Appendix

Table of Contents

33 # GATHER checklist, with description of compliance and location of information

#	GATHER checklist item	Description of compliance	Reference
Objectives and funding			
1	Define the indicators, populations, and time periods for which estimates were made.	Narrative provided in paper and appendix describing indicators, definitions, and populations	Main text (Methods) and appendix
2	List the funding sources for the work.	Funding sources listed in paper	Summary (Funding)
Data Inputs			
For all data inputs from multiple sources that are synthesized as part of the study:			
3	Describe how the data were identified and how the data were accessed.	Narrative description of data seeking methods provided	Main text (Methods) and appendix
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Narrative about inclusion and exclusion criteria by data type provided; ad hoc exclusions in cause-specific write-ups	Main text (Methods) and appendix
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	An interactive, online data source tool that provides metadata for data sources by component, geography, cause, risk, or impairment has been developed	Online data citation tools: http://ghdx.healthdata.org/gbd-2019/data-input-sources
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Summary of known biases by cause included in appendix	Appendix
For data inputs that contribute to the analysis but were not synthesized as part of the study:			
7	Describe and give sources for any other data inputs.	Included in online data source tool	http://ghdx.healthdata.org/gbd-2019/data-input-sources
For all data inputs:			
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet as opposed to a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared due to ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Downloads of input data available through online data tools (visualization/ data query, GHDx); input data not in tools will be made available upon request	Online data visualization tools, data query tools, and the Global Health Data Exchange
Data analysis			
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Flow diagrams of methods have been provided	Appendix
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Flow diagrams and methods write-ups have been provided	Main text (Methods) and appendix
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Provided in methodological write-up	Appendix
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Provided in methodological write-up	Appendix
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Narrative description of uncertainty interval calculation	Main text (Methods) and appendix

14	State how analytic or statistical source code used to generate estimates can be accessed.	Appendix	http://ghdx.healthdata.org/gbd-2019/code
Results and Discussion			
15	Provide published estimates in a file format from which data can be efficiently extracted.	GBD 2019 results available through online data tools, the Global Health Data Exchange, and online data query tool	Main text, appendix, online data tools (visualization/ data query tools, GHDx)
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Uncertainty provided with all results	Main text, appendix, online data tools (visualization/ data query tools, GHDx)

Systematic review methods

Across all five reviews, studies were required to be either population-representative or conducted in outpatient settings, were required to report the mean age of the sample, and had to report either the proportion of exposed individuals with dementia or the relative risk of dementia comparing exposed to unexposed individuals. Across all studies dementia or cognitive impairment were assessed either via clinical judgement, performance on neurocognitive tests and survey responses, or through medical records. Statistical adjustments were performed in the modeling stage to account for these differences. Each clinical condition was assessed either via clinical judgement, self-report on surveys or medical records.

Traumatic brain injury (TBI)

Case definition: TBI is a trauma to the head associated with disruption of normal function of the brain. We required that TBI be of moderate or severe severity, as defined by either a loss of consciousness or interaction with the health care system.

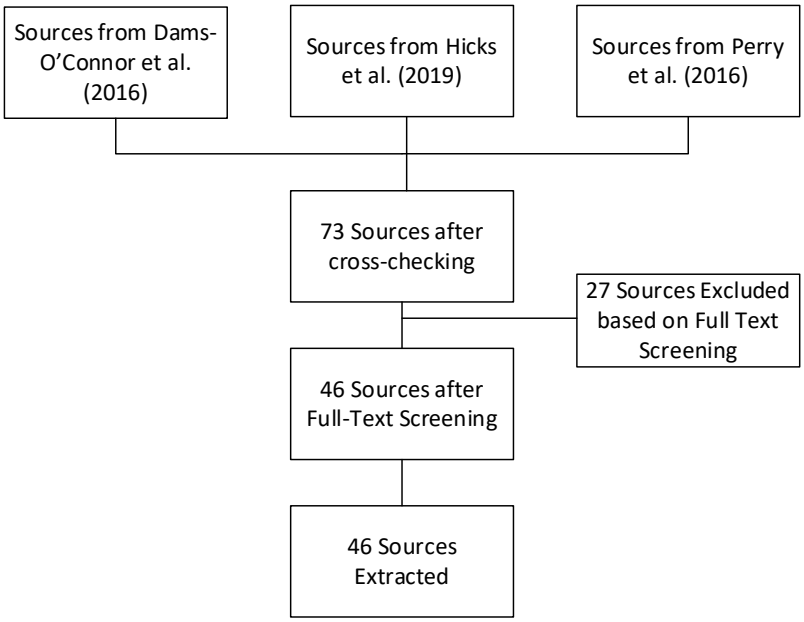
A search revealed three different recent systematic reviews on the relationship between TBI and dementia. These reviews were:

Dams-O'Connor K, Guetta G, Hahn-Ketter AE, Fedor A. Traumatic brain injury as a risk factor for Alzheimer's disease: current knowledge and future directions. *Neurodegener Dis Manag* 2016; **6**: 417–29.

Hicks AJ, James AC, Spitz G, Ponsford JL. Traumatic Brain Injury as a Risk Factor for Dementia and Alzheimer Disease: Critical Review of Study Methodologies. *Journal of Neurotrauma* 2019; published online May 21. DOI:10.1089/neu.2018.6346.

Perry DC, Sturm VE, Peterson MJ, *et al.* Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg* 2016; **124**: 511–26.

Overall, there were 73 unique sources listed across the three reviews, and 46 of these met inclusion criteria for extraction.



