Appendix:

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Studies on Relative Risk of All-Cause Mortality

Study	Location	Cohort	Years	Exposure(s)	Exposure Ascertainment	Mortality Ascertainment	Method	Control Variables
Dolbhammer & Barth (2018)	Germany	AOK Public Health Insurance Population	2004 to 2013	Dementia	ICD codes identified in AOK insurance records, with validation procedure to avoid overestimation	Date of death in AOK insurance records	Cox proportional hazard model	Neurodegenerative diseases, major risk factors including diabetes, hypertension and kidney disease, cerebrovascular disease, cancer, extremity injuries, acute diseases, including pneumonia, and pulmonary embolism
Luck et al. (2017)	Germany	German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe)	2003 to 2014	Cognitive Impairment	Individuals were assessed as cognitively impaired if the results of the Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia and Dementia of other Aetiology (SIDAM) fell below age- and education-specific norms by more than 1 standard deviation	Dates of death were obtained from relatives, GP, or from the local registry offices	Cox proportional hazard model	Age, gender, education, smoking, alcohol consumption, APOE e4 status, IADL impairment, comorbidities including hypertension, diabetes, stroke, hypercholesterolemia, hyperlipidemia, and carotid artery stenosis
Georgakis et al. (2016)	Greece	Velestino Study	2005 to 2013	Mild to Moderate and Moderate to Severe Cognitive Impairment	Patients scoring between 18 and 23 were classified with mild to moderate cognitive impairment. Individuals scoring below 18 on the MMSE were classified with moderate to severe cognitive impairment	Data were derived from death certificates in collaboration with the Local Registry Office	Cox proportional hazard model	Age, gender, educational level, social activity, family support, BMI, alcohol intake, hypertension, diabetes mellitus type 2, hypercholesterolemia, cardiovascular disease, cancer, depressive symptoms

Naseer et al. (2016)	Sweden	Swedish National Study of Aging and Care-Blekinge (SNAC-B)	2001 to 2003	Dementia	A single-item self-administered questionnaire was used. For subjects with dementia proxy measures were utilized.	Mortality data were collected from the population mortality register	Cox proportional hazard model	Age, physical activity, housing, cardiovascular disease, diabetes, ADL dependency
Wu et al. (2014)	Taiwan	National Health Insurance Database	2000 to 2010	Dementia	ICD codes identified in the NHI Database, cases needed at least three outpatient clinic visits or one admission for dementia	Deaths were identified as a withdrawal from insurance	Incidence rate ratio	None
Paddick et al. (2015)	Tanzania	Hai Demographic Surveillance Site	2010 to 2014	Mild Cognitive Impairment and Dementia	The community screening instrument for dementia was administered and 100% of those with poor performance, 50% of those with moderate performance and 5% with good performance were more formally assessed for dementia. Dementia diagnosis was based on DSM-IV criteria and MCI diagnosis was based on international consensus (Winblad, 2004).	Data on mortality were collected at each follow-up visit	Cox proportional hazard model	Age, gender and education
Bahat et al. (2015)	Turkey	Geriatrics Outpatient Clinic at a University Hospital	1999 to 2010	Mild Cognitive Impairment	MMSE scores of 24 or below were considered impaired	Mortality was assessed through the official website of the registration office	Cox proportional hazard model	Age, sex, ADL impairment, diabetes, hyperlipidemia, total number of diseases
Meng & D'Arcy (2012)	Canada	Canadian Study of Health and Aging	1991 to 2001	Cognitive Impairment Not Dementia and Dementia	Cognitive status was evaluated at consensus diagnosis by a neuropsychologist, specialist physician and nurse following DSM-III-R criteria	Not specified	Cox proportional hazard model	Age, sex, marital status, race, education, comorbidity (yes/no)

Villarego et al. (2011)	Spain	NEDICES Cohort Study	1994 to 2007	Dementia	The screening phase included the MMSE and the Pfeffer Functional Activities Questionnaire. Individuals who screened positive were examined by trained neurologists and were diagnosed according to DSM-IV criteria.	The date of death was obtained from the National Population Register of Spain	Cox proportional hazard model	Age, sex, education, comorbidity index
Beeri & Goldbourt (2011)	Israel	Israel Ischemic Heart Disease Project	1999 to 2005	Dementia	The Modified Telephone Interview for Cognitive Status was used as a screening test, and subjects with a TICS-m score of 27 or lower were assessed at their residencies by a physician and were diagnosed using DISM-IV criteria	Mortality information was collected by matching the national ID number with the Israel National Population Registry	Cox proportional hazard model	Age, SES, blood pressure, total cholesterol, smoking status,
Steenland et al. (2010)	Georgia, USA	Neurology Department at Emory Wesley Woods health Center	1993 to 2006	Mild Cognitive Impairment, Lewy body dementia, Probable Alzheimer's disease, Frontotemp oral dementia	Diagnoses are the clinical diagnoses at the time of last visit.	Mortality follow-up was conducted through matching patient IDs with the National Death Index	Cox proportional hazard model	Age, sex, race, education
Lavretsky et al. (2010)	California, USA	Ischemic Vascular Dementia Program Project	1996 to 2008	Mild Cognitive Impairment and Dementia	Cognition was evaluated using a neuropsychological battery and diagnoses were made at a multidisciplinary case conference accoriding to DSM-IV criteria	Not specified	Cox proportional hazard model	None

