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LITERATURE REVIEW

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Global hydrocephalus epidemiology and incidence: systematic review and meta-analysis

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OBJECTIVE Hydrocephalus is one of the most common brain disorders, yet a reliable assessment of the global burden of disease is lacking. The authors sought a reliable estimate of the prevalence and annual incidence of hydrocephalus worldwide.

METHODS The authors performed a systematic literature review and meta-analysis to estimate the incidence of congenital hydrocephalus by WHO region and World Bank income level using the MEDLINE/PubMed and Cochrane Database of Systematic Reviews databases. A global estimate of pediatric hydrocephalus was obtained by adding acquired forms of childhood hydrocephalus to the baseline congenital figures using neural tube defect (NTD) registry data and known proportions of posthemorrhagic and postinfectious cases. Adult forms of hydrocephalus were also examined qualitatively.

RESULTS Seventy-eight articles were included from the systematic review, representative of all WHO regions and each income level. The pooled incidence of congenital hydrocephalus was highest in Africa and Latin America (145 and 316 per 100,000 births, respectively) and lowest in the United States/Canada (68 per 100,000 births) (p for interaction < 0.1). The incidence was higher in low- and middle-income countries (123 per 100,000 births; 95% CI 98–152 births) than in high-income countries (79 per 100,000 births; 95% CI 68–90 births) (p for interaction < 0.01). While likely representing an underestimate, this model predicts that each year, nearly 400,000 new cases of pediatric hydrocephalus will develop worldwide. The greatest burden of disease falls on the African, Latin American, and Southeast Asian regions, accounting for three-quarters of the total volume of new cases. The high crude birth rate, greater proportion of patients with postinfectious etiology, and higher incidence of NTDs all contribute to a case volume in low- and middle-income countries that outweighs that in high-income countries by more than 20-fold. Global estimates of adult and other forms of acquired hydrocephalus are lacking.

CONCLUSIONS For the first time in a global model, the annual incidence of pediatric hydrocephalus is estimated. Low- and middle-income countries incur the greatest burden of disease, particularly those within the African and Latin Ameri-

ABBREVIATIONS AFR = African Region; AMR-L = Region of the Americas, Latin America; AMR-US/Can = Region of the Americas, United States/Canada; EMR = Eastern Mediterranean Region; EUR = European Region; HIC = high-income country; IHME = Institute for Health Metrics and Evaluation; IQR = interquartile range; LMIC = low- and middle-income country; NPH = normal pressure hydrocephalus; NTD = neural tube defect; PHH = posthemorrhagic hydrocephalus; PIH = postinfectious hydrocephalus; SEAR = South-East Asia Region; WPR = Western Pacific Region.

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can regions. Reliable incidence and burden figures for adult forms of hydrocephalus are absent in the literature and warrant specific investigation. A global effort to address hydrocephalus in regions with the greatest demand is imperative to reduce disease incidence, morbidity, mortality, and disparities of access to treatment.

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KEYWORDS epidemiology; global; hydrocephalus; incidence; prevalence; volume; worldwide

Hydrocephalus is the most common childhood brain disorder and among the most common entities addressed by neurosurgeons. Associated with a variety of etiologies and with competing theories of pathophysiology, untreated hydrocephalus might result in macrocephaly, cognitive dysfunction, and even death. Once diagnosed, treatment consists of CSF diversion by means of a shunt or third ventriculostomy, performed by a surgeon adept at the management of hydrocephalus.

Geographic disparities in hydrocephalus incidence have been demonstrated. In sub-Saharan Africa, Warf et al. estimated an annual incidence of more than 225,000 new cases of infant hydrocephalus, the majority likely resulting from neonatal or childhood CNS infection.[96,99] This would translate into approximately 750 new cases per 100,000 live births. In contrast, Munch et al. recently calculated an incidence of 110 cases of infantile hydrocephalus per 100,000 live births in a European cohort.[62] Generally, hydrocephalus diagnosed during childhood represents a chronic disease that is carried into adulthood and requires continued CSF diversion. Adult-onset hydrocephalus can result from tumor-related obstruction, infection, trauma, and idiopathic causes (e.g., normal pressure hydrocephalus [NPH]).

