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The Burden of Dementia due to Down Syndrome, Parkinson's Disease, Stroke, and Traumatic Brain Injury: A Systematic Analysis for the Global Burden of Disease Study 2019

GBD 2019 Dementia Collaborators

Abstract

Background: In light of the increasing trend in the global number of individuals affected by dementia and the lack of any available disease-modifying therapies, it is necessary to fully understand and quantify the global burden of dementia. This work aimed to estimate the proportion of dementia due to Down syndrome, Parkinson's disease, clinical stroke, and traumatic brain injury (TBI), globally and by world region, in order to better understand the contribution of clinical diseases to dementia prevalence.

Methods: Through literature review, we obtained data on the relative risk of dementia with each condition and estimated relative risks by age using a Bayesian meta-regression tool. We then calculated population attributable fractions (PAFs), or the proportion of dementia attributable to each condition, using the estimates of relative risk and prevalence estimates for each condition from the Global Burden of Disease Study 2019. Finally, we multiplied these estimates by dementia prevalence to calculate the number of dementia cases attributable to each condition.

Findings: For each clinical condition, the relative risk of dementia decreased with age. Relative risks were highest for Down syndrome, followed by Parkinson's disease, stroke, and TBI. However, due to the high prevalence of stroke, the PAF for dementia due to stroke was highest. Together, Down syndrome, Parkinson's disease, stroke, and TBI explained 10.0% (95% UI: 6.0–16.5) of the global prevalence of dementia.

Interpretation: Ten percent of dementia prevalence globally could be explained by Down syndrome, Parkinson's disease, stroke, and TBI. The quantification of the proportion of dementia attributable to these 4 conditions constitutes a small contribution to our overall understanding of what causes dementia. However, epidemiological research into modifiable risk factors as well as basic science research focused on elucidating intervention approaches to prevent or delay the neuropathological changes that commonly characterize dementia will be critically important in future efforts to prevent and treat disease.

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The 'GBD 2019 Dementia Collaborators' are listed in the online supplementary material www.karger.com/doi/10.1159/000515393.

Statement of Ethics

This GBD study used de-identified data, and the waiver of informed consent was reviewed and approved by the University of Washington Institutional Review Board (Study 9060).

Keywords

Dementia; Global health; Burden of disease; Meta-analysis; Public health

Introduction

Over the past few decades, there have been large increases in the numbers of people affected by dementia due to population aging and population growth [1–3]. These rising trends in the global burden of dementia are only expected to continue into the future [4–6]. Given these increases and the lack of any significant progress toward disease-modifying therapies, increasing attention has been directed toward dementia prevention and the development of a better understanding of disease etiology [7].

Recently, modifiable risk factors for dementia have received increasing attention, with the 2020 update to the Lancet Commission report concluding that 39.7% of dementia can be attributed to 12 major modifiable risk factors encompassing a range of modifiable lifestyle factors and clinical conditions [8]. Additionally, evidence based on autopsy studies has pointed to several neuropathological features, including neuritic and diffuse plaques, neurofibrillary tangles, and small vessel vascular disease, as the key drivers of dementia at the biological level [9–11]. However, these analyses do not directly address the fraction of dementia that can be etiologically caused by other clinical diseases, such as clinical stroke (stroke) or Parkinson's disease. Interactions with the health system for the diagnosis or treatment of these other clinical conditions may provide a critical delivery point for interventions designed to prevent or delay the development of dementia in individuals with these conditions.

This paper will specifically focus on dementia due to stroke, Parkinson's disease, Down syndrome, and traumatic brain injury (TBI). These diverse conditions were selected as the set of clinical conditions currently quantified within the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2019 and for which there is evidence supporting a quantifiable and potentially causal association with dementia [12–16]. Evidence suggesting a link between these conditions and dementia may indicate that preventing or treating these conditions could delay the onset of dementia. Risk factors for some of these conditions may also overlap with known modifiable risk factors for dementia, strengthening the evidence for previous identified associations.

Previous efforts to quantify the relationships between dementia and clinical conditions such as stroke and Parkinson's disease have remained isolated, and results have not been summarized across disease topics [12, 16–19] Additionally, while recent work has shown that the proportion of dementia attributable to lifestyle factors may vary substantially by geography, the impact of differences in the prevalence of clinical disease by geography on the proportion of dementia prevalence that can be attributed to these conditions has not previously been explored [20]. This paper aims to synthesize the evidence on the association between dementia and each of these disease categories and to calculate the proportion of dementia attributable to each disease by age and sex, both globally and by world region.

Materials and Methods

The entity “dementia” as referenced in this paper is equivalent to the disease category of “Alzheimer’s disease and other dementias” within the Global Burden of Disease (GBD) study. The case definition for dementia is a clinical or adjudicated diagnosis of dementia using *Diagnostic Statistical Manual of Mental Disorders* (DSM) (III, III-R, IV, or 5) or International Classification of Diseases (ICD) definitions from within population-representative studies [21, 22]. Briefly, dementia prevalence in the GBD study is estimated by collating all information on prevalence and incidence globally through systematic review, adjusting the data to account for nonstandard case definitions or ascertainment methods, and using Bayesian meta-regression methods to estimate prevalence [23]. Other general GBD methods can be found in previous publications on dementia and the GBD overview papers [3, 23, 24].