Wilson et al. (2009)	Illinois, USA	Chicago Health and Aging Project	1998 to 2008	Mild Cognitive Impairment, Alzheimer's disease, other dementia	Each participant had a structured, uniform clinical evaluation and complete neurological examination and cognitive function testing. An experienced physician classified individuals with dementia and AD using the NINCDS-AD criteria. MCI was based on education-specific cutoff scores for each domain for those without a dementia diagnosis	Death information was compiled through attempted follow-ups, obituaries in local newspapers. All deaths were also verified using death records from the National Death Index	Cox proportional hazard model	Age, sex, education, race
Sund-Levander (2007)	Sweden	Sample of special housing for the elderly	2000 to 2003	Dementia	Diagnoses were noted on clinical medical records	Mortality information was abstracted from death certificates	Cox proportional hazard model	Age, ADL status, BMI, Smoking, Chronic Diseases
Ganguli (2005)	Pennsylvania, USA	The Monongahela Valley Independent Elders Survey	1987 to 2002	Alzheimer's disease	Participants who were classified as cognitively impaired at screening underwent the assessment protocol of the Consortium to Establish a Registry for Alzheimer's Disease and the University of Pittsburgh Alzheimer Disease Research Center protocol. Consensus diagnosis was used to classify patients using the NINCDS-AD criteria	Mortality information was derived from death certificates	Cox proportional hazard model	Age, sex
Nitrini (2005)	Brazil	Catanduva, Sao Paulo	1997 to 2000	Dementia	All subjects who screened positive for diagnostic evaluation completed a neuropsychological battery and the CDR scale. All data were then analyzed by three neurologists who made diagnoses according to the DSM-IV criteria.	Mortality information was obtained from relatives or through the town obituary records	Cox proportional hazard model	Age, visual impairment, cardiovascular disease history

Tschanz et al. (2004)	Utah, USA	Cache County Study on Memory and Aging	1995 to 2001	Dementia	Screened subjects with the 3MS and IQCODE questionnaires; those flagged by screen and everyone over 90 were evaluated further. Findings were reviewed by a board-certified geriatric psychiatrist and neuropsychologist who assigned diagnoses according to DSM-III-R criteria	Mortality information was obtained by reviewing local obituaries and from quarterly reports from the Utah Department of Vital Statistics	Cox proportional hazard model	Age, education, APOE4, asthma, cerebrovascular disease, coronary heart disease, hypercholesterolemia, hypertension, pneumonia, peptic ulcer disease, pulmonary disease, head injury, Parkinson's disease, diabetes
Yamada et al. (2004)	Japan	Adult Health Study of Hiroshima	1992 to 1999	Alzheimer's disease and Vascular dementia	All subjects were administered cognitive function tests, neurological examinations and informant questionnaires and DSM-III-R criteria were applied	Deaths were confirmed thought he Japanese family registration system and information was collected from death certificates	Poisson regression analysis	Age, sex, heart disease, stroke and cancer history
Noale et al. (2003)	Italy	Italian Longitudinal Study on Aging	1992 to 1996	Dementia	Participants who scored less than 24 on the MMSE or for whom proxy respondents reported previous diagnoses were examined further. In the second phase, medical records were reviewed and participants were examined by a specialist for the diagnosis of dementia according to DSM-III-R criteria	For individuals who had died before the follow-up assessment, death certificates were obtained from the national registry	Cox proportional hazard model	Age, sex

