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The global macroeconomic burden of epilepsy and the role for neurosurgery: A modelling study based upon the 2016 Global Burden of Disease data

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ABSTRACT

Background: Although the significant morbidity and mortality burden associated with epilepsy is well understood, associated economic consequences have not been estimated on a global scale. We sought to; (1) estimate the value of lost economic welfare attributable to epilepsy among countries included in the 2016 Global Burden of Disease study, (2) evaluate differences in disease burden between countries of varied income classification and location, and (3) understand the proportion of this burden that requires neurosurgical consultation and intervention.

Methods: Publicly available morbidity and mortality data were incorporated into a 'full-income' model to generate estimates of the cumulative value of lost welfare (VLW) related to epilepsy. Results from a survey of neurosurgeons were then used to estimate the VLW attributable to the proportion of disease requiring neurosurgical consultation and intervention.

Results: A total of 195 countries and territories were included in this analysis. We estimate that the cumulative VLW related to epilepsy was $647.37 billion (2016 USD, PPP). Economic welfare losses were equivalent to a mean of 1.45% (± 1.00) of gross domestic product. The value of economic losses attributable to the proportion of the burden necessitating neurosurgical consultation and intervention was $258.95 billion (2016 USD, PPP) and $155.37 (2016 USD, PPP) respectively.

Conclusions: Our results indicate that the economic consequences of epilepsy related morbidity and mortality are substantial. When considered with evidence supporting the cost-effectiveness of various interventions for improved epilepsy diagnosis and management, our findings suggest that the implementation of simple and affordable measures may avert significant economic loss.

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INTRODUCTION

Epilepsy is one of the most common chronic neurological conditions, directly affecting approximately 70 million people worldwide. [1] A recent estimate has suggested that this number is increasing by 4.6 million incident cases per year. [2] The vast majority of people with epilepsy reside in low- and middle-income countries, [1, 3] where the associated morbidity and mortality are significantly greater. [1, 4] Although most patients do not receive appropriate treatment, [5, 6] 70% to 85% will achieve remission with appropriately selected antiepileptic medications alone. [7, 8] The remainder, however, continue to experience seizures and it has been suggested that these patients account for approximately 80% of the total direct healthcare costs attributable to epilepsy. [9] Surgical intervention has been demonstrated to be an efficacious and cost-effective intervention for a proportion of patients experiencing medically refractory epilepsy. [7, 10-12] Despite this, access to epilepsy surgery remains poor, particularly in low- and middle-income countries. [13]

In addition to associated morbidity and mortality, people with epilepsy are at greater risk of poor educational, vocational, psychological and social outcomes. [14, 15] Previous studies have adopted a number of perspectives from which to estimate the direct and indirect economic impact of these consequences. [16] However, to date, there has not been any published assessment of the global macroeconomic burden of epilepsy. When taken alongside cost-effectiveness data, such estimates could be utilised to inform decision-making regarding resource allocation and priority-setting. With this in mind, we sought to; (1) estimate the total value of lost economic welfare attributable to epilepsy at the global, regional and national level among the 195 countries and territories included in the Institute for Health Metrics and Evaluation (IHME) 2016 Global Burden

of Disease (GBD) Study, [17] (2) evaluate differences in disease burden between countries of varied income classification cohorts and locations, and (3) understand the proportion of this burden that requires neurosurgical consultation and intervention. The counterfactual scenario in this analysis was the absence of disease.

METHODS

This study has been reported according to the Guidelines for Accurate and Transparent Health Estimates Reporting. [18] A detailed description of the construction of our model can be found in Appendix 1, and a worked example can be found in Appendix 2.

Data Sources

Burden of disease estimates and life-expectancies were obtained from the IHME 2016 GBD study. [17] GDP values for 2016 were extracted from the World Bank, measured in US dollars (USD) and adjusted for purchasing power parity (PPP). [19] All countries were stratified into low-income (LIC), lower middle-income (LMIC), upper middle-income (UMIC) and high-income (HIC) according to the World Bank's classification system. [20] Socio-demographic index (SDI) values were obtained from the IHME.

Given that their estimates are derived from a comprehensive meta-analysis, we utilised the VSL published by the US Environmental Protection Agency for 2006, updated to the year of analysis ($8,932,431).