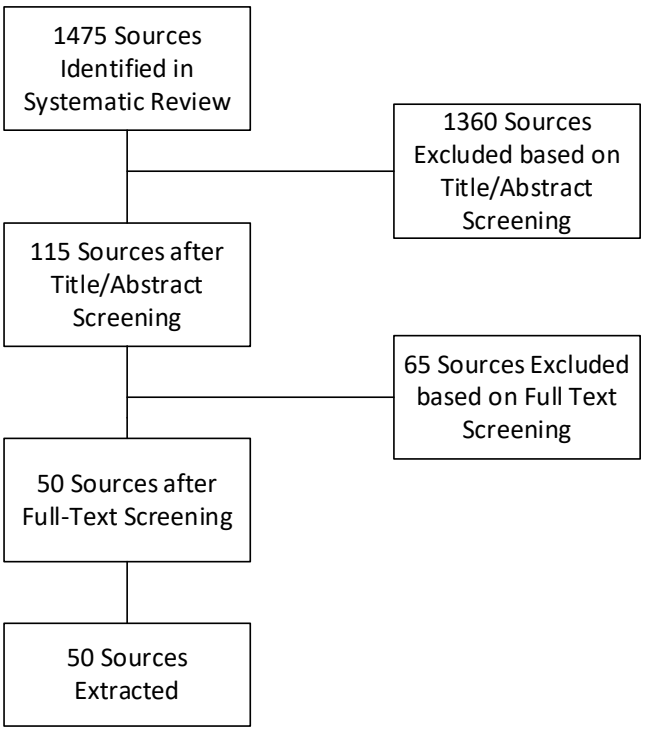
Parkinson's disease

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.

For the review on Parkinson's disease, we conducted a PubMed search on 2/14/2019 using the search string:

((((((Dementia[Title/Abstract] OR Alzheimer's Disease[Title/Abstract] OR Cognitive Impairment[Title/Abstract] OR Dementia[MeSH Major Topic]) AND (Parkinson*[Title/Abstract] OR Parkinson Disease[MeSH Major Topic]) AND (prevalence[Title/Abstract] OR epidemiology[Title/Abstract] OR incidence[Title/Abstract]) NOT (animals[MeSH] NOT humans[MeSH])))))).

This search resulted in 1475 hits, and of these 115 passed title/abstract screening. Ultimately, 50 sources were accepted and extracted.



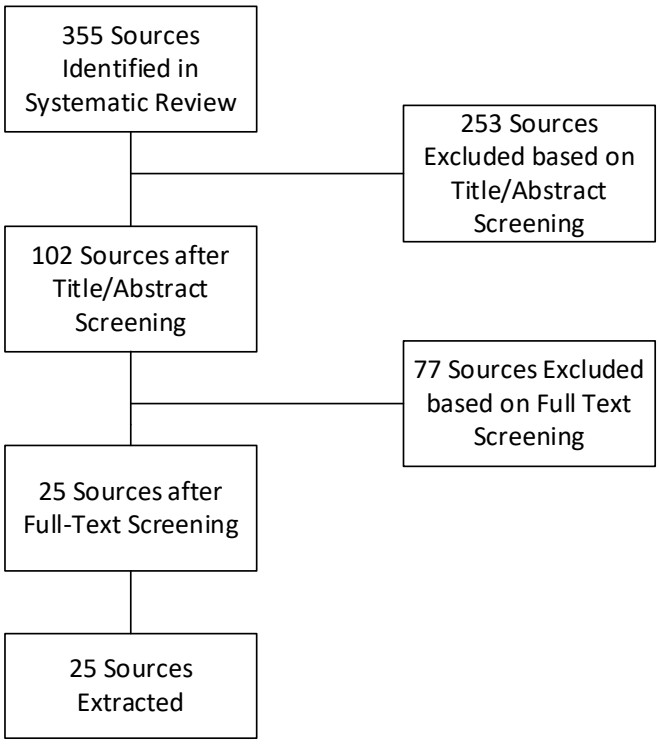
Down syndrome

Case definition: Down syndrome, also known as Trisomy 21, is the presence of a third copy of chromosome 21, typically caused by nondisjunction during the production of gametes. Down syndrome is associated with several specific physical characteristics, including decreased muscle tone, flat facial features, an upward slant to the eyes, abnormally shaped ears, a single deep crease across the center of the palm, folded skin on the inner corners of the eyes, and ability to extend joints beyond the usual, among others. The GBD case definition of Down syndrome includes ICD-10 codes Q90.0, Q90.1, Q90.2, and Q90.9.

We searched PubMed on 5/31/2019 using the search string:

(((((dement*[Title/Abstract] OR alzheimer*[Title/Abstract] OR cognitive impairment[Title/Abstract] OR dementia[MeSH]) AND (down syndrome[Title/Abstract] OR down's syndrome[Title/Abstract] OR down syndrome[MeSH]) AND (prevalence[Title/Abstract] OR epidemiology[Title/Abstract] OR predict*[Title/Abstract] OR risk factor*[Title/Abstract] OR hazard[Title/Abstract] OR determinant*[Title/Abstract]) NOT (animals[MeSH] NOT humans[MeSH])))).

Of 355 total hits, 102 passed title/abstract screening. Out of these sources, 25 passed full text screening and were extracted.



Stroke

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. Data on transient ischaemic attack (TIA) were not included.