Qiu et al. (2001)	Sweden	Kungsholmen Project	1987 to 1998	Dementia and Alzheimer's disease	Participants underwent neurological and physical examination as well as cognitive testing. DSM-III-R criteria were used to diagnose dementia and all diagnoses were reviewed by a specialized clinician. Diagnosis of Alzheimer's disease required gradual onset, progressive deterioration and lack of any other specific causes of dementia. For deceased subjects, clinical records, discharge diagnoses and death certificates were reviewed	Mortality was ascertained through death certificates	Cox proportional hazard model	Age, sex, MMSE baseline score, comorbidity, socioeconomic status
Helmer et al. (2001)	France	Personnes Agees Quid (PAQUID)	1988 to 1998	Dementia and Alzheimer's disease	Participants who met the criteria for memory impairment, impairment of at least one other cognitive function and interference with social or professional life based on a series of psychometric tests were seen by a senior neurologist to diagnosed dementia based on DSM-II-R criteria and Alzheimer's disease based on NINCDS-ADRDA criteria	Mortality was assessed from death certificates from the national registry of mortality statistics	Cox proportional hazard model	Age, sex, education, comorbidity index, baseline ADL dependency

Witthaus et al. (1999)	Netherlands	The Rotterdam Study	1999 0 to 1992	Dementia	The MMSE and Geriatric Mental State Schedule were used to screen participants and those who screened positive underwent further testing based on the Cambridge Examination for Mental Disorders of the Elderly. Diagnoses were based on all available information and were assigned by an expert panel and based on DSM-III-R criteria	Not specified	Mortality Rate Ratios	None
Katzman et al. (1994)	China	Population Survey in Shanghai	1987 to 1992	Alzheimer's disease, Vascular dementia and other dementia	Participants were screened with the Chinese version of the MMSE and those who screened positive based on education specific cutoffs underwent an intensive evaluation. Dementia was diagnosed based on DSM-III criteria and Alzheimer's disease was diagnosed based on NINCDS-ADRDA criteria by consensus diagnosis	Mortality data for all initial participants was obtained from the Shanghai registry of vital data	Cox proportional hazard model	Age, sex, education, chronic conditions

Beydoun et al. (2013)	Maryland, USA	Baltimore Longitudinal Study of Aging	1958 to 2009	Mild Cognitive Impairment, dementia, Alzheimer's disease	All participants are reviewed annually if they screen positive on the Blessed Information Memory Concentration Test or the Dementia Questionnaire, or if their Clinical Dementia Rating score is 0.5 or higher using subject or informant report. Diagnoses for dementia are determined based on DSM-III-R criteria and Alzheimer's disease by NINCDS-ADRDA criteria. MCI was diagnosed when cognitive impairment was evident without any significant functional loss	All participants were followed for vital status and a consensus of three physicians determined cause and date of death using death certificates, hospital and physician records and autopsy data as available	Cox proportional hazard model	Age, sex, race, education, smoking status, BMI, APOE4
James et al. (2014)	United States	Religious Orders Study and Rush Memory and Aging Project	1994 to 2013	Dementia and Alzheimer's disease	Participants were evaluated annually, including a medical history, neurologic examination and cognitive testing. Diagnoses were the result of a three-stage process with computer scoring of cognitive tests, followed by clinical judgment by neuropsychologist and finally diagnostic classification by an experienced clinician. Diagnoses were made given the NINCDS-ADRDA criteria	Dates of death are largely known due to the high rates of autopsy. Deaths are occasionally detected during quarterly contacts with an informant, and in a small number of cases through the Social Security Death Index	Cox proportional hazard model	Age, sex, race, parent study

Fitzpatrick et al. (2005)	United States	Cardiovascular Health Study	1992 to 2002	Dementia, Alzheimer's disease, vascular dementia	Those failing the screening with 3MSE and other parameters were invited back fro detailed neuropsychological testing. A committee of neurologists and psychiatrists from all four centers evaluated data to classify dementia. The clinical definition required progressive or static deficit impairing activities of daily living, with impairments in two cognitive domains. Type of dementia was classified with NINCDS-ADRDA criteria	Deaths were identified during surveillance calls, during scheduling calls or through local daily newspaper obituaries	Cox proportional hazard model	Age, sex, race
Koller et al. (2012)	Germany	Gmünder ErsatzKasse (GEK) health insurance company	2005 to 2011	Dementia	Dementia patients were identified by those who had at least one ICD-10 code for dementia in ambulatory care in at least three of four consecutive quarters	Not specified	Cox proportional hazard model	Age, sex, level of care dependency, Elixhauser index for comorbidities
Rait et al. (2010)	United Kingdom	The Health Improvement Network (THIN)	1990 to 2007	Dementia	All adults 60 years or over with a first ever code for dementia	Mortality data was derived from primary care records	Conditional Poisson model	Age, sex, deprivation index, smoking, alcohol, chronic disease