Inclusion and Exclusion Criteria

Data from all countries included in the IHME 2016 GBD study were eligible for inclusion in this research. GDP data were not available for 11 of the included countries and territories (American Samoa, Andorra, Bermuda, Cuba, Djibouti, Eritrea, Greenland, Guam, North Korea, Northern Mariana Islands and Palestine), which precluded the calculation of a country specific VSL. Given that these regions constituted such a small proportion of the overall population (0.66%), we assumed that these data were 'missing at random' and linearly projected existing estimates to

encompass the entire target population. Disaggregated morbidity and mortality data were not available beyond 89 years of age and, therefore, the model was capped at this age.

Estimation of surgical burden

In the absence of quantitative, context-specific data to describe the surgical burden of epilepsy, the results of a survey were utilised to generate our estimates. [21] This survey involved eighty-five neurosurgeons from 57 countries who were asked to estimate the proportion of epilepsy that should, in ideal circumstances, receive neurosurgical consultation and intervention, respectively. Mean values supplied by the survey instrument suggested that 40% of epilepsy cases require neurosurgical consultation and 24% require neurosurgical intervention.

Sensitivity Analyses

The sensitivity of our model to uncertainty intervals published by the IHME and the use of discounting were both evaluated with sensitivity analyses. Similarly, given debate surrounding the relationship between VSL and income, [22, 23] the sensitivity of our estimates to variations in IE-VSL was also investigated. Consistent with previous work by Alkire et al, [24] we utilised an IE-VSL of 0.55 for HICs and UMICs and 1.0 for LMICs and LICs as a upper bound, and an IE-VSL of 1.0 for HICs and UMICs and 1.5 for LMICs and LICs as a lower bound for these analyses. The estimate of epilepsy burden mandating neurosurgical intervention was also subjected to sensitivity analysis utilising prevalence estimates of pharmacoresistant disease of 22.5% and 37%, which were derived from large Scottish and French populations respectively. [25, 26]

Statistical Analysis

Descriptive categorical data were summarized using absolute values and proportions, with numerical data expressed with the mean (± SD). Comparisons of central tendency between normally-distributed, independent groups were undertaken with a one-way analysis of variance. Tukey and Games-Howell post-hoc analyses were conducted when the assumption of homogeneity of variances was met, and violated, respectively.

Where data were normally distributed, without outlier values, the presence and direction of a linear relationship between continuous variables was determined using the Pearson product-moment correlation. The strength of the association was described according to Cohen, with coefficient values of 0.1-0.3 considered small in strength, 0.3-0.5 described as moderate and >0.5 as strong. [27]

Statistical analysis was conducted with Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and Statistical Package for the Social Sciences (SPSS) Version 24 (IBM Corporation, Armonk, NY, USA). Graphs and figures were produced using Tableau (Tableau Software Inc, WA, USA). A p-value of <0.05 was considered to be statistically significant. All monetary estimates are expressed in terms of 2016 US dollars, adjusted for PPP.

RESULTS

A total of 195 countries and territories were included in this analysis, with an estimated cumulative population of 7,434,043,990, which accounts for 99.86% of the global population in 2016. The mean GDP of included regions was $19,212.11 (± 20,599.59) and over 99% of countries and territories from each of the World Bank income classifications were included in the model.

We estimate that the cumulative value of lost economic welfare related to epilepsy in 2016 was $647.37 billion. The short-run impact of morbidity accounted for a majority ($494.81 billion, 76.43%) of the overall burden of disease, while the long-run effects of mortality were responsible for $152.55 billion (23.57%) of lost economic welfare. There was no difference in the proportion of lost welfare attributable to mortality between income (Welch's $F(3.00, 87.49) = 1.72$, $p=0.17$) or geographic classification groups (Welch's $F(6.00, 12.85) = 1.15$, $p=0.39$). The age-specific burden of lost economic welfare is presented in Figure 1.

Figure 1: Total value of lost welfare (2016 USD, PPP) stratified by age-group

Economic welfare losses were equivalent to a mean of 1.45% of GDP (± 1.00). There was a statistically significant difference in VLW as a percentage of GDP between income classification

groups (Welch's F (3.00, 82.44) = 40.56, p<0.0005). Post-hoc analyses revealed significant differences between LICs and HICs (1.31, 95% CI 0.84-1.78, p<0.0005), LMICs and HICs (1.19, 95% CI 0.77-1.61, p<0.0005) and UMICs and HICs (0.98, 95% CI 0.60-1.35, p<0.0005).