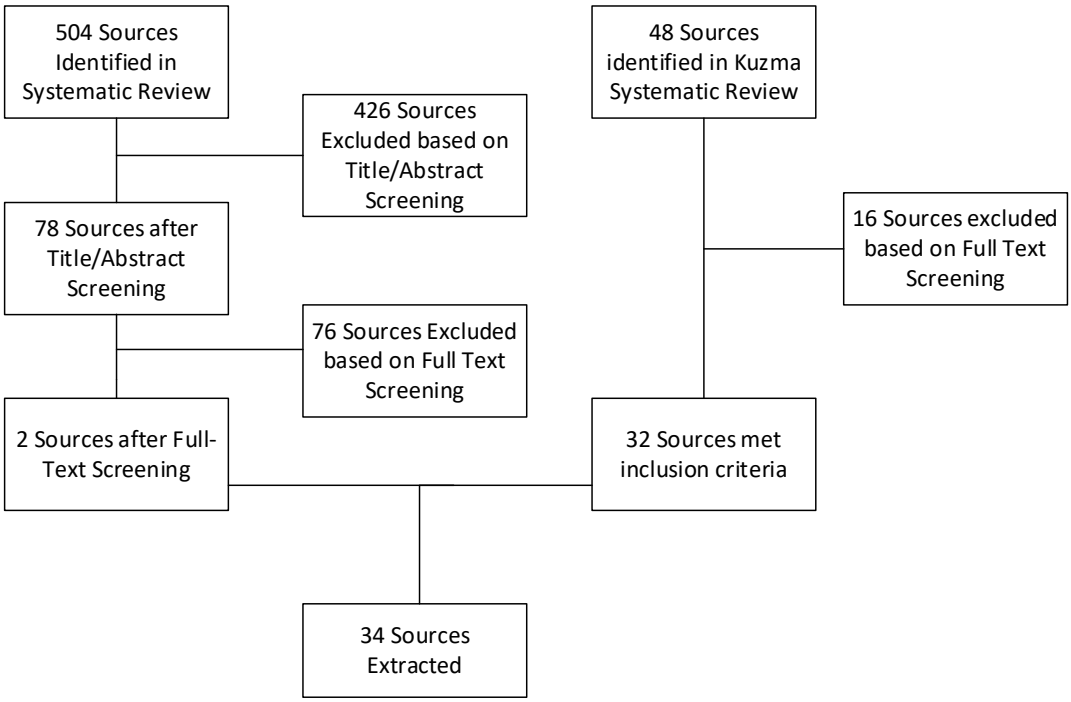
A recent systematic review was identified describing the relationship between clinical stroke and dementia:

Kuźma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: A systematic review and meta-analysis. *Alzheimers Dement* 2018; **14**: 1416–26.

Of the 48 studies included in this review, 32 met our inclusion criteria. The initial component studies were identified and data were extracted. We also updated this review through a PubMed search conducted on 04/3/2019, using the search string:

(((((dement*[Title/Abstract]) OR (alzheimer*[Title/Abstract])) AND ((stroke[Title/Abstract]) OR (ischemic stroke[Title/Abstract]) OR (ischaemic stroke[Title/Abstract]) OR (intracerebral hemorrhage[Title/Abstract]) OR (intracerebral haemorrhage[Title/Abstract]) OR (hemorrhagic stroke[Title/Abstract]) OR (cerebrovascular accident*[Title/Abstract]) OR (cerebral vascular accident*[Title/Abstract]) OR (brain infarct*[Title/Abstract]) OR (cerebral infarct*[Title/Abstract]) OR (poststroke[Title/Abstract]) or (post stroke[Title/Abstract]) OR (haemorrhagic stroke[Title/Abstract]) OR (subarachnoid hemorrhage[Title/Abstract]) OR (subarachnoid haemorrhage[Title/Abstract]) OR (subarachnoid hemorrhage[Title/Abstract]) OR (subarachnoid haemorrhage[Title/Abstract])) AND ((prevalence[Title/Abstract]) OR (epidemiology[Title/Abstract]) OR (predict*[Title/Abstract]) OR (risk factor*[Title/Abstract]) OR (hazard[Title/Abstract]) OR (determinant*[Title/Abstract]) NOT (animals[MeSH] NOT humans[MeSH]))))) AND ("2017/04/27"[Date - Publication] : "3000"[Date - Publication]).

This search targeted studies published after 4/27/2017, the publication date of the most recent study included in the Kuzma review. This search identified 504 studies. 78 studies passed title/abstract screening and ultimately two additional studies were accepted and extracted.



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573 # Study characteristics table

574

Disease	Study Characteristic	Level	Count (%)
Down syndrome	Outcome category (%)	Alzheimer's disease	5 (19.2)
		DSM/ICD dementia	21 (80.8)
	Sample assessed (%)	Assessed hospital sample	3 (11.5)
		Assessed other sample	23 (88.5)
	Dementia diagnosis method (%)	Diagnosed by study physician or alternate	22 (84.6)
		Diagnosed with clinical records	4 (15.4)
Parkinson's disease	Outcome category (%)	All cognitive impairment	6 (9.4)
		DSM/ICD dementia	37 (57.8)
		Mild cognitive impairment	13 (20.3)
		Parkinson's disease dementia	8 (12.5)
	Sample assessed (%)	Assessed clinical sample	40 (62.5)
		Assessed population representative sample	24 (37.5)
	Dementia diagnosis method (%)	Diagnosed by study physician or alternate	58 (90.6)
		Diagnosed with clinical records	6 (9.4)
Stroke	Exposure category (%)	Stroke	34 (82.9)
		Stroke and TIA combined	7 (17.1)
	Timing of stroke ascertainment (%)	Incident stroke	12 (100.0)
	Stroke reporting (%)	Confirmed stroke	21 (51.2)
		Self reported stroke	20 (48.8)
	Use of clinical records (%)	Stroke identified with clinical records	12 (29.3)
		Stroke identified without clinical records	29 (70.7)
	Study design (%)	Case-control study	4 (9.8)
		Longitudinal study	37 (90.2)
	Sample assessed (%)	Assessed clinical sample	1 (2.4)
		Assessed population representative sample	40 (97.6)
	Dementia diagnosis method (%)	Diagnosed by study physician or alternate	34 (82.9)
		Diagnosed with clinical records	7 (17.1)
	Controlled for age and sex (%)	Controlled	35 (85.4)
		Did not control	6 (14.6)

Disease	Study Characteristic	Level	Count (%)
	Controlled for education (%)	Controlled	21 (51.2)
		Did not control	20 (48.8)
	Controlled for other cardiovascular disease (%)	Controlled	17 (41.5)
		Did not control	24 (58.5)
TBI	Outcome category (%)	Alzheimer's disease	32 (56.1)
		DSM/ICD Dementia	25 (43.9)
	Dementia diagnosis method (%)	Diagnosed by study physician or alternate	43 (75.4)
		Diagnosed with clinical records	14 (24.6)
	Two-phase dementia ascertainment (%)	No, one stage diagnostic procedure	35 (61.4)
		Yes, screening completed	22 (38.6)
	TBI reporting (%)	Self reported TBI	41 (71.9)
		TBI ascertained through physician or clinical records	16 (28.1)
	TBI intensity (%)	All TBI	20 (35.1)
		Lost consciousness or sought medical treatment	37 (64.9)
	Study design (%)	Case-control study	33 (57.9)
		Longitudinal study	24 (42.1)
	Controlled for age and sex (%)	Controlled	51 (89.5)
		Did not control	6 (10.5)
	Controlled for education (%)	Controlled	24 (42.1)
		Did not control	33 (57.9)
	Controlled for cardiovascular disease (%)	Controlled	10 (17.5)
		Did not control	47 (82.5)

*The number of studies for Down's syndrome and Parkinson's disease do not match the number of studies reported in the paper, as some studies reported multiple data points with different study attributes, and these are counted distinctly here.