A reliable estimate of the global burden of hydrocephalus has remained elusive because of the combined result of sparse population-based data, competing definitions, underdiagnosis and underreporting, and radiographic limitations in resource-poor settings. While difficult to measure, understanding the scope of the problem is essential to any coordinated, multinational public health effort. This is particularly true in many low-income countries where children, who are at higher risk for hydrocephalus, constitute a near majority of the populace.[10] In this report, we aggregate data from a systematic review of the literature to estimate region-specific incidence figures via a meta-analysis, ultimately culminating in a global estimation of the incidence of childhood hydrocephalus. Data regarding the incidence of adult hydrocephalus are summarized qualitatively and contextualized in relation to the literature shortcomings.

Methods

Systematic Review

Our review was conducted in accordance with the guidelines outlined by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[58] Consistent with the methodology proposed by the Pediatric Hydrocephalus Systematic Review and Evidence-Based Guidelines Task Force,[7] a comprehensive literature search was conducted using the MEDLINE/PubMed database and the Cochrane Database of Systematic Reviews in September 2016 to capture studies published between 1990 and 2016. The full list of search terms, which aimed to capture region-specific epidemiological data on hydrocephalus, can be found in the *Appendix*. Briefly, MeSH and title/abstract terms were included to maximize inclusion of any article related to hydrocephalus epidemiology (e.g., incidence, prevalence, burden, mortality) published in countries recognized by the World Bank. An initial set of reviewers screened the titles (A.R. and L.J.G.) and abstracts (A.R. and L.J.G.) of resulting articles. Included papers contained epidemiological data for a given population pertaining to hydrocephalus volume (incidence, prevalence), hydrocephalus burden of disease (including disability-adjusted life years, years of life lost, and years lost due to disease), or hydrocephalus etiology proportion. Case reports, case-control studies, comparison studies, randomized controlled trials, commentaries, historical articles, and practice guidelines were excluded. Discrepancies between article inclusion and exclusion were resolved by an arbiter (M.C.D.) before full-text review. At a subsequent stage, a review team (A.R., L.J.G., and M.C.D.) obtained the full-text articles and performed data extraction. At both the abstract review and full-text review stages, reviewers jointly reviewed a random subset of articles to ensure selection accuracy, and this process was repeated until a general consensus was reached across all reviewers. During this stage, article references were also cross-checked for relevant cited studies, which were included if they fulfilled the selection criteria. A detailed account of the inclusion/exclusion process is shown in Fig. 1.

The methodological quality of each study was rated on a 6-point scale from lowest (0—not population-based, small sample size) to highest (5—population-based, large sample size).[25] To account for publication bias from high-income countries, a relatively lower score was accepted as a minimal inclusion threshold for published papers from low- and middle-income countries.

Meta-Analysis

Data analysis was performed using Comprehensive Meta-Analysis (version 3, Biostat, Inc.) and Stata14 software. The random-effects model according to the method of DerSimonian and Laird that accounted for variation between studies in addition to within-study variance was used to obtain the overall incidence estimates and the 95% confidence intervals.[17] Forest plots were generated to visualize the individual and summary estimates. Heterogeneity was evaluated among studies using the Cochran's Q test ($p < 0.10$) and I^2 statistic to measure the proportion of total variation due to that heterogeneity. An $I^2 > 50\%$ was