Literature Reviews

We conducted literature reviews on the association between dementia and Parkinson’s disease, Down syndrome, stroke, and TBI. We searched all articles in PubMed and did not restrict articles based on publication date. The PubMed search for Down syndrome resulted in 355 hits, and 25 were ultimately extracted. For Parkinson’s disease, the PubMed search terms yielded 1,475 hits, of which 53 were accepted and extracted. A recent systematic review (2018) on the relationship between stroke and dementia yielded 31 sources [17]. This review was updated with a PubMed search on articles published after the most recent source identified in the systematic review. Of 504 hits, 2 were accepted and added. Three recent meta-analyses (2016, 2016, and 2019) were identified on the relationship between TBI and dementia, and we cross-checked all articles cited by these reviews to identify 47 unique sources for inclusion [19, 25, 26]. As the most recent systematic review was published within a year of this analysis, we did not conduct an additional literature review. Additional details on literature reviews including search strings are available in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000515393).

All of the literature reviews targeted papers on population-representative samples and excluded studies on patients in nursing homes. However, clinical samples (studies that recruited patients from a health-care setting) were accepted and were adjusted for in the meta-regression. We accepted case-control, cross-sectional, and longitudinal studies that reported on relative risks, hazard ratios, and odds ratios for dementia or the proportion of exposed individuals with dementia. We required that each source reported on the mean age of the study population or presented results by age. For stroke, we excluded studies on the risk of dementia with transient ischemic attacks or other markers of subclinical vascular disease, as this analysis was limited to overt clinical stroke, a subset of all vascular dementia.

The available data on stroke and TBI primarily described the relationship between these causes and dementia using relative risks or odds ratios, and these data were modeled together. However, the literature on dementia and Parkinson’s disease or Down syndrome more commonly reported the proportion of patients who had dementia. Using these data, we approximated relative risks by dividing each extracted proportion by the age-sex-location-year-specific dementia prevalence estimate from GBD.

Relative Risk Models

We modeled the relative risk of dementia, given the exposure of each disease included, using a Bayesian meta-regression modeling framework. This model includes trimming, a form of outlier detection within the likelihood function. Using this framework, a data point with very low variance, and which is a moderate distance from the mean at a given set of age and covariate values, is more likely to be identified as an outlier than a data point with high variance farther from the mean (additional details are given in the online suppl. material).

Each model included dummy variables on the following study characteristics: study population (clinical vs. population-based samples), diagnosis (Alzheimer's disease vs. all dementia), and factors controlled for in each component study, such as education, smoking, or vascular risks (full list of study characteristics is given in the online suppl. material). We also specified cubic splines on age with 3 knots equally spaced across the density of the input data and priors of zero slope on the terminal segments to prevent the extrapolation of trends based on small amounts of data at the youngest and oldest ages. Relative risks were estimated by predicting out 1,000 draws from each model for the set of gold standard covariates in each analysis (e.g., exposure definition of DSM dementia rather than Alzheimer's disease). Negative draws were set to zero as these exposures were a priori believed to be harmful, not protective.

Calculation of Population Attributable Fractions and Attributable Prevalence

Population attributable fractions (PAFs) were estimated using relative risk estimates from the meta-regression models and the GBD 2019 age-sex-location-year-specific estimates of the prevalence of each clinical condition included. They were calculated using the formula below [27]:

$$PAF = \frac{prevalence \times (RR - 1)}{[prevalence \times (RR - 1)] + 1}.$$

PAFs were then multiplied by the corresponding age-sex-location-year-specific estimates of dementia prevalence from GBD to estimate the amount of dementia prevalence attributable to each disease.

Compilation of Results

Age-standardized estimates were calculated using weights derived from the global age distribution of dementia cases in 2019 [23]. All calculations were done with 1,000 draws to incorporate uncertainty from each step of the modeling process. Uncertainty intervals were defined as the 25th and 975th values of the ordered draws. Differences were defined as statistically significant if the uncertainty intervals did not intersect the null value.

Results

The literature reviews for the 4 conditions modeled in this analysis yielded 158 sources on the association between dementia and Down syndrome (n = 25), Parkinson's disease (n =

53), stroke (n = 33), and TBI (n = 47). The majority of the data were from North America and Western Europe (shown in Table 1 and online suppl. Appendix 1).

For all 4 diseases included in the analysis, although the absolute risk of dementia increased with age, the relative risk of dementia decreased with age due to the increasing prevalence of dementia in the oldest age groups of the unexposed (individuals without each clinical condition) populations. This decrease in relative risk was most extreme for Down syndrome. The relationship between stroke and dementia was approximately logarithmic over age, and for Parkinson's disease, the relative risk of dementia was high in the youngest ages but decreased fairly quickly from age 70 onward. When compared to the other diseases evaluated, the relative risks for dementia in those with TBI were the lowest in the youngest age group and decreased further across the age range (shown in Fig. 1).

The proportion of dementia cases due to Down syndrome decreased with age, while for the other diseases, the proportion of dementia cases attributable displayed an inverted U-shaped curve over age, increasing until approximately age 70 years before decreasing. For TBI, Parkinson's disease, and stroke (in younger ages), the proportions of dementia attributable to each condition were higher in men than in women, owing to the higher prevalence of these conditions in men (shown in Fig. 2). However, these sex differences were not statistically significant.