Guhne et al. (2006)	Germany	Leipzig Longitudinal Study of the Aged (LEILA75+)	1997 to 1999	Dementia	The Structured Interview for Diagnosis of Dementia of Alzheimer-type, Multi-infarct Dementia and Dementia of Other Etiology (SIDAM) was administered and the diagnostic algorithm was used to derive diagnoses of dementia, Alzheimer's disease and vascular dementia. Consensus conferences were held on each case and clinical diagnosis was made according to DSM-IV criteria	Mortality data were obtained from structured proxy interviews or from the official registry office	Cox proportional hazard model	Age, sex, education, institutionalization, and co-morbidity
Aevarsson, Savnborg & Skoog (1998)	Sweden	Longitudinal Gerontological and Geriatric Population Studies	1985 to 1993	Dementia and Alzheimer's disease	Diagnosis of dementia was based on clinical and neuropsychiatric examination and informant interview using DSM-III-R criteria. Alzheimer's disease was diagnosed based on NINCDS-ADRDA criteria	Mortality data was available from the census register	Cox proportional hazard model	Age, sex, lung disease, cancer, hypertension, myocardial infarction, cerebrovascular disease, congestive heart failure
Cruz-Oliver et al. (2012)	Missouri, USA	Geriatric Research, Education and Clinical Center Veterans Affairs Hospital	2003 to 2011	Mild Cognitive Impairment	Participants were considered impaired if they scored 24 or lower on the MMSE	Vital status was determined by the presence of a date of death listed in the electronic medical record. Death was confirmed through the review of death certificates	Cox proportional hazard model	Age, number of anticholinergic medications, and comorbidities

Baldereschi et al. (1999)	Italy	Italian Longitudinal Study on Aging	1992 to 1995	Dementia	Those who score less than 24 on the MMSE were invited for further examination. Participants were then diagnosed according the DSM-III-R criteria and doubtful cases were extensively reviewed by a panel of senior clinicians	Participants were followed up by telephone interview to determine vital status and death certificates were collected for each individual who died	Cox proportional hazard model	Age, sex, institutionalization, education, chronic conditions
Tsuji et al. (1995)	Japan	Sendai Longitudinal Study of Aging	1988 to 1991	Dementia	Those who screened positive were invited for a physical and psychiatric examination by the trained public health nurses. Based on information collected, diagnostic evaluation was made according to DSM-III-R criteria by a committee of psychiatrists	Deaths were identified through the residents registration card and verified by death certificates	Cox proportional hazard model	Age, sex
Matsui et al. (2008)	Japan	Hisayama Study	1985 to 2002	Dementia	Subjects who tested below the cutoff scores of either the Hasegawa dementia scale, Hasegawa revised dementia scale or the MMSE, patients were invited for comprehensive investigations, including interviews of the families or attending physicians, physical and neurological exams and a review of clinical records. Diagnosis of dementia was based on DSM-III-R criteria	Not specified	Cox proportional hazard model	Age, sex

Dementia Prevalence Estimation

Case definition

Dementia is a progressive, degenerative, and chronic neurological disorder typified by memory impairment and other neurological dysfunctions. For the purposes of GBD 2017, 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

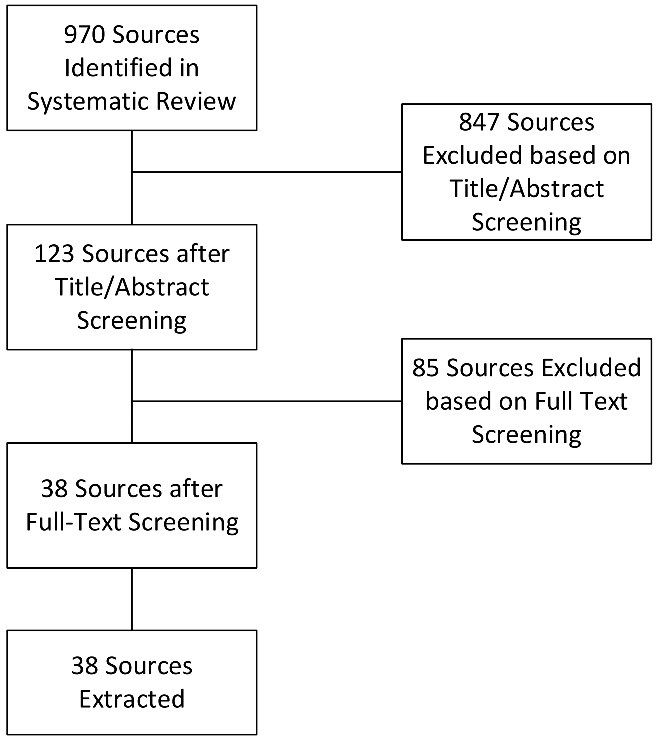
A wide array of diagnostic and screening instruments exists, including Clinical Dementia Rating scale (CDR), Mini Mental State Examination (MMSE), and the Geriatric Mental State (GMS). For severity rating purposes we use the CDR as the reference. The relevant ICD-10 codes for dementia are F00, F01, F02,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

Input data

To inform our estimates of the prevalence of dementia we used prevalence data from surveys, and administrative data such as claims sources.

