incidence	86	24
Proportion	29	20

For studies that reported epidemiologic measures (generally prevalence or incidence) by age for both sexes combined, and also by sex for all ages combined, we calculated the sex-ratio of cases in that study and applied it to the age-specific measures to estimate age-sex-specific measures.

To estimate sex-specific measures from studies that reported only for both sexes combined, we modeled the log sex ratio in MR-BRT using all sex-specific measurements from all other studies in the database and combined these with the GBD sex-specific population estimates for the relevant age-group. For prevalence, this estimate was 0.63 (0.069 to 1.2); for incidence this estimate was 0.86 (0.53 to 1.2). These were applied by calculating male prevalence:

$$prev_{male} = prev_{both} * \frac{pop_{both}}{(pop_{male} + ratio * pop_{female})}$$

and then calculating female prevalence:

$$prev_{female} = ratio * prev_{male}$$

(Equivalent equations were used for incidence.)

A pre-modelling bias adjustment was then made to data from USA claims in the year 2000 - a dataset that only covers a small commercially insured sub-population. This adjustment was modeled as difference in logit prevalence between USA claims data and reference data matched on year, age, sex and location. The estimated mean logit differences were applied to the USA claims data for 2000 prior to modeling in DisMod-MR 2.1 (below).

The process of adjusting for non-reference data using MR-BRT with the logit-transformation method is described below:

1. Identify data points with overlapping year, age, sex, and location between claims (alternative case definition) and other (reference case definition)
2. Logit transform overlapping data points of alternative and reference case definitions
3. Convert overlapping data points into a difference in logit space using the following equation: $logit(altnerative) - logit(reference)$
4. Use the delta method to compute standard errors of overlapping data points in logit space, then calculate standard error of logit difference using the following equation: $\sqrt{(variance\ of\ alternative) + (variance\ of\ reference)}$
5. Using MR-BRT, conduct a random effects meta-regression to obtain the pooled logit difference of alternative to reference
6. Apply the pooled logit difference to all data points of alternative case definitions using the following equation:

$$new_{estimate} = inverse.logit((logit(alternative)) - (pooled\ logit\ difference))$$

7. Calculate new standard errors using the delta method, accounting for gamma (between-study heterogeneity)

The table below shows bias correction factors.

MR-BRT Crosswalk Adjustment Factors for Multiple sclerosis

Data input	Reference or alternative data	Gamma	Beta Coefficient, Logit difference (95% CI)	Adjustment factor*
McDonald's diagnostic criteria OR Other published diagnostic criteria OR Clinical neuro exam OR Claims for location-years other than USA 2000	Reference	0.32	---	---
Data from USA claims in 2000	Alternative		-0.57 (-1.79 to 0.62)	0.36 (0.14 to 0.65)

**Adjustment factor is the inverse-logit transformed Beta coefficient; <0.5 represents that alternative is adjusted upward; >0.5 represents that alternative is adjusted downward*

Subsequently, data-points for samples spanning 25 years of age or more were disaggregated by applying the age-pattern observed in the global fit for the GBD 2017 model.

After extraction and processing, some studies were marked as outliers and excluded on a case-by-case basis if they were inconsistent with established regional or temporal trends or if concerns about study quality were identified during extraction and processing.

Modelling strategy

Compartmental model

We used DisMod 2.1 as the main analytical tool for the MS estimation process. Inputs included prevalence and incidence data, as described above, as well as the cause-specific mortality rate (CSMR) estimated in the GBD causes of death analysis, and excess mortality rate (EMR) obtained by dividing CSMR by prevalence data-points. Prior settings included zero remission for all ages, no incidence or excess mortality for persons under 5 years old, and incidence limited to less than 0.000005 after the age of 60 years. We also constrained the super-region random effects for prevalence, incidence, and excess mortality to -1 and 1 for all locations except Greenland, United States, and Canada, where location random effects for incidence were constrained to -4, 2 and 2, respectively.

We employed the following covariates to improve model predictions:

Covariate	Measure	Beta coeff (95% CI)	Exponentiated
Absolute value of average latitude	prevalence	0.041 (0.037 to 0.042)	1.04 (1.04 to 1.04)

Absolute value of average latitude	incidence	0.041 (0.036 to 0.045)	1.04 (1.04 to 1.05)
Healthcare Access and Quality index	excess mortality rate	-0.027 (-0.037 to -0.022)	0.97 (0.96 to 0.98)

As described in the literature, extreme latitude is associated with higher prevalence and incidence of MS, although the pathway to explain the association is not understood. Our operationalisation of latitude is created by a population-weighted average of latitude by country and taking the absolute value. The underlying population distribution rasters are part of the Gridded Population of the World dataset.