Bayesian meta-regression model settings

In our models for the estimation of relative risks, we specified that covariates on study characteristics effected both the mean effect and the variance of the estimate. Gaussian priors of zero effect with a variance of 0.01 were included for each covariate on study characteristics in order to prevent the model from estimating spuriously large effect sizes when informed by sparse data. For each model, we tested a covariate on sex, but as the majority of data extracted were not sex-specific, we did not find a relationship between sex and relative risk in any of the models and the covariate was excluded. To estimate relative risk over age, we included a cubic splines on age with three knots, equally spaced across the distribution of data over age. Each spline had priors on the slope of the terminal segments, to prevent undue influence of sparse data towards the tails of the spline.

Bayesian meta-regression methods

(Reprinted from "Global burden of 369 diseases, injuries, and impairments, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019" by GBD 2019 Diseases, Injuries, and Impairments Collaborators, in press)

This section details the statistical models underlying MR-BRT, and the fitting procedure used to obtain estimates. Further details on models and algorithms can be found in the technical report.[1]

The MR-BRT program is a set of wrappers customised for global health problems that use the open-source mixed effects package `LimeTr` (https://github.com/zhengp0/limetr).[1] We describe the basic functionality in the sections below.

Mixed-effects model

We consider the following non-linear mixed effects model:

$$\begin{aligned} \boldsymbol{y}_i &= \mathbf{F}_i(\beta) + \mathbf{Z}_i \boldsymbol{u}_i + \boldsymbol{\epsilon}_i \\ \boldsymbol{u}_i &\sim N(\mathbf{0}, \boldsymbol{\Gamma}),\ \boldsymbol{\Gamma} = \mathrm{diag}(\gamma), \qquad \boldsymbol{\epsilon}_i \sim N(\mathbf{0}, \boldsymbol{\Lambda}), \end{aligned} \tag{1}$$

where $y_i \in \mathbb{R}^{n_i}$ is the vector of observations from the ith study, $\varepsilon_i \in \mathbb{R}^{n_i}$ are measurement errors with given covariance $\boldsymbol{\Lambda}, \boldsymbol{u}_i\ y_i \in \mathbb{R}^{k_y}$ are independent random effects, and $\boldsymbol{Z}_i \in \mathbb{R}^{n_i + k_y}$ is a linear map, and β are regression coefficients. The models F_i may be non-linear.

To fit (β, γ) we solve the marginal likelihood problem:

$$\min_{\beta,\gamma} f(\beta,\gamma) \coloneqq \sum_{i=1}^{m} \frac{1}{2} \left(y_i - \mathbf{F}_i(\beta)\right)^{\top} \left(\mathbf{Z}_i \boldsymbol{\Gamma} \mathbf{Z}_i^{\top} + \boldsymbol{\Lambda}_i\right)^{-1} \left(\boldsymbol{y}_i - \mathbf{F}_i(\beta)\right) + \frac{1}{2} ln \left|\mathbf{Z}_i \boldsymbol{\Gamma} \mathbf{Z}_i^{\top} + \boldsymbol{\Lambda}_i\right|. \tag{2}$$

When the model is linear, we can write:

$$\mathbf{F}_i(\beta) = \boldsymbol{X}\beta. \tag{3}$$

Constraints and priors

The ML estimate can be extended to incorporate non-linear inequality constraints

$$\mathbf{C}(\boldsymbol{\theta}) \leq c,$$

where $\boldsymbol{\theta} = (\beta, \gamma)$. Constraints play a key role for polynomial splines.

It is also essential to allow priors on parameters of interest. We assume that priors are given by a functional form

$$\boldsymbol{\theta} \sim \exp(-\rho(\boldsymbol{\theta}))$$

The likelihood problem is then augmented by adding the term $(\boldsymbol{\theta})$ to the ML objective. The function ρ may be non-linear and non-convex, but we assume it is smooth.

Trimming outliers

Least trimmed squares (LTS) is a robust estimator[2,3] for the standard regression problem. Given the problem

$$\min_{\beta} \sum_{i=1}^{n} \frac{1}{2} (y_i - \langle \boldsymbol{X}_i, \beta \rangle)^2, \tag{4}$$

638

639 the LTS estimator minimises the sum of *smallest h* residuals rather than all residuals. These estimators
640 were initially introduced to develop linear regression estimators that have a high breakdown point (in
641 this case 50%) and good statistical efficiency (in this case $n^{-1/2}$). Breakdown refers to the percentage of
642 outlying points which can be added to a dataset before the resulting M-estimator can change in an
643 unbounded way. Here, outliers can affect both the outcomes and training data (features).

644 LTS estimators are robust against outliers, and arbitrarily large deviations that are trimmed do not affect
645 the final β.