An updated systematic review was conducted covering September 2016 to August 2017, and search terms were set to capture studies for all dementia, including its sub-types[1]. The search yielded 970 initial hits and 38 were marked for extraction. Inclusion criteria comprised studies that reported prevalence, incidence, remission rate, excess mortality rate, relative risk of mortality, standardized mortality ratio, or with-condition mortality rate. Studies with no clearly defined sample were excluded. A flow chart documenting this review is displayed below.

[1] ((dementia[Title/Abstract]) AND (incidence[Title/Abstract] OR prevalence[Title/Abstract] OR epidemiology[Title/Abstract])) AND ("2016/09/01"[Date - Publication] : "2017/08/29"[Date - Publication])



Additionally, a table describing the density and distribution of the epidemiological data available for GBD 2017 is presented below:

	Prevalence	**Incidence**	**Mortality Risk**
Site-years (total)	477	115	23
Number of countries with data	45	24	17
Number of GBD regions with data (out of 21 regions)	17	10	10
Number of GBD super-regions with data (out of 7 super-regions)	7	4	6

Studies with age and sex detail separately were split into age and sex specific data points. We also split data points where the age range was greater than 20 years using the age pattern from the United States, where we had the most detail by age.

We also included claims data from the US for 2010, 2011, 2012, 2014 and 2015. The algorithm used to derive prevalence from claims data counted a prevalent case where an individual has one inpatient visit, two outpatient visits, or one outpatient and one inpatient visit.

Prevalence Model (Total Dementia)

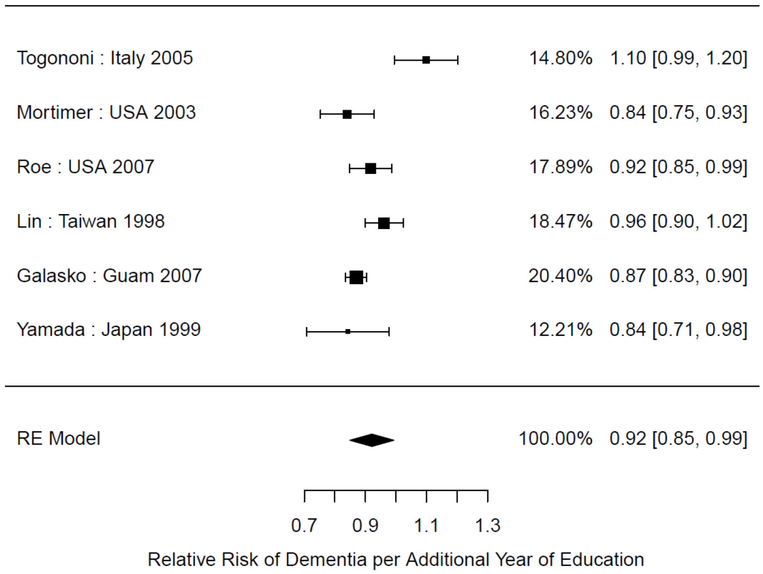
To model prevalence, we ran a DisMod-MR 2.1 model with all data on incidence, prevalence, and mortality risk (RR, SMR, or with-condition mortality rates) and a setting of zero remission and extracted 2017 prevalence by age, sex, and geography. To account for potential systematic differences between medical claims and survey data, we added a covariate to crosswalk US claims data and also added a covariate for European GP data. Additionally, to account for systematic differences in different methods of case ascertainment between different studies we included study level covariates on whether or not studies used a doctor-given diagnosis, whether or not they used clinical records to ascertain a diagnosis and whether or not a study used an algorithmic diagnosis.

We also did not allow random effects in the model in order to reduce spurious inflation of regional differences due to differences in measurement and measurement error. Because of lack of consistency between prevalence and incidence data, we excluded incidence data from the final model. In a few locations we found good consistency between prevalence and incidence and these were locations where incidence and prevalence were collected as part of the same study. In other locations (Beijing, Australia, Italy, Canada, various states in the US, Mexico, and Nigeria) we noted that DisMod-MR 2.1 was pushing the fit above the available prevalence data and below incidence – "averaging the difference." In all cases the incidence and prevalence data were collected by different studies. We decided to drop the incidence estimates as measuring incidence of dementia when symptoms are still mild is more prone to measurement bias than measuring prevalence when the diagnosis has become more obvious over time.