Although there are no known cures for MS, we expect disease management to differ globally – largely as a function of available resources. To capture this, we use the Healthcare Access and Quality index covariate to capture this relationship in the estimation of excess mortality.

Severity splits

As we have done since GBD 2013, we used Kurtzke's Expanded Disability Status Scale (EDSS) to determine severity splits for MS. The EDSS scores corresponding to each severity are as follows:

Asymptomatic: EDSS = 0
Mild: 0 < EDSS ≤ 3.5
Moderate: 3.5 < EDSS ≤ 6.5
Severe: 6.5 < EDSS ≤ 9.5

The table below illustrates severity levels, lay descriptions, and DWs.

Severity level	Lay description	DW (95% CI)
Asymptomatic	-	0 (0-0)
Mild	Has mild loss of feeling in one hand, is a little unsteady while walking, has slight loss of vision in one eye, and often needs to urinate urgently.	0.183 (0.124–0.253)
Moderate	Needs help walking, has difficulty with writing and arm coordination, has loss of vision in one eye and cannot control urinating.	0.463 (0.313–0.613)
Severe	Has slurred speech and difficulty swallowing. The person has weak arms and hands, very limited and stiff leg movement, has loss of vision in both eyes and cannot control urinating.	0.719 (0.534–0.858)

Because not all sources had information on the number of cases with EDSS stage 0, instead reporting on a mild category, we implemented a two-step meta-analysis strategy. First, we subsetted the studies to those that reported on the number of cases with EDSS stage 0, and did meta-analyses on the proportion of asymptomatic and mild cases. Then, we conducted meta-analyses on the full dataset to get the

proportion mild, moderate, and severe, and we squeezed the asymptomatic and mild categories from the previous meta-analyses into the mild category established by the meta-analysis on the full dataset.

The following figures provide the result of the first meta-analysis on the asymptomatic and mild categories.