646 Rather than writing the objective in terms of order statistics, it is far simpler to extend the likelihood
647 using an auxiliary variable $\boldsymbol{W}$:

$$\min_{\beta, \mathbf{W}} \sum_{i=1}^{n} w_i \left(\frac{1}{2} (y_i - \langle \mathbf{X}_i, \beta \rangle)\right)^2 \quad \text{s.t.} \quad \mathbf{1}^\top \boldsymbol{W} = h, \quad \mathbf{0} \leq \boldsymbol{W} \leq \mathbf{1}. \tag{5}$$

648 The set

$$\Delta_h := \{\mathbf{W} : \mathbf{1}^\top \mathbf{W} = h, \quad \mathbf{0} \leq \mathbf{W} \leq \mathbf{1}\} \tag{6}$$

649 is known as the *capped simplex*, since it is the intersection of the h-simplex with the unit box.[2] For a
650 fixed $\beta\beta$, the optimal solution of (5) with respect to $\mathbf{W}$ assigns weight 1 to each of the smallest h
651 residuals, and 0 to the rest. Problem (5) is solved *jointly* in (β, $\mathbf{W}$), simultaneously finding the regression
652 estimate and classifying the observations into inliers and outliers. This joint strategy makes LTS different
653 from post-hoc analysis, where a model is fit first with all data, and then outliers are detected using that
654 estimate.

655 To explain how trimming enters the marginal likelihood problem, we focus on a single group term from
656 the ML likelihood (2):

$$\left(\frac{1}{2}\left(\boldsymbol{y}_i - \mathbf{F}_{i(\beta)}\right)^\top \left(\mathbf{Z}_i \boldsymbol{\Gamma}^{-1} \mathbf{Z}_i^\top + \boldsymbol{\Lambda}_i\right)^{-1} \left(\boldsymbol{y}_i - \mathbf{F}_i(\beta)\right) + \frac{1}{2} \ln \left|\mathbf{Z}_i \boldsymbol{\Gamma}^{-1} \mathbf{Z}_i^\top + \boldsymbol{\Lambda}_i\right|\right)$$

657

658 We introduce auxiliary variables $\boldsymbol{W}_i \in \mathbb{R}^{n_i}$, and define

$$\boldsymbol{r}_i := y_i - \mathbf{F}_i(\beta), \quad \mathbf{W}_i := \operatorname{diag}(\mathbf{W}_i), \quad \sqrt{\mathbf{W}_i} := \operatorname{diag}\left(\sqrt{\mathbf{W}_i}\right).$$

659

660 We now form the objective

$$\frac{1}{2} \boldsymbol{r}_I^\top \sqrt{\mathbf{W}_i} \left(\sqrt{\mathbf{W}_i} \mathbf{Z}_i \boldsymbol{\Gamma}^{-1} \mathbf{Z}_i^\top \sqrt{\mathbf{W}_i} + \boldsymbol{\Lambda}_i^{\odot \mathbf{W}_i}\right)^{-1} \sqrt{\mathbf{W}_i}\, \boldsymbol{r}_i + \frac{1}{2} \ln \left| \sqrt{\mathbf{W}_i}\, \mathbf{Z}_i \boldsymbol{\Gamma}^{-1} \mathbf{Z}_i^\top \sqrt{\mathbf{W}_i} + \boldsymbol{\Lambda}_i^{\odot \mathbf{W}_i} \right|, \tag{7}$$

661

662 where $\odot$ denotes the elementwise power operation:

$$\boldsymbol{\Lambda}_i^{\odot \mathbf{W}_i} := \begin{bmatrix} (\lambda_{1j})^{w_{i1}} & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & (\lambda_{in_i})^{w_{in_i}} \end{bmatrix} \tag{8}$$

663 When $w_{ij} = 1$, we recover the contribution of the ijth observation to the original likelihood. As $ww_{ij} \downarrow 0$,
664 the ijth contribution to the residual is correctly eliminated by $\sqrt{w_{ij}} \downarrow 0$. The jth row and column of

$\sqrt{\boldsymbol{W}_i}\boldsymbol{Z}_i\boldsymbol{\Gamma}^{-1}\boldsymbol{Z}_i^{\mathrm{T}}\sqrt{\boldsymbol{W}_i}$ both go to 0, while the jth entry of $\boldsymbol{\Lambda}_{i\odot}$ goes to 1, which effectively removes all impact of the jth point on the covariance matrix.

For full details and analysis, please see the technical report.[1]

Final estimator

Putting together the trimmed ML with priors and constraints, we arrive at the following estimator.

$$\begin{aligned}\min_{\beta,\gamma,\mathbf{W}} f(\beta,\gamma,\mathbf{W}) := & \sum_{i=1}^{m}\frac{1}{2}\, r_i^{\mathrm{T}}\sqrt{\mathbf{W}_i}\left(\sqrt{\mathbf{W}_i}\,\mathbf{Z}_i\boldsymbol{\Gamma}^{-1}\mathbf{Z}_i^{\mathrm{T}}\sqrt{\mathbf{W}_i}+\boldsymbol{\Lambda}_i^{\odot \mathbf{W}_i}\right)^{-1}\\ & \sqrt{\mathbf{W}_i}\, r_i+\tfrac{1}{2}\ln\left|\sqrt{\mathbf{W}_i}\,\mathbf{Z}_i\boldsymbol{\Gamma}^{-1}\mathbf{Z}_i^{\mathrm{T}}\sqrt{\mathbf{W}_i}+\boldsymbol{\Lambda}_i^{\odot \mathbf{W}_i}\right|+\rho(\beta,\gamma,\boldsymbol{\Lambda})\\ \text{s.t. } & \boldsymbol{r}_i=\boldsymbol{y}_i-\mathbf{F}_i(\beta),\quad \mathbf{1}^{\mathrm{T}}\mathbf{W}=h,\quad 0\le\mathbf{W}\le 1,\quad \boldsymbol{C}\left(\frac{\beta}{\gamma}\right)\le c\,.\end{aligned} \tag{9}$$

The fit is obtained using iterative optimisation techniques. Problem (9) is non-linear and non-smooth, and the optimisation is implemented in the `LimeTR` package[4] (https://github.com/zhengp0), and relies on the IPopt interior point method.[5]