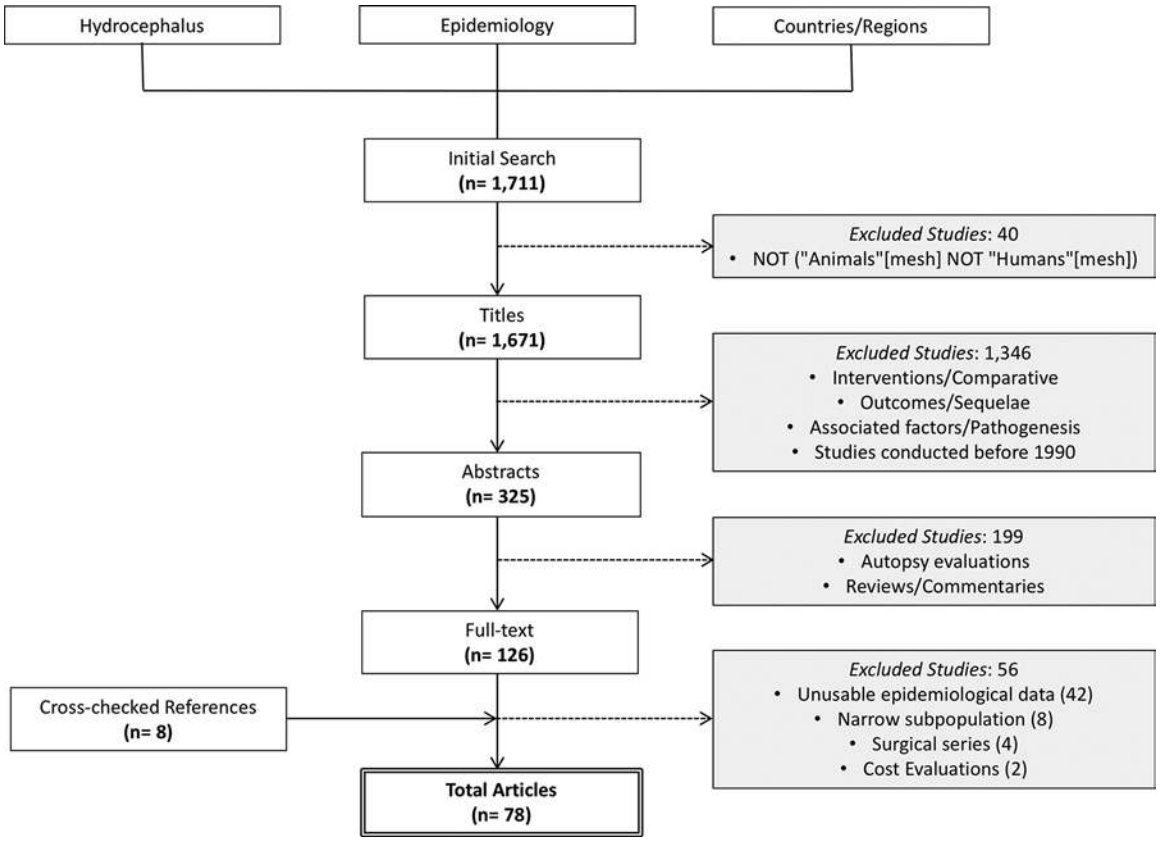

FIG. 1. PRISMA flow diagram. Seventy-eight articles were incorporated into the review from a total of 1711 titles.

considered to be high.[35] Potential sources of heterogeneity were explored using subgroup analyses by categorical covariates: individual WHO region and binary income level (high-income countries [HICs] and low- and middle-income countries [LMICs]). A univariate meta-regression was conducted on study quality (continuous) and income level (binary) for each WHO region to explore sources of heterogeneity. Potential publication bias was assessed using funnel plots, Egger's linear regression test, and Begg's correlation test. If publication bias was indicated, the number of missing studies was evaluated by the trim and fill method. A p value < 0.05 was considered significant, unless otherwise indicated.