Figure 1. Asymptomatic cases of MS

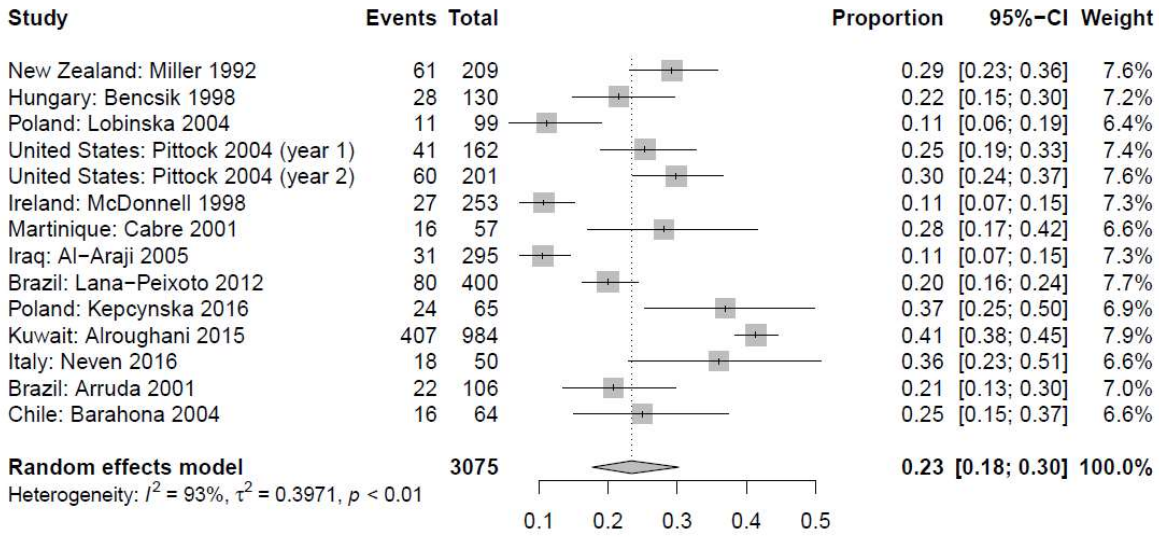
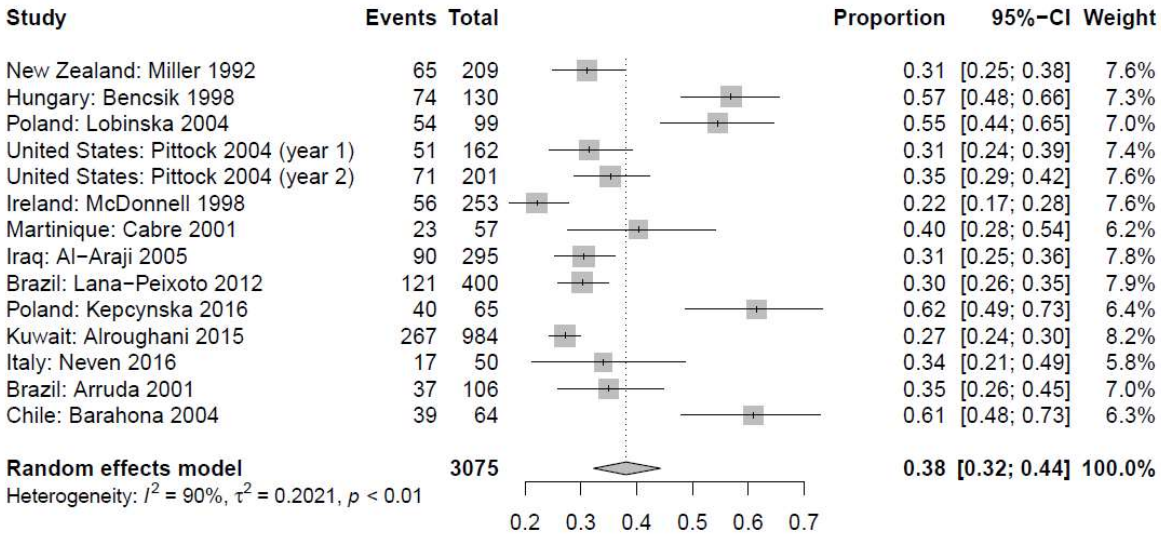


Figure 2. Mild cases of MS



The following figures provide the result of the second meta-analysis on the mild, moderate, and severe categories.

Figure 3. Mild cases of MS (including both asymptomatic and mild categories)