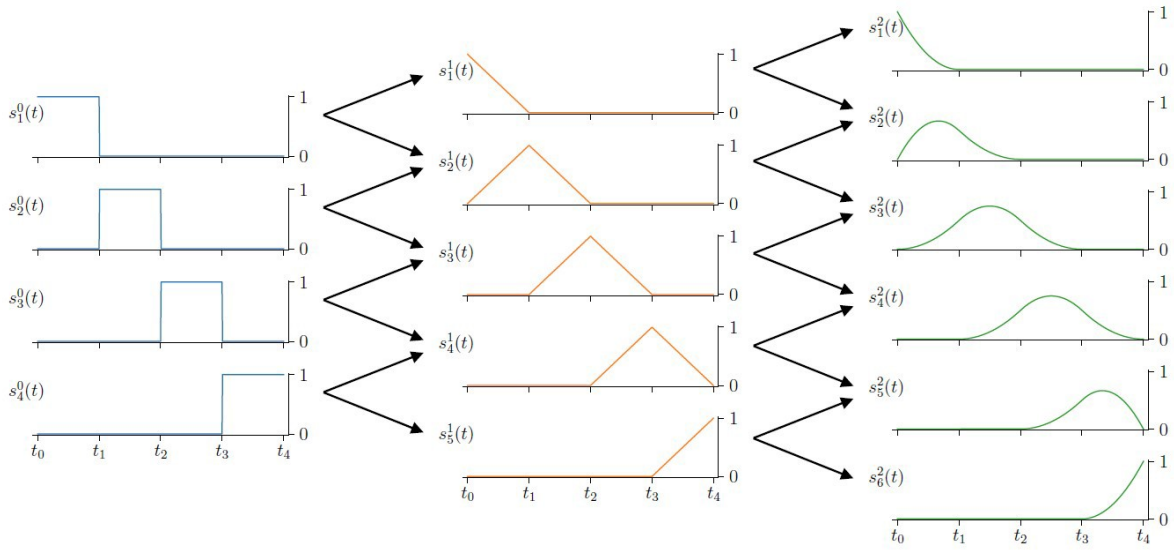
Non-linear dose-response curves with constrained splines

In this section we discuss spline models for dose-response relationships. General background on splines and spline regression are available elsewhere.[6,7]

B-splines and bases

A spline basis is a set of piecewise polynomial functions with designated degree and domain. If we denote polynomial order by p, and the number of knots by k, we need $p+k$ basis elements s_{jp}, which can be generated recursively as illustrated in Figure A.

Figure A. Recursive generation of b-spline basis elements (orders 0, 1, 2)



Given such a basis, we can represent any dose-response relationship as the linear combination of the spline basis elements, with coefficients $\beta\in\mathbb{R}^{p+k}$:

$$f(t) = \sum_{j=1}^{p+k} \beta_j^p s_j^p(t). \tag{10}$$

These coefficients are then inferred as part of the general estimator (9) as discussed in the previous section. An explicit representation of (11) is obtained by building a design matrix $\boldsymbol{X}$. Given a set of t values at which we have data, the jth column of $\mathbf{X}$ is given by the expression

$$\mathbf{X}_{\cdot,j} = \begin{bmatrix} s_j^p(t_0) \\ \vdots \\ s_j^p(t_k) \end{bmatrix}. \tag{11}$$

The model for direct observations data coming from (11) can now be written compactly as

$$\boldsymbol{y}=\mathbf{X}\beta+\mathbf{Z}_i\boldsymbol{u}_i+\boldsymbol{\epsilon}_i,$$

which is a special case of the main problem class (1).

Shape constraints

We can impose shape constraints such as monotonicity, concavity, and convexity on splines. Constraints on splines have been developed in the past through reformulation techniques.[8] The development in this section uses explicit constraints instead.

Monotonicity. Spline monotonicity across the domain of interest follows from monotonicity of the spline coefficients.[6] Given coefficients

$$\beta = \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_n \end{bmatrix},$$

the curve $f(t)$ is monotonically non-decreasing when

$$\alpha_1 \leq \alpha_2 \leq \cdots \leq \alpha_n$$

and monotonically non-increasing if

$$\alpha_1 \geq \alpha_2 \geq \cdots \geq \alpha_n.$$

The relationship $\alpha_1 \leq \alpha_2$ can be written as $\alpha_1 - \alpha_2 \leq 0$. Stacking these inequality constraints for each pair (α_i, α_{i+1}) we can write all constraints simultaneously as

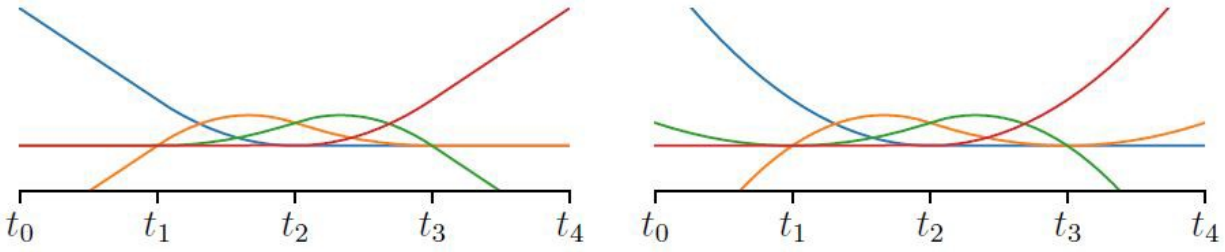
$$\underbrace{\begin{bmatrix} 1 & -1 & 0 & \cdots & 0 \\ 0 & 1 & -1 & \cdots & 0 \\ \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & \cdots & 1 & -1 \end{bmatrix}}_{\mathrm{C}} \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \\ \vdots \\ \alpha_n \end{bmatrix} \leq \begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}.$$

These linear constraints are a special case of the general estimator (9) that allows $(\beta) \leq c_\beta$.