Down syndrome, Parkinson's disease, stroke, and TBI together accounted for 10.0% (95% UI 6.0–16.5) of the all-age global prevalence of dementia. There was a strong gradient with age, with only 2.6% (0.1–6.7) of the global prevalence of dementia in 2019 explained by these conditions in the 95 years and older age group, whereas 26.8% (11.6–50.8) of dementia prevalence was explained by the 4 diseases in the 40–44 years age group (shown in Fig. 3).

For every region, stroke accounted for the largest number of dementia cases, totaling 3.70 million (95% UI 2.00–5.68) cases globally. Parkinson's disease accounted for the second largest number of global cases (1.71 million cases; 0.14–5.79), followed by Down syndrome (0.80 million cases; 0.23–2.03) and then TBI (0.42 million cases; 0.20–0.69).

Eastern Europe was the region with the highest age-standardized proportion of dementia attributable to stroke (8.5%; 95% UI 4.6–12.5). East Asia had the highest age-standardized PAFs of dementia attributable to Parkinson's disease (3.0%; 0.3–9.8). Australasia had the highest age-standardized PAF of dementia attributable to Down syndrome (2.3%; 0.7–5.3), and both central Europe and Australasia had the highest age-standardized prevalence of dementia attributable to TBI (central Europe: 1.9% [0.9–3.1]; Australasia: 1.9% [0.8–3.1]) (shown in Table 2).

Before age 60 years, Down syndrome was responsible for the largest number of dementia cases of the diseases evaluated. However, as age increases, the fraction of dementia due to both stroke and Parkinson's disease increases. The absolute numbers of dementia cases attributable to Down syndrome, Parkinson's disease, TBI, and stroke are fairly similar between men and women, despite men having a lower prevalence of dementia in each age group.

Discussion

Globally, the proportion of dementia prevalence attributable to Down syndrome, Parkinson's disease, stroke, and TBI was 10.0% (95% UI 6.0–16.5). Of these diseases, stroke accounted for the largest total number of dementia cases. However, at the youngest ages (40–50 years), Down syndrome and TBI accounted for larger proportions of dementia prevalence.

These results demonstrate the relative impact of a diverse set of clinical conditions (Down syndrome, Parkinson's disease, stroke, and TBI) on dementia prevalence. Relative risks were highest in Down syndrome, particularly at the youngest ages, which is hypothesized to be due to the overexpression of genes involved in the processing of amyloid precursor protein and Alzheimer's neuropathic changes caused by trisomy 21 in combination with the low background risk of dementia in the youngest ages [28]. Despite the fact the development of dementia is likely an eventuality among those with Down syndrome, the quantification of dementia in this population is still of interest, as risk factor-based interventions or amyloid-targeting therapies may still be able to delay the onset of dementia in this population.
The estimated relative risks were also high for Parkinson's disease, and these relative risks remained higher in older ages, where individuals may be affected by the combined burden of Lewy body pathology due to Parkinson's disease as well as other neuropathologies, which often jointly lead to the expression of clinical dementia [29].

Despite the higher relative risks in Down syndrome and Parkinson's disease, stroke was responsible for the largest number of global dementia cases due to the larger prevalence of stroke. Given that an estimated 88.8% (95% UI 86.5–90.9) of the global burden of stroke can be attributed to modifiable risk factors, this presents opportunities for interventions that could impact not only stroke outcomes but dementia outcomes as well [30]. As cardiovascular disease risk factors have also been shown to be associated with dementia independently of clinical stroke, addressing these risk factors may have an impact above and beyond affecting dementia through clinical stroke [31]. Potential gains may also be larger in low-income countries as compared to high-income countries, where there is currently inadequate identification and treatment of many of these risks [32].

The largest portion of dementia cases (90.0%; 95% UI 83.5–94.0) remained unexplained by the clinical conditions examined in this paper. Many of these cases are likely attributable to pathologies such as amyloid beta, tau, α-synuclein, or a mix of these pathologies along with subclinical vascular disease, TDP-43, and other pathological changes [33–37]. Prior work on autopsy samples reports that 25% of dementia risk is attributable to Alzheimer's disease pathologies (including amyloid plaques, neurofibrillary tangles, and cerebral amyloid angiopathy) [9]. However, additional large population-based autopsy studies are needed to better characterize the distribution of these and other etiologies.

Furthermore, the quantification of the residual dementia category within this study, that is, dementia not due to other clinical conditions, is important within the context of the GBD project, as it ensures that GBD results are mutually exclusive and collectively exhaustive. This principle of GBD facilitates valid comparisons between diseases by avoiding double counting any health loss across disease categories [38].