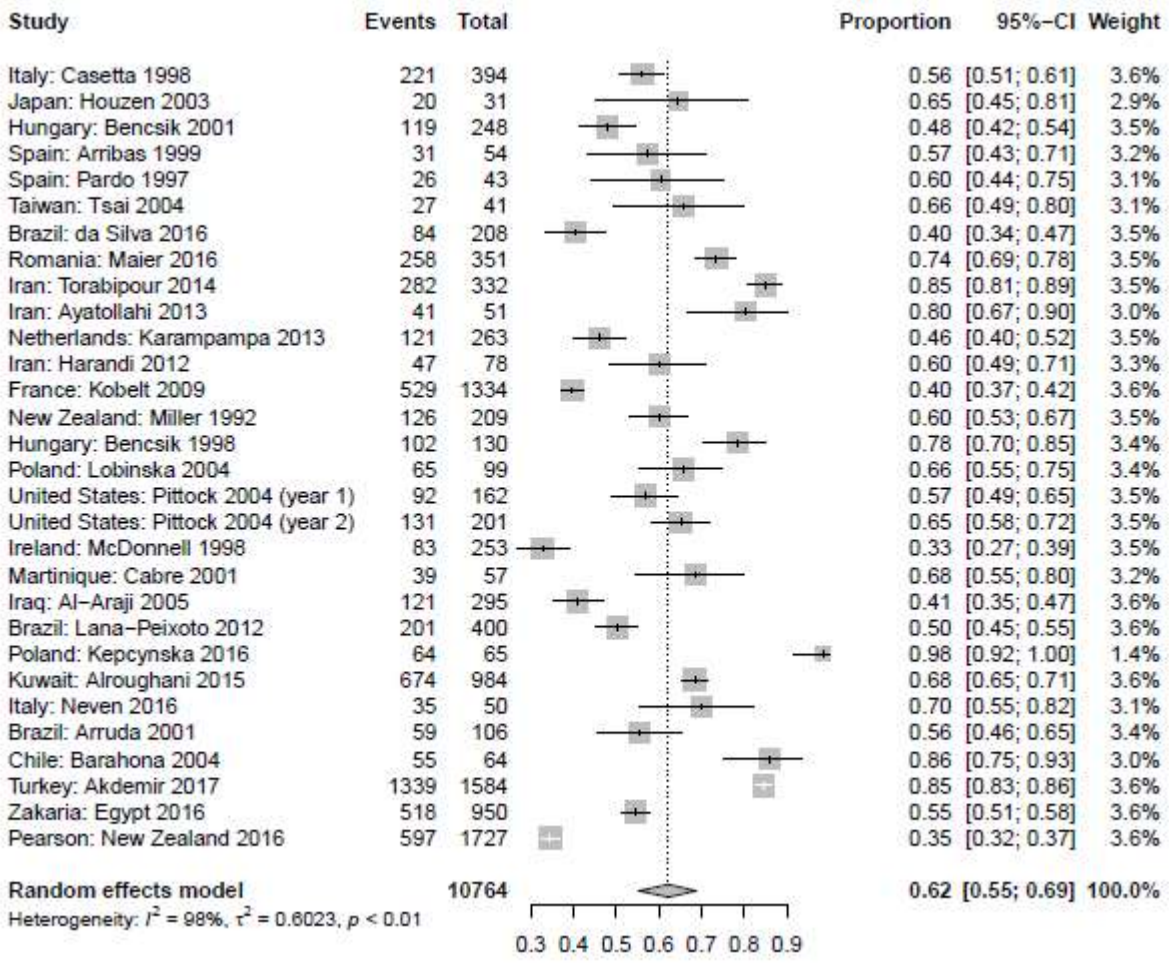


Figure 4. Moderate cases of MS