A similar difference was observed in the ratio of VLW-to-GDP between geographic groups (Welch's F(6.00, 25.81) = 14.37, p <0.0005). The mean ratio of VLW-to-GDP was highest in the Sub-Saharan Africa (2.20% ± 1.08) and South Asia (2.19% ± 0.65) groups, followed by; Middle East and North Africa (1.22% ± 0.79), East Asia and Pacific (1.20% ± 1.00), Europe and Central Asia (1.18% ± 0.91), Latin America and the Caribbean (1.17% ± 0.51) and North America (0.28% ± 0.25). The results of post-hoc analysis are presented in Table 1 and the global variation in VLW expressed as a proportion of GDP is illustrated in Figure 2, with raw values also included in Appendix 3.

Figure 2: Value of lost welfare expressed as a proportion of GDP, stratified by country

Table 1: Post hoc analysis comparing the ratio of VLW:GDP between geographic groups

Region		**Mean Difference**	**95% Confidence Interval**	**Significance**
Sub-Saharan Africa	East Asia & the Pacific	1.00	0.28 – 1.72	0.001*
	Europe & Central Asia	1.01	0.40 – 1.62	<0.0005*
	Latin America & the Caribbean	1.03	0.48 – 1.58	<0.0005*
	Middle East & North Africa	0.98	0.26 – 1.69	0.002*
	North America	1.91	1.10 – 2.71	0.0005*
	South Asia	0.006	-0.94 – 0.95	>0.99
South Asia	East Asia & the Pacific	0.99	0.02 – 1.96	0.04*
	Europe & Central	1.01	0.08 – 1.93	0.03*

	Asia			
	Latin America & the Caribbean	1.02	0.12 – 1.93	0.03*
	Middle East & North Africa	0.97	0.034 – 1.94	0.05
	North America	1.91	0.89 – 2.92	0.001*
North America	East Asia & the Pacific	-0.91	-1.73 – -0.09	0.03*
	Europe & Central Asia	-0.90	-1.71 – -0.09	0.03*
	Latin America & the Caribbean	-0.88	-1.78 – 0.02	0.05
	Middle East & North Africa	-0.93	-1.76 – -0.11	0.03*
Middle East & North Africa	East Asia & the Pacific	0.02	-0.73 – 0.78	>0.99
	Europe & Central Asia	0.03	-0.63 – 0.70	>0.99
	Latin America & the Caribbean	0.05	-0.55 – 0.66	>0.99
Latin America & the Caribbean	East Asia & the Pacific	-0.03	-0.64 – 0.58	>0.99
	Europe & Central Asia	-0.02	-0.49 – 0.45	>0.99
Europe & Central Asia	East Asia & the Pacific	-0.01	-0.68 – 0.65	>0.99

A Pearson's product-moment correlation revealed a moderate, inverse relationship between the ratio of VLW-to-GDP and SDI ($r = -0.48$, $p<0.001$). An inverse relationship of smaller magnitude was also observed between the ratio of VLW attributed to YLLs and SDI ($r = -0.24$, $p = 0.001$).

Estimate of Surgical Burden

The estimated value of economic welfare losses attributable to the proportion of the burden of epilepsy necessitating neurosurgical consultation and intervention was $258.95 billion and $155.37 billion respectively (Figure 3a and 3b).

Figure 3a: Total value of lost economic welfare attributable to epilepsy necessitating neurosurgical consultation

Figure 3b: Total value of lost economic welfare attributable to epilepsy necessitating neurosurgical intervention

Sensitivity Analysis

Utilising the upper and lower IE-VSL values applied by Alkire and colleagues, [24] the VLW estimate ranged between $552.61 billion – $862.69 billion. The model was more sensitive to variations in burden of disease estimates according to the uncertainty intervals published by the IHME, with a lower bound VLW estimate of $342.69 billion and an upper bound of $1090.26 billion. When based upon undiscounted YLL figures, the overall VLW estimate was $752.57 billion. Utilisation of the estimates of pharmacoresistance provided by Kwan [25] and Picot [26] as a surrogate for surgical burden yielded a VLW that ranged between $145.66 billion and $239.53 billion (Figure 4, Appendix 4).

Figure 4: Sensitivity analysis demonstrating estimates of value of lost economic welfare based upon; upper and lower IE-VSL estimates, upper and lower bound IHME estimates and undiscounted years of life lost.