A number of limitations require consideration. First, we only examined 4 clinical conditions, rather than all possible causes of dementia. We chose to focus on these clinical conditions because the ascertainment of these conditions is more widely standardized as compared to other causes of dementia, including Lewy body dementia and frontotemporal dementia. Additionally, while the quantification of dementia due to clinical conditions has received less attention compared to research on modifiable risk factors or neuropathological etiologies, focusing on clinical conditions that require interaction with health-care systems ensures that there are points of contact to enable the rollout of preventative interventions or potential future amyloid-targeting treatments. Stroke, Parkinson's disease, Down syndrome, and TBI were specifically chosen for inclusion in this analysis because they are currently quantified within the GBD framework, allowing for global estimation. Although HIV fulfilled our criteria for inclusion in this study, we were unable to include HIV due to the use of a different definition of dementia (HIV-associated dementia) in the HIV literature, which relies principally on neuropsychological testing cutoffs rather than the more comprehensive DSM-based diagnostic criteria for dementia [39]. Second, there was a large amount of heterogeneity in the literature on the relative risk of dementia due to Down syndrome, Parkinson's disease, stroke, and TBI. We attempted to control for some of these differences through the use of covariates, but some bias due to these study attributes may remain due to measurement error in the discretization and categorization of study traits. Third, the majority of the sparse data available on relative risks came from high-income settings in North America and Western Europe, and we have assumed that these data apply globally. To the extent that the increased risk due to each clinical condition is attributable to the biological link between each exposure and dementia, this may be a reasonable assumption, but the addition of new data sources would greatly strengthen the analysis. Fourth, when individual draws from our models of relative risk estimated protective effects (relative risks <1), we set these draws to 1 to conceptually align with our belief that these clinical conditions should lead to increased risk rather than acting as protective factors. However, this adjustment biases the mean of the draws upward. For example, in Parkinson's disease, which had the largest number of draws under 1 at the oldest ages, the relative risk in the 95 years and older age group increased from 1.50 to 1.62 after adjustment. Fifth, the estimation of attributable burden is dependent on the estimation of dementia prevalence, which is subject to limitations related to data sparsity and heterogeneity.

Further inclusion of other clinical conditions such as diabetes, alcohol use disorders, and encephalitis should be considered as well, contingent on the evaluation of the strength of the evidence suggesting an association with dementia. Additionally, to refine our current estimates, future work should seek to distinguish between ischemic and hemorrhagic stroke, as recent research indicates that the association with dementia differs by stroke subtype [40].

Despite the limitations of the data and methods, this study synthesized available data to compare the relative risk and attributable burden of clinical diseases associated with dementia. This analysis complements prior work on modifiable risk factors and neuropathological etiologies by more fully elucidating the contribution of clinical conditions to dementia prevalence. The ability to compare both across clinical conditions and across regions supports more informed decision-making related to distributing research

funds across the clinical conditions examined, as well as planning interventions to target modifiable risks for conditions such as TBI or stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Statement

G.J.H. reports personal honoraria from AC Immune for serving as Chair, Data Safety Monitoring Committee, of ACI-24-701 and AC-35-1201 trials of an immune therapy for Alzheimer's disease. J.J.J. reports personal fees from Amgen, ALAB Laboratories, Teva, Synexus, Boehringer Ingelheim, and Zentiva, outside the submitted work. W.A.K. reports NIH research Grant U01 AG016976. S.L. reports personal fees from Akcea Therapeutics, Amedes, Amgen, Berlin-Chemie, Boehringer Ingelheim Pharma, Daiichi Sankyo, Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, SYNLAB, Unilever, and Upfield, and nonfinancial support from Preventicus, all outside the submitted work. P.S.S. reports personal fees from Biogen Australia Advisory Committee, outside the submitted work. M.S. reports being an employee of Bayer. J.A.S. reports personal fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Medscape, WebMD, Clinical Care options, ClearView Healthcare Partners, Putnam Associates, Focus Forward, Navigant Consulting, Spherix, Practice Point Communications, the National Institutes of Health, the American College of Rheumatology, and Simply Speaking; owning stock options in Amarin, Viking, Moderna and Vaxart Pharmaceuticals, and Charlotte's Web Holdings; membership in the FDA Arthritis Advisory Committee, Steering Committee of OMERACT (an international organization that develops measures for clinical trials and receives arm's length funding from 12 pharmaceutical companies), Veterans Affairs Rheumatology Field Advisory Committee, and the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-Analysis, all outside the submitted work. C.E.I.S. has provided clinical consultancy and has been on scientific advisory committees for the Australian Commonwealth Scientific and Industrial Research Organisation and the Federal Department of Health; her research program has received support from the National Health and Medical Research Council (Grants 547500, 1032350, and 1062133), National Institute on Aging (Grant 320312, Alzheimer's Association), and the Royal Australian College of Physicians; she may accrue revenues from a patent in pharmacogenomics prediction of seizure recurrence. C.W. reports grants from the Ministry of Science and Technology in China, personal fees from HealthKeepers, and grants from Suzhou Municipal Science and Technology Bureau and the Kunshan Government, outside the submitted work.