Incorporating Variants of Infant Hydrocephalus

The majority of source papers reported congenital hydrocephalus or described disease states most closely representing this classification of disease. To deliver the most accurate picture of childhood hydrocephalus, several methods were employed to supplement the data with the contribution of other common forms of hydrocephalus, including neural tube defect (NTD)–related hydrocephalus (typically omitted from estimates of congenital hydrocephalus), posthemorrhagic hydrocephalus (PHH), and postinfectious hydrocephalus (PIH).

The Epi Visualization tool of the Institute for Health Metrics and Evaluation (IHME) (https://vizhub.healthdata.org/epi/) and the World Bank crude birth rate data (https://data.worldbank.org/indicator/SP.DYN.CBRT.IN) were used to obtain estimates for the contribution of NTDs to the overall volume of childhood hydrocephalus. Data from member countries within each WHO region and each income level were averaged to deliver a single birth incidence estimate of severe NTDs (Supplemental Table 1). Approximately 70% of patients with severe NTDs are anticipated to develop hydrocephalus.[57] After accounting for region- and income-specific annual birth figures, the NTD-related hydrocephalus figure was added to the congenital cases (Table 1).

Similarly, estimates for PHH were added to the overall childhood hydrocephalus estimate (Table 1). Reliable incidence estimates for PHH of prematurity only existed for high-income locations and were estimated previously.[100] Briefly, approximately 1.4% of live births in the United States are considered very low birth weight (< 1500 g)[16] and 5%–10% of very low birth weight infants suffer high-grade (III or IV) intraventricular hemorrhage, 30%–40% of whom develop hydrocephalus.[53,101] Therefore, approximately 38 neonates will develop PHH of prematurity for every 100,000 live births. To maintain conservatism in our estimates, LMICs (and regions with a predominance of LMICs) were assumed to incur a negligible burden of PHH.

Finally, PIH was incorporated into the global estimate. Since regional incidence figures do not exist, we relied on known proportions from Africa, wherein 60% cases of infantile hydrocephalus have been shown to be PIH.[96] To

TABLE 1. Estimated incidence and annual volume of childhood hydrocephalus by WHO region

WHO Region	Crude Births, Annual (no.)	Incidence of CHC	New Cases of CHC, Annual (no.)	Incidence of NTD-HC	New Cases of NTD-HC, Annual (no.)	Incidence of PHH	New Cases of PHH, Annual (no.)	New Cases of Non-PIH, Annual (no.)	Proportion of PIH Among All HC	New Cases of PIH, Annual (no.)	Total Estimated New Cases of HC, Annual (no.)
AFR	36,376,124	144.9	52,709	53.8	19,584	—		72,293	0.6	108,440	180,733
AMR-US/Can	4,408,520	67.5	2,976	22.1	974	38.5	1,697	5,647	—	—	5,647
AMR-L	10,948,403	316.1	34,608	24.3	2,661	—		37,269	0.3	15,972	53,241
EMR	17,394,811	110.1	19,152	44.1	7,664	—		26,823	0.3	11,493	38,309
EUR	11,447,692	83.3	9,536	17.7	2,025	38.5	4,407	15,968	—	—	15,968
SEAR	37,525,360	76.3	28,632	23.6	8,873	—		37,505	0.3	16,073	53,578
WPR	24,320,979	83.5	20,308	20.8	5,065	—		25,373	0.3	10,874	36,247
Worldwide	142,421,888.51		167,920		46,420		6,105	220,445		162,852	383,724

CHC = congenital hydrocephalus; HC = hydrocephalus; NTD-HC = NTD-related hydrocephalus; — = negligible.
Incidence figures are represented as number/100,000 births.

deliver a conservative estimate, we assumed that HICs and regions with predominantly HICs experience a negligible volume of PIH, and that the remaining non-African LMIC regions observe PIH in 30% of total childhood hydrocephalus (C. Deopujari, personal communication) (Table 1). For income level designations, the weighted average of proportions was taken for all non–AMR-US/Can and non-EUR regions (0.386) and applied to the total hydrocephalus case number (Table 2).