DISCUSSION

We estimate that the cumulative value of lost economic welfare related to epilepsy among the 195 included countries and territories in 2016 was $647.37 billion. Economic welfare losses were equivalent to a mean of 1.45% of GDP (± 1.00) and a significant difference was observed in the

ratio of VLW-to-GDP between income classification groups (Welch's F (3.00, 82.44) = 40.56, $p<0.0005$). By providing the first global estimate of the macroeconomic burden of epilepsy, these findings extend upon those reported in a recent systematic review by Allers and colleagues, [16] which summarised and critically appraised 22 studies describing the direct and indirect economic burden associated with epilepsy from the societal, health system and household perspective in a number of contexts.

In most circumstances, VLW estimates in HICs will exceed those in LICs by virtue of the more substantial VSLs found in wealthier economies. This can lead to the spurious conclusion that the macroeconomic burden of disease is greater in HICs than in their low- and middle-income counterparts. Therefore, although it is necessary to understand that our VLW estimates do not represent actual losses in GDP, their expression in this context provides an important sense of scale. The greater VLW-to-GDP ratio observed among low- and middle-income countries is a function of the greater burden of epilepsy found in regions with lower economic productivity, which is multifactorial in aetiology. Firstly, most epidemiologic studies suggest that the prevalence of epilepsy is highest in resource poor settings, [2, 17] and that focal onset epilepsy is disproportionately represented when compared with HICs. [28, 29] This observation supports the suggestion that the greater morbidity and mortality burden of epilepsy in LICs and LMICs reflects increased exposure to potentially epileptogenic insults such as; birth trauma, central nervous system infections, head injury and micronutrient deficiencies. The considerable incidence and prevalence of disease is compounded by a treatment gap of approximately 75% in many resource-poor countries. [5, 6] While the cause of this undertreatment varies according to prevailing socio-cultural, geopolitical and economic conditions, inadequate access to skilled manpower, prohibitive treatment costs, poor availability of medications or diagnostic services, entrenched cultural beliefs regarding epilepsy causation and a preference toward traditional healers for treatment, have all been identified as contributing factors. [5, 6]

Although mortality accounted for a minority ($152.55 billion (23.57%)) of lost economic welfare, an inverse relationship, of modest magnitude, was observed between the ratio of VLW attributed to YLLs and SDI ($r = -0.24$, $p = 0.001$). This is consistent with evidence suggesting that the standardised mortality ratio in people with epilepsy in resource-poor settings such as Uganda (7.2) [30] and China (4.0) [31] significantly exceeds that in developed countries (1.6-3.0). [32] It is

likely that this is attributable to the significant burden of untreated epilepsy discussed above, and may also relate to an increased risk of fatal seizure complications such as drowning, burns and falls among those with poorer health literacy. [33]

A number of studies have utilised similar methodology to estimate the economic value of lost welfare associated with various diseases. [24, 34-36] In 2015, Alkire and colleagues calculated the present value of economic losses attributable to the cumulative surgical burden of injury, neoplasm, digestive disease and maternal and neonatal disorders to be $14.5 trillion (2010 USD, PPP), equivalent to 17% of 2010 GDP. [24] More recently, Rudolfson et al estimated that the VLW associated with neurosurgical disease (excluding epilepsy) in 2015 was $3 trillion (2013 USD, PPP). [34] Two smaller studies reported that the VLW associated with head and neck cancer in three South Asian countries, and the surgical proportion of cleft-palate repair in Sub-Saharan Africa was $16.9 billion (2010 USD, PPP) [35] and 5.4 billion – 9.7 billion (2008 USD, PPP) [36] respectively. Although, the differing sample populations, years of analysis and incorporated assumptions preclude direct comparison between our results, it is reassuring that they do not appear grossly disproportionate to those reported in this study.

Surgical Burden

Based upon the results of a survey involving neurosurgeons from all WHO regions, we estimate that the total value of economic welfare losses attributable to the proportion of epilepsy necessitating neurosurgical consultation and intervention was $258.95 billion and $155.37 billion respectively. Despite this significant burden, epilepsy surgery is globally underutilised, [13] particularly in low- and middle-income countries. [37, 38] The nature and causes of this underutilisation have been comprehensively discussed elsewhere, [13] and vary according to local socio-economic, cultural and geopolitical circumstances. Broadly speaking however, the increased penetration of epilepsy surgery centres relies upon the establishment of accessible medical infrastructure and expertise required to both evaluate patients for surgery and perform the necessary procedures. Clearly, given that 75% of people with epilepsy do not receive any treatment in some contexts, [5] it is not justifiable to recommend universal scaling-up of surgical epilepsy services. Nevertheless, as the treatment gap continues to narrow, epilepsy surgery

services should be considered as an important element of a comprehensive epilepsy management strategy, particularly for those patients with medically refractory epilepsy.