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Online Supplementary Appendix 1

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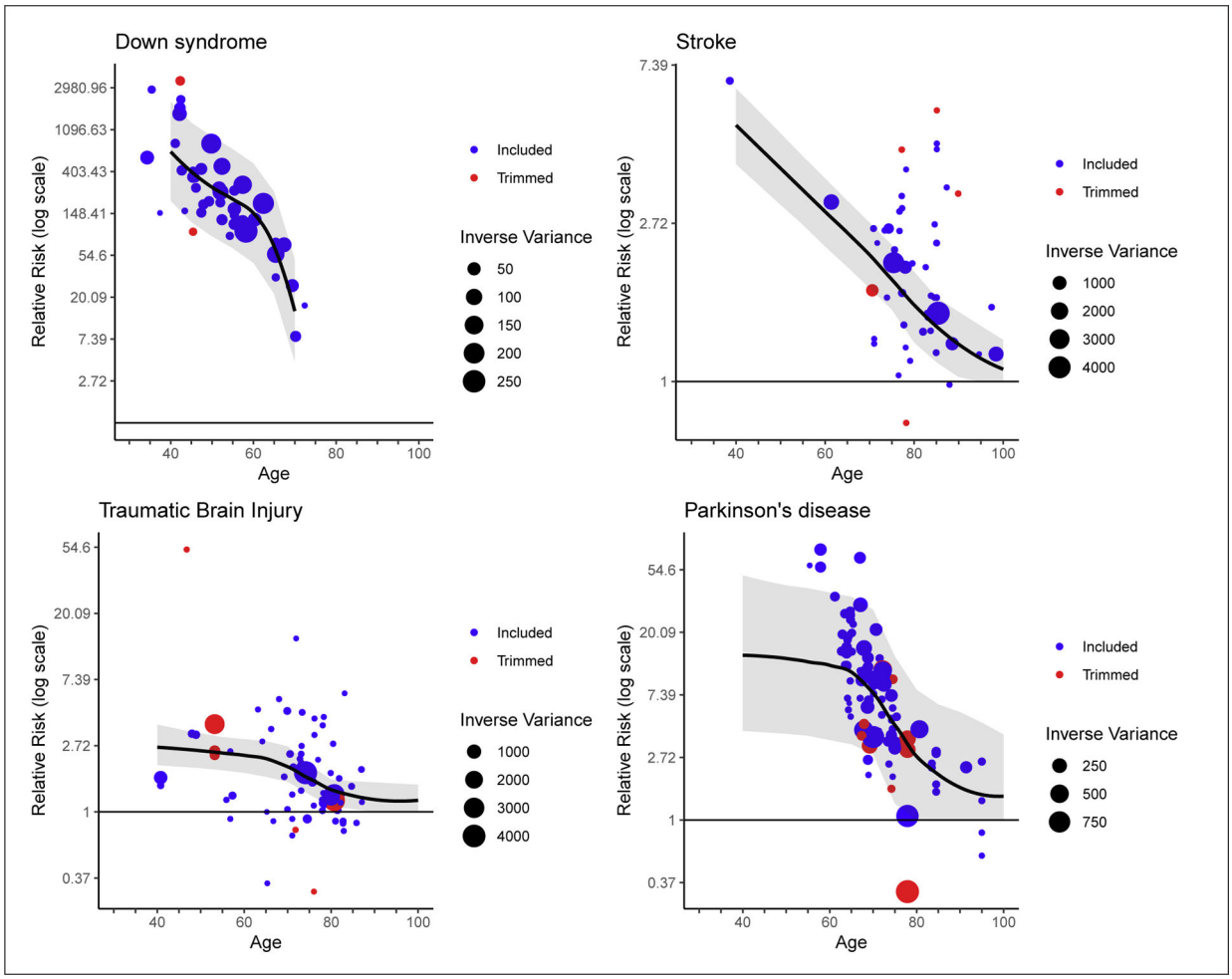

Fig. 1.

Meta-regression of relative risk of dementia by age for Down syndrome, stroke, TBI, and Parkinson's disease. Trimmed data refer to data points that were identified as outliers in the modeling framework. The inverse variance scale sizes the data points according to the certainty of the data such that larger points have less uncertainty and more weight in the model. TBI, traumatic brain injury.