Convexity and concavity. For any twice continuously differentiable function: $f: \mathbb{R} \to \mathbb{R}$, convexity and concavity are captured by the signs of the second derivative. Specifically, f is convex if $f''(t) \geq 0$ is everywhere, and concave if $f''(t) \leq 0$ everywhere. We can compute $f''(t)$ for each interval and impose linear inequality constraints on these expressions.

Enforcing linear tails. For large consumption with few data, we need the capability to ensure that the last segment of the spline is linear, with slopes that match the adjacent segment at the knot. The estimated spline is then a best fit to the data, subject to this specification. Priors on the tails can also be provided.

Figure B. Spline extrapolation. Left: linear extrapolation. Right: non-linear extrapolation.



In general, using linear head and/or tail pieces to extrapolate outside the original domain or interpolate in the data-sparse region is far more stable than using higher-order polynomials; see Figure B. The figure shows symmetric linear tail modifications, but for the analyses in the paper we only impose a right linear tail shape constraint.

Posterior variance estimation

To obtain posterior uncertainty, we use a parametric bootstrap.[9] Once we solve (9) to obtain estimates β and γ, we have a model distribution of the errors (1):

$$\boldsymbol{y}_i = \mathbf{F}_i\left(\hat{\beta}\right) + \mathbf{Z}_i\boldsymbol{u}_i + \boldsymbol{\epsilon}_i$$

We sample datasets from this distribution to generate full datasets $\{\boldsymbol{Y}\}^j$, for j=1,…,. For each dataset $\mathbf{Y}_j$, we then re-solve the fitting problem (9) to obtain estimates β_j and γ_j, and the set $\{\beta_j,\gamma_j\}$ over all j allows us to estimate any posterior statistic we need.

In particular, the posterior set of dose-response curves is given by

$$\left\{f(t)_j + u_j^0\right\}$$

where $f(t)_j$ is the curve obtained by using the re-fit value β_j, and u_j^0 is a sample from $N\left(0,\gamma_j^0\right)$, the associated unexplained heterogeneity parameter.

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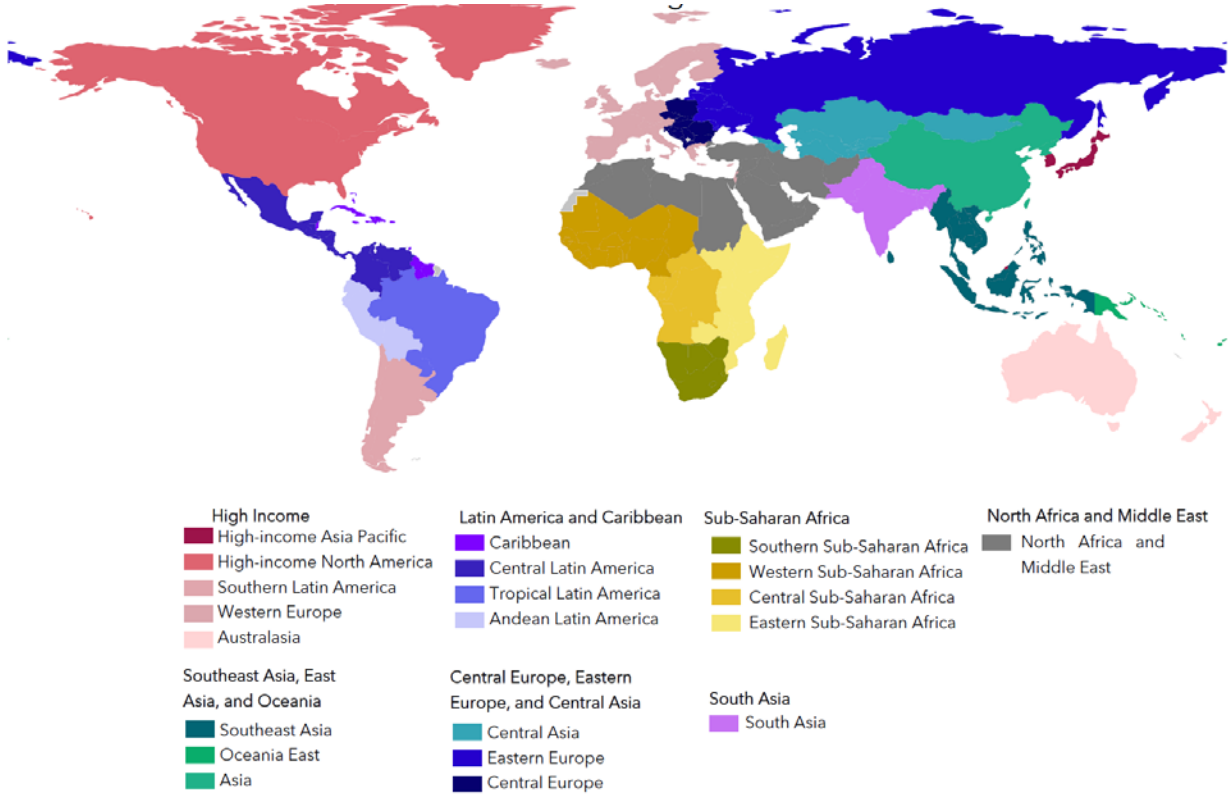
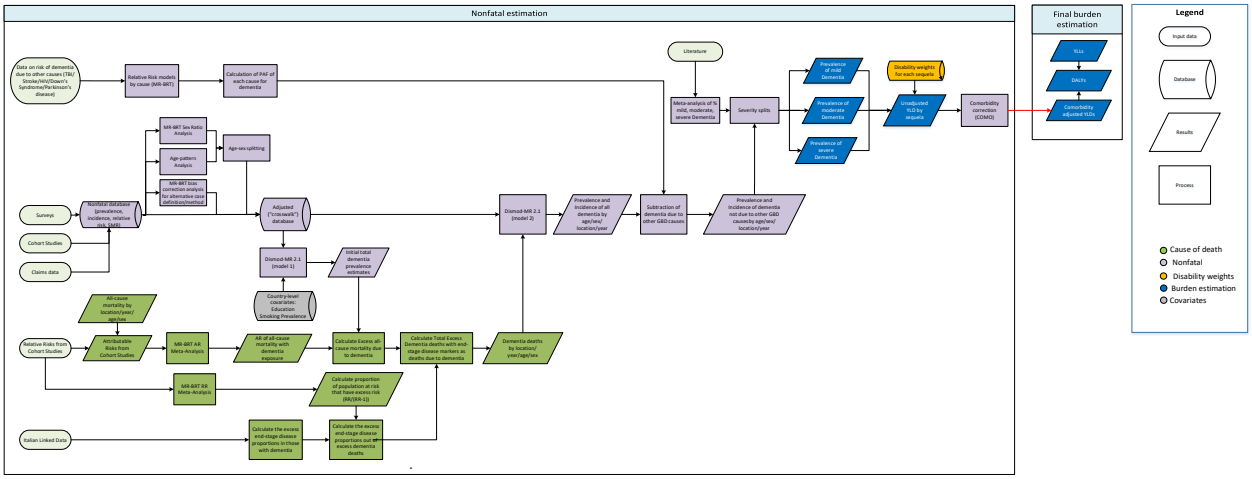
Global Burden of Disease world regions