The table below provides additional information on the country covariates and study-level covariates used in this model, as well as beta and exponentiated beta values.

Variable	Measure	Beta	Exponentiated Beta Value (CI)
Mean years of education, age-standardized	prevalence	-0.083	0.92 (0.92 to 0.92)
Smoking prevalence, age-standardized both sex	prevalence	1.00	2.71 (1.03 to 7.36)
US claims data	prevalence	-0.51	0.60 (0.59 to 0.61)
European GP Data	prevalence	-0.86	0.42 (0.39 to 0.46)
Diagnosed using cutoff score algorithm	prevalence	0.16	1.18 (1.11 to 1.25)
Diagnosed using only clinical records	prevalence	-0.17	0.84 (0.79 to 0.91)

We did a meta-analysis of the effect of education (in years) on dementia to set bounds on the covariate value. A literature search yielded 6 sources reporting specifically the effect of a single year of education. The meta-analysis estimated a relative risk of 0.92 for each additional year of education, which was used to set bounds on the country-level covariate in DisMod. The forest plot is shown below.



As described above, we used a crosswalk to standardize the claims data relative to existing literature data. This year we also added study level covariates for studies that did not complete an in-person doctor diagnosis, that diagnosed dementia using a cutoff score algorithm, or that diagnosed dementia using only clinical records. We tested all covariates and where a covariate was significant we retained it in the final model. The covariate on no in-person doctor diagnosis was not significant so was added as a z-cov, which increases the uncertainty. Age-standardized 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.

Correction for Dementia caused by other GBD 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, HIV, 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.

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 were unable to adjust for causes not included in ADAMS (Down’s syndrome, HIV).

We first fit logistic regression models predicting the outcome of dementia given each exposure, with an additional covariate on age. We tested adjusting the stroke regression model for potential confounders including BMI, smoking and blood pressure, but as none of these were significant in the expected direction, we did not retain them in the model. Below is a table showing the exponentiated betas, for the condition and age effects for the three regression models.

Regression	Condition Effect (SE)	Age Effect (SE)
Stroke	4.2 (1.24)	1.15 (1.02)
Parkinson’s disease	5.74 (2.47)	1.16 (1.02)
TBI	1.59 (1.31)	1.16 (1.02)

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.

End-Stage Disease Code Lists

Decubitus:

ICD-9: 707.0/2/8/9, ICD-10: L89 (all)

Malnutrition:

ICD-9: 262 (all), 263 (all), 261 (all), ICD-10: E41 (all), E43 (all), E44 (all), E46 (all)

Pneumonia:

ICD-9: 507.0, 514 (all), 482 (all), 483 (all), 486 (all), 485, ICD-10: J69 (all), J18 (all), J15 (all)

Sepsis:

ICD-9: 038 (all), ICD-10: A40 (all), A41 (all)

Fall from Bed:

ICD-9: E884.4, ICD-10: W06 (all)

UTI:

ICD-9: 599.0, 590.1 (all), 595, 595.0 ICD-10: N10 (all), N30, N30.0, N39.0

Senility:

ICD-9: 797 (all), ICD-10: R41.81, R54 (all)

Dehydration:

ICD-9: 276.5 (all), ICD-10: E86 (all)

Sodium Imbalance:

ICD-9: 276.0/1/8/9, ICD-10: E87.0/1/6/8

Muscular Wasting:

ICD-9: 728.2, ICD-10: M62.5 (all)

Bronchitis:

ICD-9: 466 (all), ICD-10: J20 (all)

Dysphagia:

ICD-9: 787.2 (all), ICD-10: R13 (all)

Hip Fracture:

ICD-9: 820 (all), ICD-10: S72.0 (all), S72.1 (all), S72.2 (all)

Bedridden:

ICD-9: V4984, ICD-10: Z74.0 (all)

Meta-Regression Model

Developed by Peng Zheng and Aleksandr Arakvin (March 29, 2019)