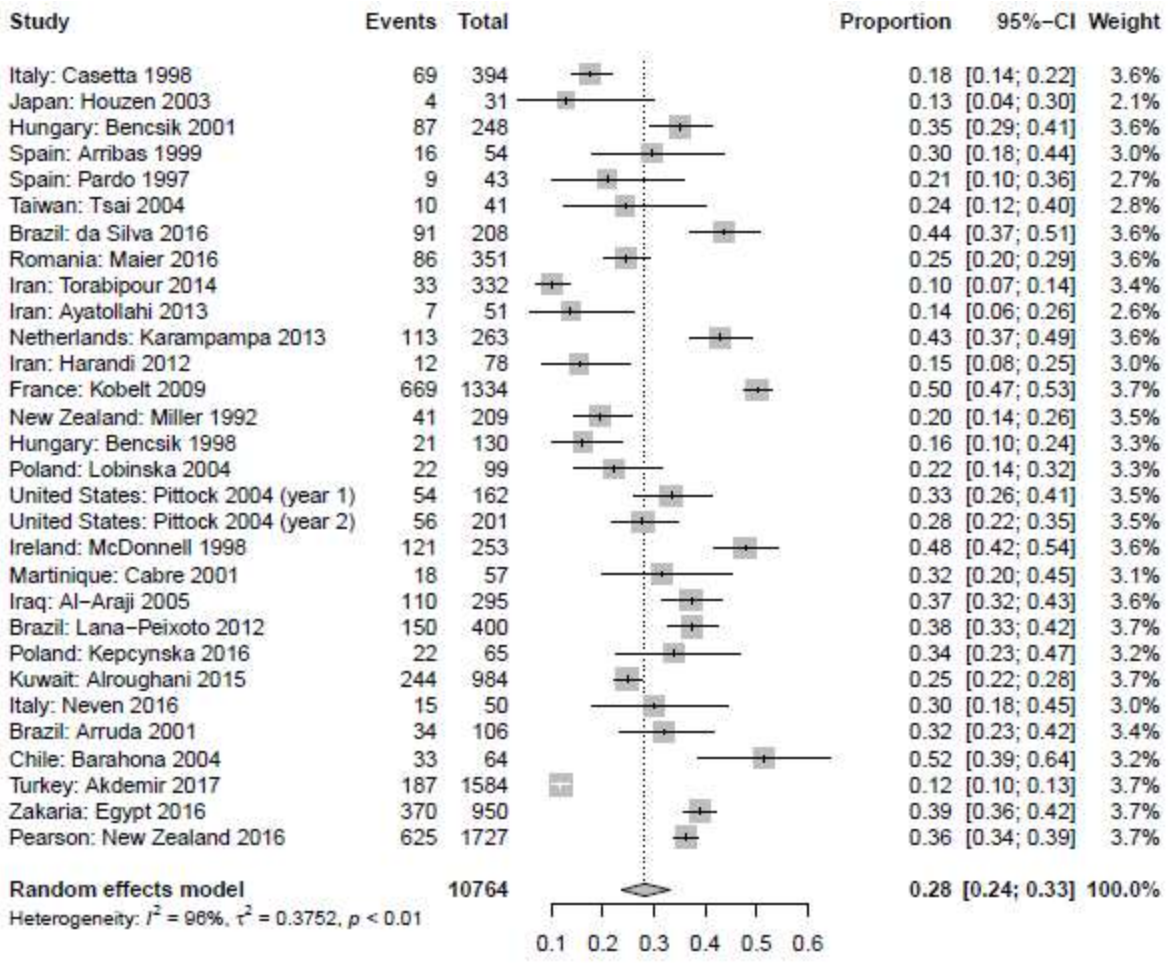