Dementia prevalence estimation

(Reprinted from "Global burden of 369 diseases, injuries, and impairments, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019" by GBD 2019 Diseases, Injuries, and Impairments Collaborators, in press)

Flowchart



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 characterised 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 vital registration systems, as well as prevalence data from surveys and administrative data such as claims sources. All data sources used in this analysis (on relative risk, prevalence, incidence, etc.) can be accessed at http://ghdx.healthdata.org/gbd-2019/data-input-sources.

Item response theory for prevalence prediction

The prevalence models for dementia are data-sparse, and there aren't 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 harmonisation of these scales. Once the scales are harmonised, the subsamples can be used 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 modelling to estimate prevalence. HRS is a nationally representative survey in the US that 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.

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 imply 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.

Modelling strategy

First, prevalence data were sex-split, crosswalked, and age-split. Studies with age and sex detail separately were split into age-specific and sex-specific datapoints. Data specified as "both"-sex data were split into male- and female-specific datapoints 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:

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

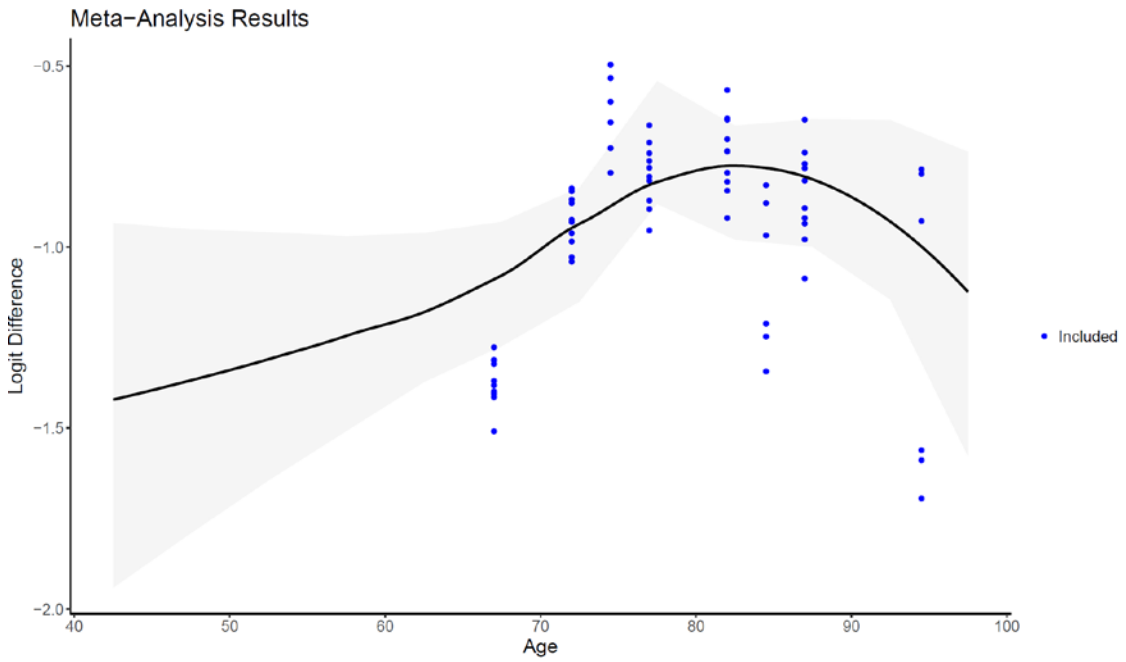
We also split datapoints where the age range was greater than 25 years using the global age pattern.

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 who 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. US MarketScan data were separately crosswalked to standardise 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 to 0.61)	0.51
Algorithm diagnosis criteria (AGECAT)	Alt		0.08 (–0.59 to 0.74)	0.50
US MarketScan	Alt		–0.95 (–1.61 to –0.28)	0.50
NIA-AA diagnosis criteria	Alt		0.51 (–0.16 to 1.17)	0.53
10/66 algorithm diagnosis criteria	Alt		0.97 (0.30 to 1.64)	0.50
GP records used for diagnosis	Alt		–1.21 (–1.88 to –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 summarise country-level covariates used in each of these DisMod models.

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

Covariate	Type	Exponentiated beta (95% uncertainty interval)
Smoking prevalence (age-standardised)	Prevalence	2.71 (1.03–7.36)
Educational attainment (age-standardised)	Prevalence	0.92 (0.92–0.92)

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

Covariate	Type	Exponentiated beta (95% uncertainty interval)

Smoking prevalence (age-standardised)	Prevalence	1.00 (1.00–1.01)
Educational attainment (age-standardised)	Prevalence	0.92 (0.92–0.92)

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893 As mentioned previously, the estimation of morbidity due to dementia occurs in conjunction with the
894 mortality estimation. Additional details on this process can be found in the appendix to the GBD Causes
895 of Death summary paper.

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