Mixed Effects Model for Meta-Regression

In this section, we formulate the meta-regression problem in the mixed effects setting, and explain the difference between a closely related and well-known simple linear mixed effects model. Meta-regression is classically formulated as follows:

$$y_i = \langle \boldsymbol{x_i}, \boldsymbol{\theta}^* \rangle + u_i + \varepsilon_i$$

where θ_j^* any regression coefficients, so $x_i = [1; x_{i,1}; \dots; x_{i,n}]$, $u_i \sim \mathcal{N}(0, \tau_i)$is a common error source across studies with variance τ_i, and $\varepsilon \sim \mathcal{N}(0, \sigma_i^2)$ are reported study-specific error sources with known variances σ_i^2 . The term τ_i in the simplest case is an unknown constant γ that does not depend on i. In general

$$\tau_i = \langle z_i, \gamma \rangle$$

is a function of known covariates z_i that vary by study and unknown multipliers γ common to all studies. The τ is a sufficient statistic, so we can state the likelihood terms using τ , even though the parameters we are fitting are the γ. The goal of meta-analysis is to estimate $\boldsymbol{\theta}^*$ and γ^* from observations. The mixed effects framework provides a natural statistical model which can be used for this inference. Under the mixed effects model, variables are partitioned into three groups:

- Fixed effects: θ, γ
- Random effects: u_i
- Measurement error: ε_i

The joint distribution of figured and random effects is given by

$$p(\boldsymbol{\theta}, \tau, \boldsymbol{u}|\boldsymbol{y}) = p(\boldsymbol{\theta}, \tau|\boldsymbol{u}, \boldsymbol{y}) p(\boldsymbol{u}|\boldsymbol{y}) = \prod_{i=1}^{m} \frac{1}{2\pi\sqrt{\sigma_i^2 \gamma^2}} exp\left(-\frac{(y_i - \langle \boldsymbol{x_i}, \boldsymbol{\theta} \rangle - u_i)^2}{2\sigma_i^2}\right) exp\left(-\frac{u_i^2}{2\tau_i^2}\right)$$

Integrating out the random effects, and taking the negative log of the resulting distribution, we arrive at an equivalent maximum likelihood formulation that does not depend on u, but only depends on θ and τ.

$$\begin{aligned}\mathcal{M}(\theta, \tau|y) = & -\ln\left(\int_{\mathbb{R}^m} p(\theta, \tau, u|y) du\right) \\ & = \sum_{i=1}^{m} \frac{1}{2(\tau_i + \sigma_i^2)} (y_i - \langle x_i, \theta \rangle)^2 \\ & + \frac{1}{2} \ln\left(2\pi(\tau_i + \sigma_i^2)\right) = \frac{1}{2} \ln|2\pi V(\tau)| + \frac{1}{2} (\boldsymbol{y} - \mathbf{X}\boldsymbol{\theta})^T \boldsymbol{V}(\tau)^{-1} (\boldsymbol{y} - \mathbf{X}\boldsymbol{\theta}),\end{aligned}$$

with variance model

$$\boldsymbol{V}(\tau) = \begin{bmatrix} \sigma_1^2 + \tau_1 & & \\ & \ddots & \\ & & \sigma_m^2 + \tau_m \end{bmatrix}.$$

Additionally, the ML estimates can be updated using prior information on γ.

Detail for Covariates Used in Meta-Regression Model

We give some specific detail of the evidence score model, specifying variables that detect bias and affect heterogeneity

$$y_i = \langle \alpha^*, x_i \rangle + \langle \beta^*, \chi_i \rangle + u_i + \varepsilon_i \ , i = 1, \dots, m$$

where $\alpha^*$are within-study covariates (e.g. dose), β^* are between-study covariates (e.g. study design) that may detect and explain bias, $u_i \sim \mathcal{N}(0, \tau_i)$ includes common error source across studies with $\tau_i = \langle z_i, \gamma \rangle$ (containing explained and unexplained heterogeneity), while ε_i is the study specific error source with known variance σ_i^2. Our goal is to estimate α^*; β^* and γ^*.

To match the previous section, we let $\theta := \begin{bmatrix} \alpha \\ \beta \end{bmatrix}$. We abuse notation by letting X represent both the standard covariates ($\mathrm{X}\alpha$) and the union of standard covariates and bias covariates ($\mathrm{X}\theta$).

Multiple measurements within the same study

The likelihood changes when we have multiple measurements present within the same study. Let i denote the study id, and j represent the measurement id. The jth measurement of ith study follows,

$$y_{ij} = \langle \boldsymbol{x_i}, \boldsymbol{\theta} \rangle + u_{\boldsymbol{i}} + \varepsilon_{ij}, \quad j = 1, \dots, n_i.$$

where random effect $u_i \sim \mathcal{N}(0, \tau_i^2)$, measurement error $\varepsilon_{ij} \sim \mathcal{N}\left(0, \sigma_{ij}^2\right)$ and the variance model of the random effect satisfies, $\tau_i^2 = \langle z_i, \gamma \rangle$. The computations simplify if we only allow $\sigma_{ij} = \sigma_i$, that is, force all observation models coming from within the same study to have the same variance. Howeverthere is general flexibility in the variance model.