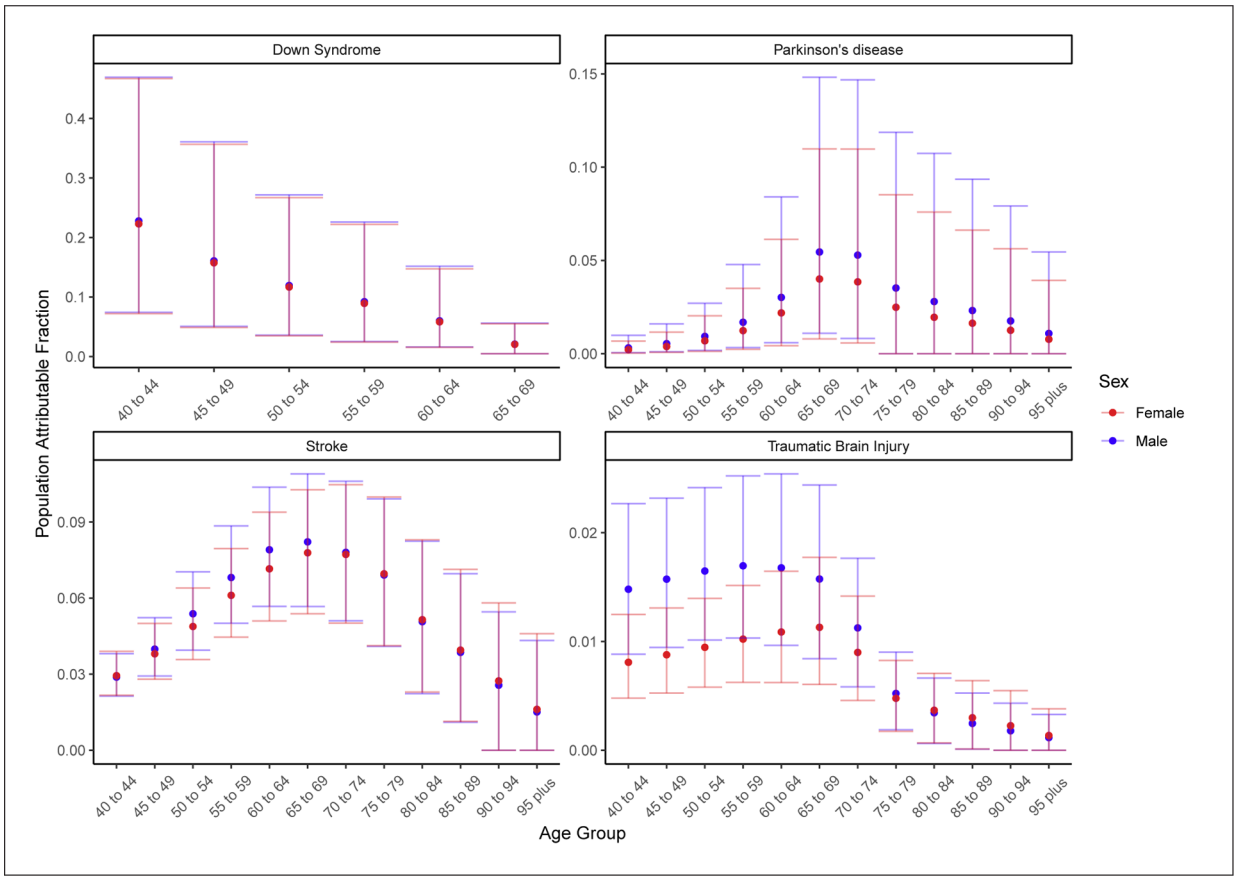

Fig. 2.

Global PAFs of dementia for Down syndrome, stroke, TBI, and Parkinson's disease, by age and sex in 2019. PAF, population attributable fraction; TBI, traumatic brain injury.

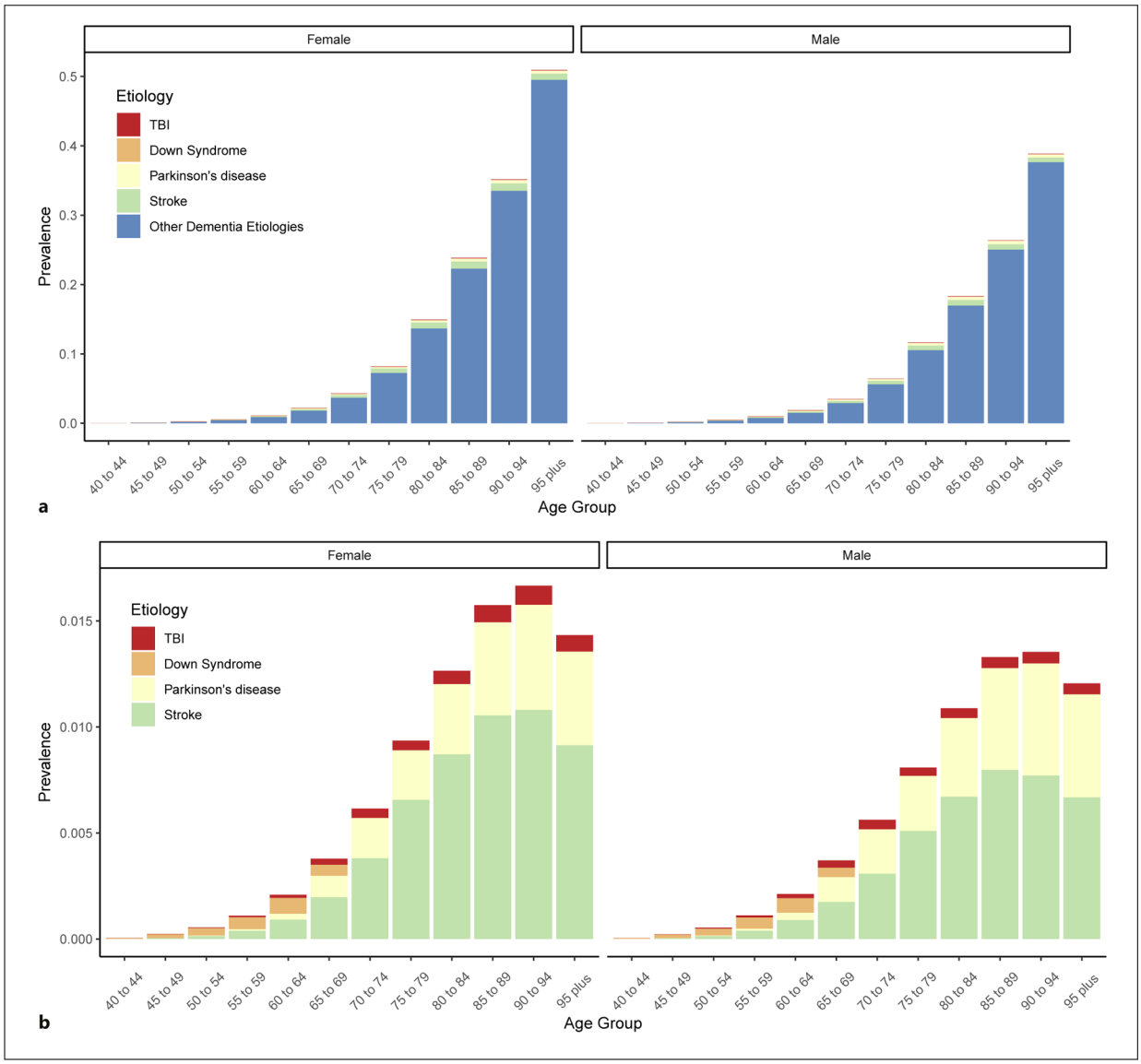

Fig. 3.