Strengths and Limitations

It is important that our estimates be interpreted in the knowledge of their limitations. Firstly, although we believe that it provides fullest measure of total economic welfare losses, there are empirical concerns with the 'full income' model, with many proposing that the derivation of VSL from willingness-to-pay estimates is likely to be over simplistic. [39] Similarly, given that it places the largest value on each DALY incurred, this methodology consistently generates larger estimates of economic loss than comparable cost-of-illness methodologies. We must also acknowledge the significant role played by various assumptions in the generation of estimates in the IHME GBD study and in our model. The impact of the most salient of these assumptions has been interrogated with sensitivity analysis and this is supplemented with a detailed explanation of the rationale for each of the assumptions in order to permit appraisal of the validity of our estimates. Similarly, although there will likely be some debate regarding the estimates of disease burden mandating neurosurgical consultation and intervention, in the absence of more compelling information from a range of settings, we thought it reasonable to derive these proportions from a geographically and socio-economically representative sample of neurosurgeons, [21] which is consistent with previous similar studies. [24, 34-36] We also acknowledge that the application of a uniform proportion of surgical burden to all countries is likely to be simplistic. Indeed, given that focal epilepsy appears to be more prevalent in LICs and LMICs, it is possible that epilepsy surgery has a greater role in these settings than it does in more developed countries, although this proposal remains conjectural and any attempt to account for it in this analysis would be speculative. GDP data were missing for a small number of countries, which prohibited the derivation of a country-specific VSL and, thus, estimation of VLW. Although some may protest their inclusion in the headline figures, this had minimal impact on our overall estimate (0.62%). Finally, it is vital to emphasise the limitations of conclusions that may be reached from economic impact studies. Indeed, although our estimate of the macroeconomic burden of epilepsy may be valuable, these data must be validated with context specific estimates and considered alongside cost-effectiveness data before making allocative decisions.

In spite of these limitations, which are commonplace in much of the health economic literature, this study is notable because it utilises a commonly accepted economic methodology, which incorporates both market and non-market losses, to provide the first global macroeconomic estimate of the burden of lost economic welfare related to epilepsy and the proportion that may be amenable to neurosurgical consultation or intervention.

CONCLUSION

The significant morbidity and mortality burden of epilepsy has been clearly established in the IHME 2016 GBD study. [17] Consistent with these findings, our results indicate that the cumulative value of associated economic welfare losses is substantial. After adjustment for GDP, it is clear that this economic impact disproportionately affects resource poor countries. When considered alongside evidence supporting the cost-effectiveness of various interventions for improved epilepsy diagnosis and management in countries of all income classifications, our findings suggest that the implementation of simple and affordable interventions may avert significant economic loss. We also suggest that the value of economic losses attributable to cases of epilepsy requiring neurosurgical consultation or intervention is considerable. Although the prioritisation of epilepsy surgery services cannot be advocated in all settings, it is clear that cost-effective surgical interventions can be delivered in resource limited countries and will likely adopt an increasing role in epilepsy management strategies worldwide. We hope that these estimates act as a stimulus for further research and collaboration between neurologists, neurosurgeons and policy-makers to better understand and respond to the diverse challenges facing cost-effective epilepsy care across the world.