Writing the model in vector notation, we have

$$\boldsymbol{y_i} = \mathbf{X}_{\boldsymbol{i}} \boldsymbol{\theta} + u_i \mathbf{1} + \boldsymbol{\varepsilon_i}.$$

Robust Extension via Trimming

Trimming estimators is a general methodology for robust estimation[1,2]. Given any likelihood problem of form

$$\min_{\boldsymbol{\theta}, \gamma} \sum_{i=1}^{m} f_i(\boldsymbol{\theta}, \gamma) + R(\boldsymbol{\theta}, \gamma),$$

With f_i as the contribution from the ith datapoint, while $R(\boldsymbol{\theta}, \gamma)$ collects all terms that do not depend on the data. Then the trimmed estimator is formulated as

$$\min_{\boldsymbol{\theta},\gamma,\boldsymbol{w}} \sum_{i=1}^{m} w_i f_i(\boldsymbol{\theta},\gamma) + R(\boldsymbol{\theta},\gamma), \;\; 0 \le w_i \le 1, \;\; \mathbf{1}^T\boldsymbol{w} = h$$

Where $h \le m$ is the estimate of inlier datapoints. The set

$$\Delta_h := \{\boldsymbol{w}: 0 \le w_i \le 1, \mathbf{1}^T\boldsymbol{w} = h\}$$

Is known as the *capped simplex,* since it is the intersection of the simplex with the unit box. The estimator is compactly written as

$$\min_{\boldsymbol{\theta},\boldsymbol{\gamma}.\boldsymbol{w}\epsilon\Delta_h} \sum_{i=1}^{m} w_i f_i(\boldsymbol{\theta},\gamma) + R(\boldsymbol{\theta},\gamma).$$

Optimization

We develop a customized efficient algorithm that uses variable projection[3–5]. In particular we separate variables into two tiers: $(\boldsymbol{\theta},\gamma)$, which have a low dimension but inform a highly nonlinear constrained problem, and $\boldsymbol{w}$, which have a high dimension but affect the problem in a simple way.

The variable projection framework allows us to leverage a third-party solver, IPOPT, to project out $(\boldsymbol{\theta}.\gamma)$, and view the entire problem only in terms of $\boldsymbol{w}$; a problem we then solve directly[6].

Consider the joint likelihood

$$\min_{\boldsymbol{\theta},\boldsymbol{\gamma}.\boldsymbol{w}\epsilon\Delta_h} \sum_{i=1}^{m} L(\boldsymbol{\theta},\gamma,\boldsymbol{w}) + R(\boldsymbol{\theta},\gamma)$$

Where L is a maximum likelihood, while R includes priors and constraints. We define the value function $v(\boldsymbol{w})$ and optimal values $\big(\boldsymbol{\theta}(\boldsymbol{w}),\gamma(\boldsymbol{w})\big)$ by

$$v(\boldsymbol{w}) = \min_{\boldsymbol{\theta},\boldsymbol{\gamma}} L(\boldsymbol{\theta},\gamma.w) + R(\boldsymbol{\theta},\gamma)$$

$$\big(\boldsymbol{\theta}(\boldsymbol{w}),\gamma(\boldsymbol{w})\big) = \arg\min_{\boldsymbol{\theta},\boldsymbol{w}} L(\boldsymbol{\theta},\gamma,w) + R(\boldsymbol{\theta},\gamma).$$

The term *variable projection* refers to partially minimizing over $\boldsymbol{\theta}$ and γ. We can use IPOPT to solve this problem for each fixed $\boldsymbol{w}$, thereby reducing the problem to

$$\min_{\boldsymbol{w}\in\Delta_h} v(\boldsymbol{w}).$$

Where $v(\boldsymbol{w})$ is differentiable with derivative given by

$$\nabla v(\boldsymbol{w}) = \partial_{\boldsymbol{w}} L|_{\boldsymbol{\theta}=\boldsymbol{\theta}(\boldsymbol{w}),\gamma=\gamma(\boldsymbol{w}),\boldsymbol{w}}$$

The top level algorithm is simply a projected gradient method

$$\boldsymbol{w}^+ = \mathrm{proj}_{\Delta_h}\big(\boldsymbol{w} - \alpha\nabla v(\boldsymbol{w})\big)$$

for an appropriately chosen step size α. Each evaluation of ∇v requires a full minimization step of $L + R$ with respect to $(\boldsymbol{\theta}, \gamma)$ using IPOPT. The capped simplex Δ_h is a closed convex set with a simple projection; proximal gradient with line search converges in this case.

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