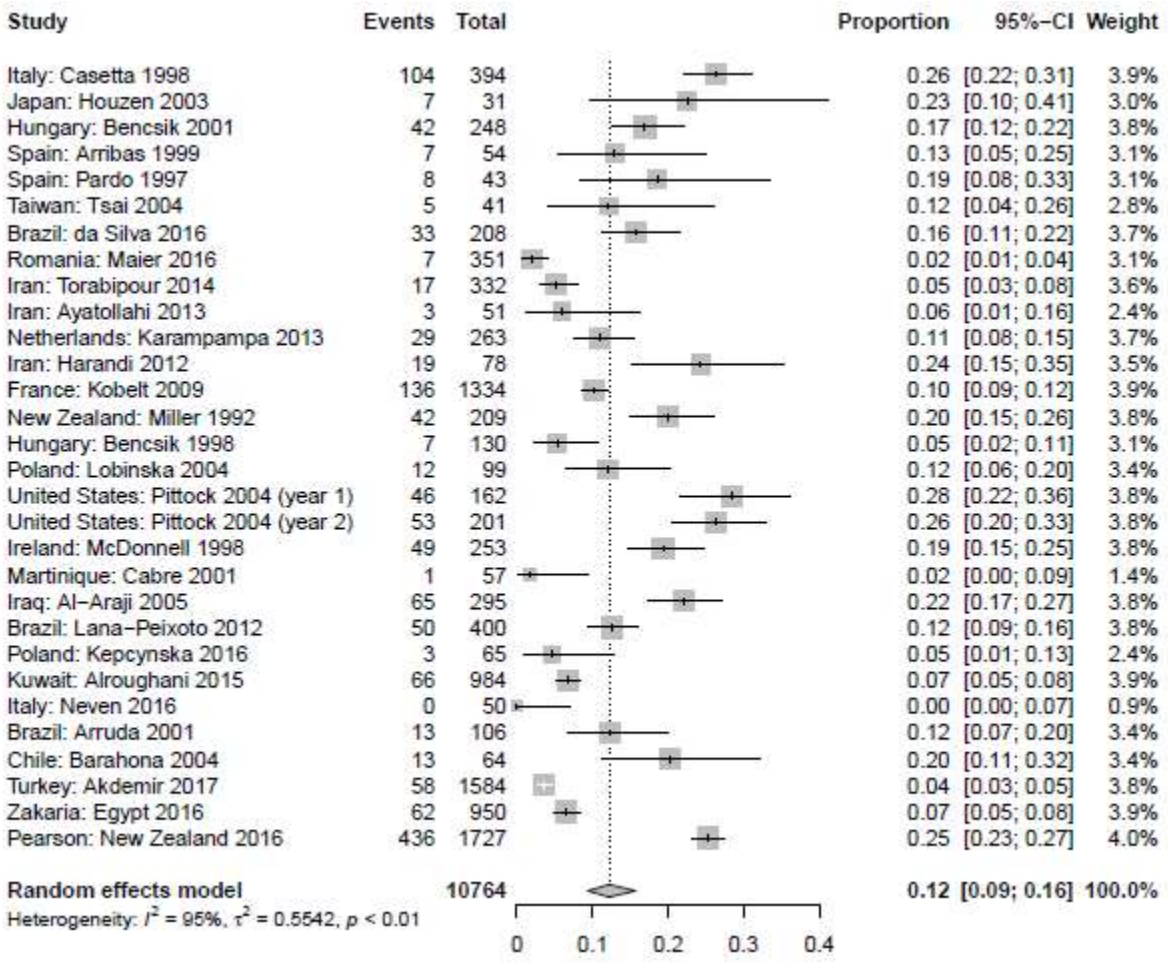
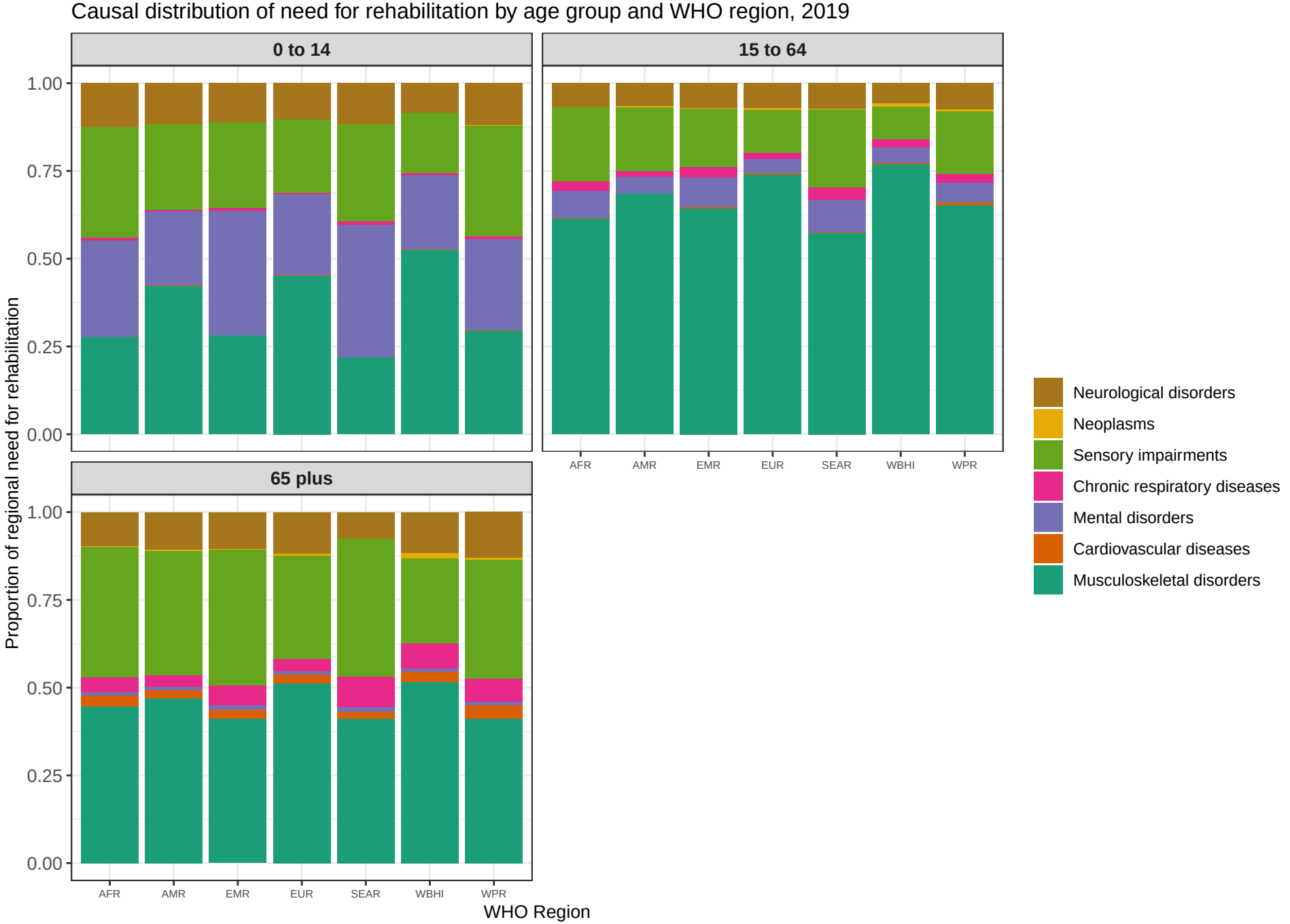