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FIGURE LEGENDS

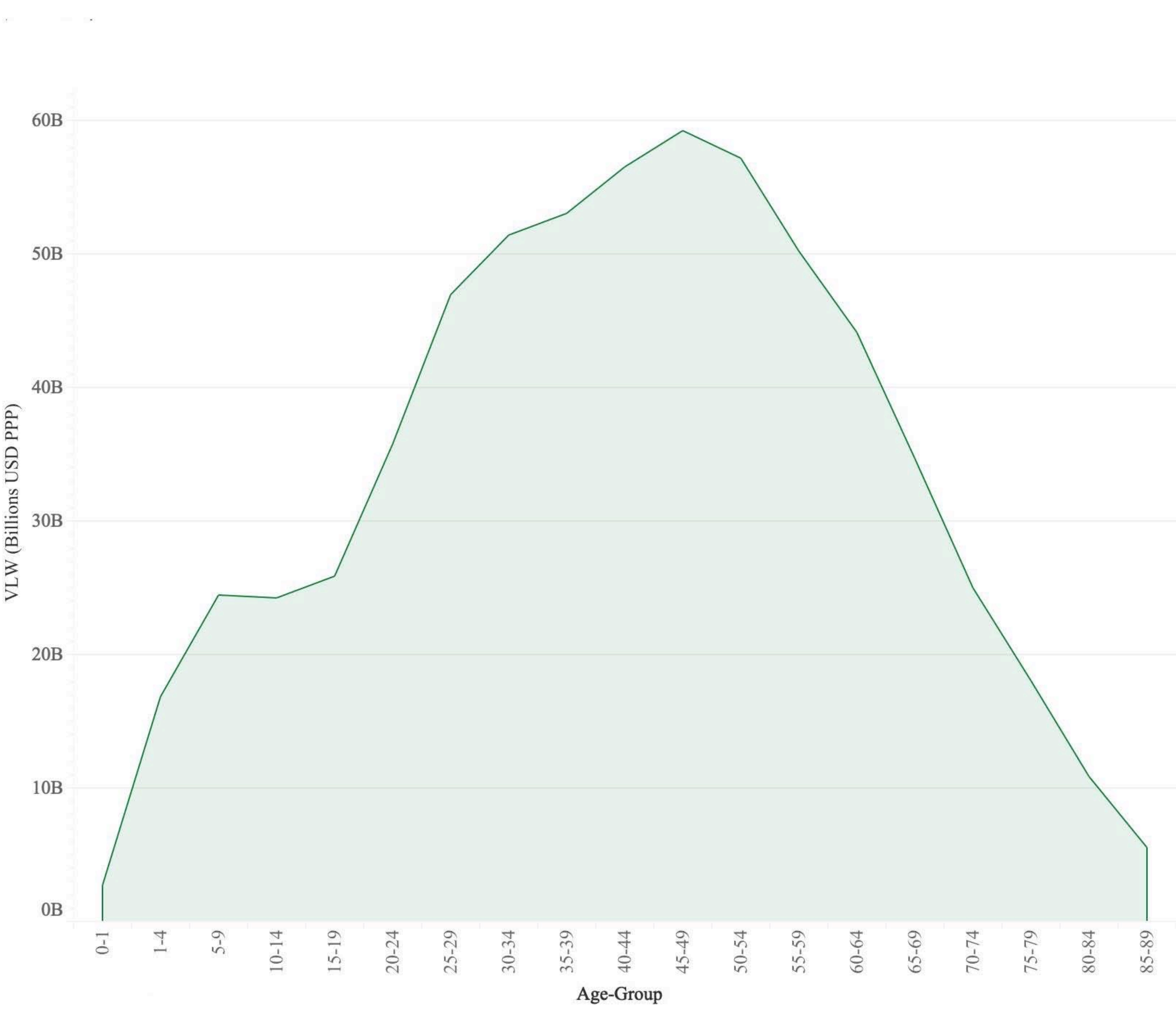
Figure 1: Total value of lost welfare (2016 USD, PPP) stratified by age-group

Figure 2: Value of lost welfare expressed as a proportion of GDP, stratified by country

Figure 3a: Total value of lost economic welfare attributable to epilepsy necessitating neurosurgical consultation

Figure 3b: Total value of lost economic welfare attributable to epilepsy necessitating neurosurgical intervention

Figure 4: Sensitivity analysis demonstrating estimates of value of lost economic welfare based upon; upper and lower IE-VSL estimates, upper and lower bound IHME estimates and undiscounted years of life lost.


60B
50B
40B
30B
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VLW (Billions USD PPP)
0-1
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
Age-Group

SUM(VLW/GDP (%))

0.000 4.929

Total VLW

Proportion of VLW Requiring Neurosurgical Consultation

VLW (Billions USD PPP)