Global dementia prevalence due to Down syndrome, stroke, TBI, and Parkinson's disease, and the prevalence of dementia unaccounted for by these 4 clinical conditions in 2019. **a** All categories including the residual category of dementia prevalence not attributable to the clinical conditions examined in this paper. **b** A zoomed-in view of the prevalence attributable to each clinical condition. TBI, traumatic brain injury.

Table 1.

Distribution of data sources by world region and disease exposure, *N* (%)

	Down syndrome, *n* (%)	**Parkinson's disease, *n* (%)**	**Stroke, *n* (%)**	**TBI, *n* (%)**
Sources, *N*	25	54	36	49
Global	0 (0)	0 (0)	0 (0)	3 (6.1)
Andean Latin America	0 (0)	0 (0)	0 (0)	0 (0)
Australasia	1 (4)	4 (7.4)	3 (8.3)	2 (4.1)
Caribbean	0 (0)	0 (0)	0 (0)	0 (0)
Central Asia	0 (0)	0 (0)	0 (0)	0 (0)
Central Europe	0 (0)	0 (0)	0 (0)	0 (0)
Central Latin America	0 (0)	0 (0)	0 (0)	0 (0)
Central sub-Saharan Africa	0 (0)	0 (0)	0 (0)	0 (0)
East Asia	0 (0)	3 (5.6)	3 (8.3)	4 (8.2)
Eastern Europe	0 (0)	1 (1.9)	0 (0)	1 (2)
Eastern sub-Saharan Africa	0 (0)	0 (0)	0 (0)	0 (0)
High-income Asia Pacific	1 (4)	4 (7.4)	2 (5.6)	1 (2)
High-income North America	5 (20)	11 (20.4)	15 (41.7)	25 (51)
North Africa and Middle East	0 (0)	1 (1.9)	0 (0)	0 (0)
Oceania	0 (0)	0 (0)	0 (0)	0 (0)
South Asia	0 (0)	1 (1.9)	0 (0)	0 (0)
Southeast Asia	0 (0)	1 (1.9)	0 (0)	0 (0)
Southern Latin America	0 (0)	2 (3.7)	0 (0)	0 (0)
Southern sub-Saharan Africa	0 (0)	0 (0)	0 (0)	0 (0)
Tropical Latin America	1 (4)	2 (3.7)	0 (0)	0 (0)
Western Europe	17 (68)	24 (44.4)	13 (36.1)	12 (24.5)
Western sub-Saharan Africa	0 (0)	0 (0)	0 (0)	1 (2)

Sources labeled "Global" used individual level data in >1 region and therefore are not tagged to 1 specific location. TBI, traumatic brain injury.

Table 2.

Global and regional numbers of attributable cases of dementia and age-standardized PAFs for dementia cases attributable to Down's syndrome, Parkinson's disease, stroke and TBI in 2019