Data Reporting

Descriptive statistics are reported as proportions of a population and as medians (interquartile range [IQR]) where appropriate. Because the majority of childhood hydrocephalus studies reported incidence in relation to birth figures, the pooled incidence here was reported per 100,000 births. The total number of expected births for each region was summed from figures reported by the World Bank data library.[99] NPH was considered separately from pediatric and congenital forms of hydrocephalus, given the heterogeneity and to avoid misrepresentation of the reported findings.

To deliver a geographic breakdown of disease, results were organized and presented in relation to the WHO region from which each study was conducted. WHO regions were classified as follows: African Region (AFR), Region of the Americas (here, divided into Latin America [AMR-L] and United States/Canada [AMR-US/Can]), South-East Asia Region (SEAR), European Region (EUR), Eastern Mediterranean Region (EMR), and Western Pacific Region (WPR) (http://www.who.int/about/regions/en/). Income level for each country was categorized by the World Bank using gross national income per capita (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups).

Results

Literature Yield

The initial PubMed literature search yielded 1711 articles, 40 of which were animal studies and removed (Fig. 1). After a review of titles, 1346 articles were excluded if they 1) were conducted before 1990, 2) were randomized trials (e.g., interventional, comparative studies), 3) were long-term outcomes or sequelae studies, or 4) analyzed associated factors or pathogenesis. Two reviewers then independently reviewed abstracts (A.R. and L.J.G.) of the remaining 225 articles and applied the inclusion criteria stated above. A total of 126 full-text articles were fully examined, and 56 articles were removed for the reasons outlined in Fig. 1. The majority were excluded for one of two reasons: 1) disease incidence or prevalence was not explicitly reported, or there was insufficient affected/unaffected population data to allow reliable calculation thereof, or 2) the study focused on a specific subpopulation, such as a single variant of hydrocephalus (e.g., tumor-related hydrocephalus), or a nonrepresentative demographic cohort. Review of each paper's reference section added an additional 8 relevant papers, yielding a total of 78 papers included in this review (Supplemental Table 1).[1–6,8,9,11,12,14,15,19–24,26–30,31–34,36–40,42,44–47,49–51,54,55,59,60,62–64,66–69,

TABLE 2. Estimated incidence and annual volume of childhood hydrocephalus by World Bank income level

Income Level	Crude Births, Annual (no.)	Incidence CHC	New Cases of CHC, Annual (no.)	Incidence of NTD-HC	New Cases of NTD-HC, Annual (no.)	Incidence of PHH	New Cases of PHH, Annual (no.)	New Cases of Non-PIH, Annual (no.)	Proportion of PIH Among All HC	New Cases of PIH, Annual (no.)	Total Estimated New Cases of HC, Annual (no.)
LMIC	129,585,579	123.3	159,779	27.4	35,506	—	—	195,285	0.386	122,769	318,055
HIC	12,892,214	78.7	10,146	20.8	2,682	38.5	49,635	12,828	—	—	12,828
Worldwide	142,477,793		169,925		35,545			205,470		122,769	330,883

Incidence figures are represented as number/100,000 births.

[72,73,75–77,79,81,83,85–87,90,91,93,102,103–106] The Cochrane Database of Systematic Reviews yielded zero relevant articles. Characteristics of papers and relevant considerations are noted in Supplemental Table 1.

The search results yielded studies well representative of the global community with reports from 34 countries on 6 continents with all WHO regions represented: AFR = 8 (12 studies), AMR-L = 2 (2 studies), AMR-US/Can = 2 (8 studies), EMR = 4 (8 studies), EUR = 12 (32 studies, in which 2 studies incorporated multiple EUR countries), SEAR = 1 (2 studies), and WPR = 5 (15 studies). One study was listed twice because distinct data sets were provided (Kenya and Canada).[71] Although Taiwan is not currently categorized by the WHO or World Bank, we included it in the WPR and high-income classifications. The number of patients included in individual studies ranged widely (4–3850), with a median of 56 patients (IQR 22–190 patients). Forty-four studies provided population-based data, relative to 35 with hospital- or facility-based reporting. Article details including individual considerations and relative limitations are outlined further in Supplemental Table 1.