80B

70B

60B

50B

40B

30B

20B

10B

0B

0-1

1-4

5-9

10-14

15-19

20-24

25-29

30-34

35-39

40-44

45-49

50-54

55-59

60-64

65-69

70-74

75-79

80-84

85-89

Age-Group

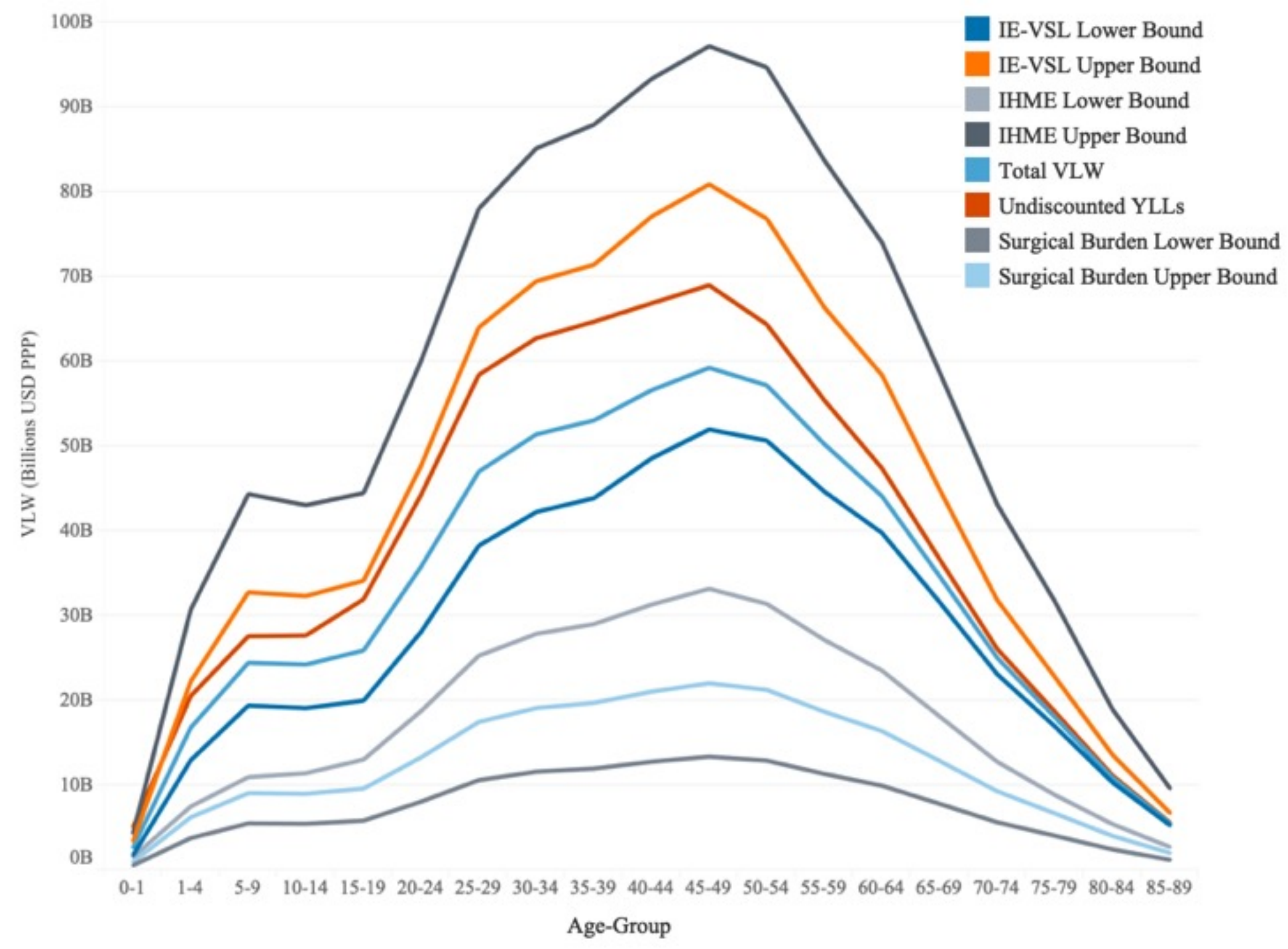
Total VLW
Proportion of VLW Requiring Neurosurgical Intervention

70B
60B
50B
40B
30B
20B
10B
0B

VLW (Billions USD PPP)

0-1
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
0-44
5-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89

Age-Group


IE-VSL Lower Bound
IE-VSL Upper Bound
IHME Lower Bound
IHME Upper Bound
Total VLW
Undiscounted YLLs
Surgical Burden Lower Bound
Surgical Burden Upper Bound
VLW (Billions USD PPP)
100B
90B
80B
70B
60B
50B
40B
30B
20B
10B
0B
0-1
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
Age-Group