Figure 5. Severe cases of MS



Detailed description on all health condition and their sequelae included in this article can be accessed here: https://cloud.ihme.washington.edu/s/Sn4Fq4kef9P5Pdz


Causal distribution of need for rehabilitation by age group and WHO region, 2019
0 to 14
15 to 64
65 plus
Proportion of regional need for rehabilitation
1.00
0.75
0.50
0.25
0.00
AFR
AMR
EMR
EUR
SEAR
WBHI
WPR
WHO Region
Neurological disorders
Neoplasms
Sensory impairments
Chronic respiratory diseases
Mental disorders
Cardiovascular diseases
Musculoskeletal disorders
AFR=African Region, AMR=Region of the Americas, SEAR=South−East Asia Region,
EUR=European Region, EMR=Eastern Mediterranean Region, WPR=Western Pacific Region, WBHI=World Bank High Income

All global, region- and country-specific results reported in the paper can be accessed here: https://cloud.ihme.washington.edu/s/Sn4Fq4kef9P5Pdz

Evidence on the effectiveness of rehabilitation interventions

This table includes evidence on the effectiveness of rehabilitation interventions for different functioning outcomes for the 25 selected health conditions. The evidence is based on Cochrane systematic reviews and is further grouped into 1) moderate to high quality evidence and 2) low quality evidence. It is important to note that the low-quality evidence in some of the reviews is either due to insufficient number of trials or due to the fact that blinding and randomization which are considered in the evaluation of the evidence are nearly impossible to be applied in rehabilitation trials.

Health Condition	Rehabilitation interventions based on Cochrane systematic reviews	
	Moderate to high quality evidence	**Low quality evidence**
Musculoskeletal disorders		
Low back pain	Multidisciplinary rehabilitation for return to work and disability (1), Back school for pain (2), Motor control exercise for pain (3), Exercise for low back pain and pelvic pain (4), Therapeutic ultrasound for back specific functioning (5), Biopsychosocial rehabilitation for pain and disability (6), Exercise for reduction of recurrences (7), Staying active for pain relief and functioning (8), Operant therapy and Behavioural treatment for pain relief (9)	Rehabilitation for pain and disability (10), Intense physical conditioning for return to work (11)
Neck pain	Exercise, Cervico-scapulothoracic and upper extremity strength training for pain and function (12), Static-dynamic cervico-scapulothoracic strengthening/endurance exercises including pressure biofeedback immediate post treatment for pain and function (12), Cervical manipulation for pain, function and quality of life (13), Thoracic manipulation for pain and function (13)	Cognitive behavioural therapy for pain and quality of life (14)
Fractures	Use of a removable type of immobilisation combined with exercise for activity limitations (15)	Hand therapy for hand function (16), Weight-bearing programme, quadriceps muscle strengthening exercise programme and electrical stimulation for mobility (17)
Other injuries		Hamstring stretching exercises for recovery (18)
Osteoarthritis	Exercise for physical function, depression, pain, self-efficacy and social function (19, 20,21), Aquatic exercise for pain, disability, and QoL (22), Electromagnetic field treatment for pain relief (23)	Exercise for hand pain, function and finger joint stiffness (24), Ultrasound for pain and function (25)
Amputation		Prosthetic rehabilitation – safety and optimal weight (26,27)
Rheumatoid arthritis	Physical activity and Psychosocial interventions for fatigue (28), Land-based aerobic capacity and muscle strength training for aerobic capacity and muscle strength (29)	Mobile and fixed bearing for knee pain, health-related quality of life (30)
Neurological disorders		
Cerebral palsy	Occupational therapy plus BoNT-A for reducing impairment, improving activity level outcomes and goal achievement (31)	Constraint induced movement therapy, for bimanual performance and unimanual capacity (32), Aerobic exercise for gross motor function (33)