Location	Down's syndrome		Parkinson's disease		Stroke		TBI	
	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)
Global	802.2 (226.3–2,030.7)	1.2 (0.3–2.9)	1,705.2 (141.8–5,787.1)	2.6 (0.2–8.6)	3,689.2 (2,003.6–5,677.7)	5.6 (3.0–8.5)	415.9 (197.0–694.5)	0.6 (0.3–1.0)
Central Asia	10.0 (2.8–25.2)	1.5 (0.4–3.6)	11.6 (1.0–37.6)	2.6 (0.2–8.6)	28.3 (16.3–42.7)	5.9 (3.3–8.8)	4.4 (2.3–7.1)	0.8 (0.4–1.3)
Central Europe	28.1 (8.0–69.8)	1.9 (0.5–4.5)	61.0 (3.9–207.1)	2.7 (0.2–9.1)	139.1 (70.3–218.2)	6.2 (3.3–9.4)	38.7 (17.3–64.6)	1.9 (0.9–3.1)
Eastern Europe	56.3 (16.3–136.5)	2.2 (0.6–5.1)	79.9 (5.6–276.8)	2.5 (0.2–8.2)	272.4 (143.8–420.3)	8.5 (4.6–12.5)	39.6 (18.9–66.7)	1.3 (0.7–2.1)
Australasia	7.1 (2.1–16.9)	2.3 (0.7–5.3)	11.4 (0.8–38.6)	2.6 (0.2–8.5)	13.3 (6.2–22.0)	3.0 (1.5–4.6)	8.0 (3.1–14.3)	1.9 (0.8–3.1)
High-income Asia Pacific	47.2 (13.6–116.9)	1.9 (0.5–4.5)	95.9 (4.9–346.5)	1.9 (0.2–6.4)	248.9 (114.6–411.8)	5.1 (2.7–7.6)	21.8 (8.9–38.3)	0.5 (0.3–0.8)
High-income North America	84.8 (25.0–206.2)	1.8 (0.5–4.4)	177.7 (11.6–602.4)	2.8 (0.2–9.2)	344.7 (163.0–557.7)	5.4 (2.7–8.2)	26.3 (12.2–44.0)	0.5 (0.2–0.7)
Southern Latin America	11.2 (3.3–26.7)	2.0 (0.6–4.6)	19.6 (1.2–66.3)	2.8 (0.2–9.3)	26.1 (13.1–41.7)	3.8 (2.0–5.7)	5.4 (2.5–9.2)	0.8 (0.4–1.4)
Western Europe	82.8 (24.0–202.9)	1.7 (0.5–4.2)	221.8 (11.2–775.0)	2.7 (0.2–9.0)	296.9 (134.9–489.8)	3.6 (1.9–5.5)	71.9 (27.7–128.9)	1.0 (0.5–1.6)
Andean Latin America	4.8 (1.3–12.5)	1.1 (0.3–2.7)	8.4 (0.7–28.6)	2.4 (0.2–8.0)	12.1 (6.6–18.7)	3.3 (1.8–5.0)	1.8 (0.8–3.0)	0.5 (0.2–0.8)
Caribbean	7.3 (2.2–17.5)	1.9 (0.5–4.4)	7.0 (0.5–23.8)	2.2 (0.2–7.3)	14.1 (7.7–21.8)	4.3 (2.4–6.5)	1.6 (0.7–2.7)	0.5 (0.2–0.8)
Central Latin America	35.5 (10.5–87.0)	1.8 (0.5–4.3)	31.3 (2.4–106.3)	2.2 (0.2–7.4)	46.9 (25.1–73.5)	3.1 (1.7–4.8)	5.1 (2.4–8.7)	0.3 (0.2–0.6)
Tropical Latin America	32.1 (8.8–82.5)	1.2 (0.3–3.0)	46.2 (4.2–157.3)	2.1 (0.2–7.0)	96.8 (54.2–148.0)	4.3 (2.3–6.5)	4.5 (2.2–7.3)	0.2 (0.1–0.3)
North Africa and Middle East	47.0 (12.9–120.6)	1.1 (0.3–2.7)	77.1 (6.9–255.9)	2.3 (0.2–8.0)	229.4 (128.7–344.9)	6.8 (3.8–10.0)	20.6 (10.5–33.6)	0.6 (0.3–0.9)
South Asia	58.7 (15.7–157.0)	0.7 (0.2–1.8)	143.3 (14.0–470.1)	2.3 (0.2–7.7)	241.7 (142.3–362.0)	3.6 (2.0–5.4)	30.3 (15.5–48.6)	0.4 (0.2–0.7)
East Asia	230.4 (62.4–599.3)	1.1 (0.3–2.7)	579.8 (57.0–1,857.4)	3.0 (0.3–9.8)	1,390.7 (784.1–2,114.7)	7.3 (3.9–11.0)	107.9 (56.3–174.9)	0.5 (0.3–0.8)
Oceania	0.5 (0.1–1.4)	0.9 (0.2–2.3)	0.9 (0.1–2.9)	2.9 (0.3–9.5)	2.0 (1.2–3.0)	6.1 (3.3–9.1)	0.1 (0.1–0.2)	0.3 (0.2–0.5)

Location	Down's syndrome		Parkinson's disease		Stroke		TBI	
	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)	cases, *n* (in 1,000s) (95% UI)	age-standardized PAF (95% UI)
Southeast Asia	34.2 (9.1–91.6)	0.6 (0.1–1.5)	91.5 (9.6–291.6)	2.5 (0.2–8.2)	190.7 (111.8–285.7)	5.0 (2.7–7.5)	15.8 (8.4–25.3)	0.4 (0.2–0.6)
Central sub-Saharan Africa	3.5 (1.0–9.3)	0.8 (0.2–2.0)	5.4 (0.5–17.6)	1.8 (0.1–6.3)	12.5 (7.4–18.7)	4.0 (2.2–6.0)	1.5 (0.8–2.4)	0.4 (0.2–0.7)
Eastern sub-Saharan Africa	6.4 (1.7–17.5)	0.5 (0.1–1.3)	13.3 (1.2–43.9)	1.7 (0.1–5.6)	31.3 (17.9–47.4)	3.7 (2.0–5.6)	4.6 (2.4–7.5)	0.5 (0.2–0.8)
Southern sub-Saharan Africa	4.0 (1.1–10.5)	1.0 (0.3–2.4)	5.7 (0.4–19.7)	1.7 (0.1–6.0)	15.6 (8.6–24.1)	4.6 (2.4–7.1)	1.8 (0.9–3.0)	0.5 (0.2–0.8)
Western sub-Saharan Africa	10.1 (2.7–26.6)	0.7 (0.2–1.8)	16.4 (1.4–54.2)	2.2 (0.1–7.5)	35.5 (20.4–53.6)	4.3 (2.3–6.4)	4.0 (2.1–6.5)	0.4 (0.2–0.7)

PAF, population attributable fraction; TBI, traumatic brain injury.