Stroke	Action observation therapy for upper limb motor function (34), Electromechanical and robotic assisted training for generic activities of daily living (35), Mirror therapy for upper extremity motor function, motor impairment, activities of daily living, and pain (36), Speech and language therapy for functional communication, reading, writing, and expressive language (37), Repetitive task training for upper and lower limb function (38), Cardiorespiratory and mixed training for disability, mobility and balance (39), Physical rehabilitation for recovery of function and mobility (40)	Swallowing therapy for length of hospital stay, dysphagia, chest infections, and swallowing ability (41), Occupational therapy for performance in activities of daily living and risk of deterioration in these abilities (42), Cognitive rehabilitation for subjective measures of memory (43)
Traumatic brain injury	Cognitive rehabilitation for return to work (44)	Fitness training for cardiorespiratory deconditioning (45)
Alzheimer's disease and dementia		Cognitive training for global cognition and verbal semantic fluency (46), Music-based therapy for depressive symptoms, behavioural, emotional well-being and quality of life (47), Personally tailored activities for behavioural problems (48), Exercise for ability to perform ADLs (49), Cognitive stimulation for cognition (50)
Spinal Cord Injury	Respiratory muscle training for respiratory muscle strength and lung volumes (51)	
Parkinson's disease	Treadmill training for gait speed and stride length (52), Physiotherapy and treadmill training for gait hypokinesia (52), Physiotherapy for speed, walking, gait, functional reach and balance (53)	
Multiple sclerosis	Structured, multidisciplinary rehabilitation and physical therapy (exercise or physical activities) for functional outcomes (mobility, muscle strength, aerobic capacity), and quality of life (54)	
Motor-neuron disease		Respiratory exercise for fatigue (55)
Guillain-Barre syndrome	Plasma exchange for recovery (56)	Exercise for physical outcomes such as muscle strength and functional mobility (57*), multidisciplinary ambulatory rehabilitation for disability (58*)
Sensory impairments		
Hearing loss	Hearing aids use for hearing-specific health-related quality of life, general health-related quality of life and listening ability (59)	Self-management support and complex interventions combining self-management support and delivery system design for hearing aids use (60)
Vision loss		Psychological therapies and methods for enhancing vision for vision related quality of life (61), Stand-mounted electronic devices for reading speeds (62)
Mental disorders		
Developmental intellectual disabilities		Task-oriented interventions for motor performance (63), Treadmill intervention for development of independent walking and motor skill attainment (64)
Schizophrenia		Cognitive remediation for cognitive impairment and social skills, Psychoeducation for reducing relapses, and Cognitive therapy for distress (65*)
Autism spectrum disorders		Verbally based and ACC interventions for spoken and non-verbal communication (66), Early intensive behavioural intervention for

		communication and language skills, socialization and daily living skills (67), Social skills groups for social competence (68)
Chronic respiratory diseases		
COPD	Pulmonary rehabilitation for health-related quality of life and exercise capacity (69) and for dyspnoea and fatigue, emotional function and sense of control (70), Breathing exercise for functional exercise capacity (71)	Psychological therapies (using a CBT-based approach) for COPD-related depression (72), Neuromuscular electrostimulation for quadriceps force and endurance, and severity of leg fatigue (73), Water-based exercise training for exercise capacity and quality of life (74), Airway clearance techniques for reductions in the need for increased ventilatory assistance, duration of ventilatory assistance and hospital length of stay (75)
Cardiovascular diseases	Exercise-based cardiac rehabilitation for reduction in the risk of death due to a cardiovascular cause, hospital admission and health-related quality of life (76, 77), Combined interventions for return to work (78)	
Neoplasms	Physical activity interventions for HRQoL, emotional or perceived physical and social function, anxiety, cardiorespiratory fitness, and physical activity (79), Multidisciplinary interventions for return to work (80)	Physical exercise added to standard care for fatigue and depression (81), Exercise training for decline in exercise capacity and disease-specific global HRQoL (82), Educational interventions for reducing fatigue intensity, fatigue's interference with daily life, and general fatigue, anxiety and global quality of life (83), Exercise for fatigue, physical fitness, cancer site-specific quality of life and cognitive function (84), Music interventions for anxiety, pain, fatigue, QoL, heart rate, respiratory rate and blood pressure (85), High-intensity ambulatory multidisciplinary rehabilitation for reducing motor disability (continence, mobility and locomotion, cognition) (86), Psychosocial interventions for wellbeing (87), Progressive resistance training for shoulder dysfunction, pain, disability, range of motion (88), Exercise for quality of life, body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain (89)

Note: References 27, 57, 58 and 65 are not Cochrane systematic reviews and have been included because they provide additional information on the effectiveness of rehabilitation interventions for the specific health conditions.

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