Forty-four studies representative of a uniform infant population were incorporated in our meta-analysis for congenital hydrocephalus (Fig. 1). Studies on NPH and other forms of adult hydrocephalus were separated from the childhood cohort in an independent meta-analysis (Supplemental Table 1) and are examined below qualitatively.

Incidence, Demographics, and Subtype

The pooled estimated incidence of congenital hydrocephalus was highest in Africa and Latin America (145 and 316 per 100,000 births, respectively) and lowest in the United States/Canada (68 per 100,000 births) (p for interaction < 0.1; Figs. 2 and 3, Table 1).[1,2,5,6,11,14,15,21–23,26–29,31,33,34,39,41,44,54,63,65,67–69,72,76–81,83,84,86,88,93,102,104] Each subgroup presented with a high heterogeneity ($I^2 > 50\%$ for all). For the 15 studies conducted in Europe, a univariate meta-regression revealed that study quality (slope = −0.28, p = 0.04) and income level (slope = 0.69, p = 0.02) are a significant source of heterogeneity, so that a higher incidence was associated with a lower study quality or a low- to middle-income country. No other sources of heterogeneity were identified for the other WHO regions. Considering specific countries with population-based data, Ekanem et al. (Nigeria) reported the lowest incidence of congenital hydrocephalus (34/100,000),[22] while Zheng et al. documented the highest (405/100,000).[106] Most countries reported figures between 50 and 160 new cases per 100,000 births (Supplemental Table 1). Taking into account regional populations, the greatest estimated annual volume of hydrocephalus cases is in AFR, AMR-L, and SEAR (180,733, 53,241, and 53,578 cases, respectively), representing 60% of all new cases of pediatric hydrocephalus. Worldwide, this model estimated a total of more than 383,000 new cases of childhood hydrocephalus each year.

Male children were more commonly affected by hydrocephalus than their female counterparts in all studies reporting data on gender, except one from Mozambique (male/female ratio of 1:1). The gender gap was greatest in Pakistan, with males affected at more than twice the rate of females.[73] The lowest gender differences were reported by studies from Taiwan and Papua New Guinea (1.04:1 and 1.03:1, respectively), while most reported a ratio around 1.05:1–1.41:1 (M/F).[44,50] Most studies involved pediatric patients only, while 13 examined adults with hydrocephalus (Supplemental Table 1).

Regarding pediatric hydrocephalus, most authors reported a congenital hydrocephalus cohort. However, across studies the definition of and distinction between congenital hydrocephalus and infantile hydrocephalus was not uniform. Naturally, studies of fetal hydrocephalus were generally conducted utilizing prenatal ultrasonograph. In these studies, a live-birth rate was not always reported; therefore, calculating a true postnatal incidence was not possible.

On average, studies from more developed regions were of higher study quality than those from resource-poor settings (Fig. 4). Out of 5, the average study quality was 3.75 for AMR-US/Can studies and 3.13 for EUR studies. On the other hand, methodological quality was lower for studies from AFR (2.25 of 5), AMR-L (2 of 5), and SEAR (1.5 of 5).

Low- and Middle-Income Countries Versus High-Income Countries

Consistent with the expected publication bias, source papers from HICs (46) were encountered more frequently than those from LICs (5) and MICs (26) (1 study included data from several countries). The mean study quality in HICs was also higher than that in LMICs (3.3 vs 2.4). Using the random-effects model, the incidence of congenital hydrocephalus was significantly higher in LMICs (incidence: 123.3 per 100,000 live births; 95% CI 97.5–151.9)

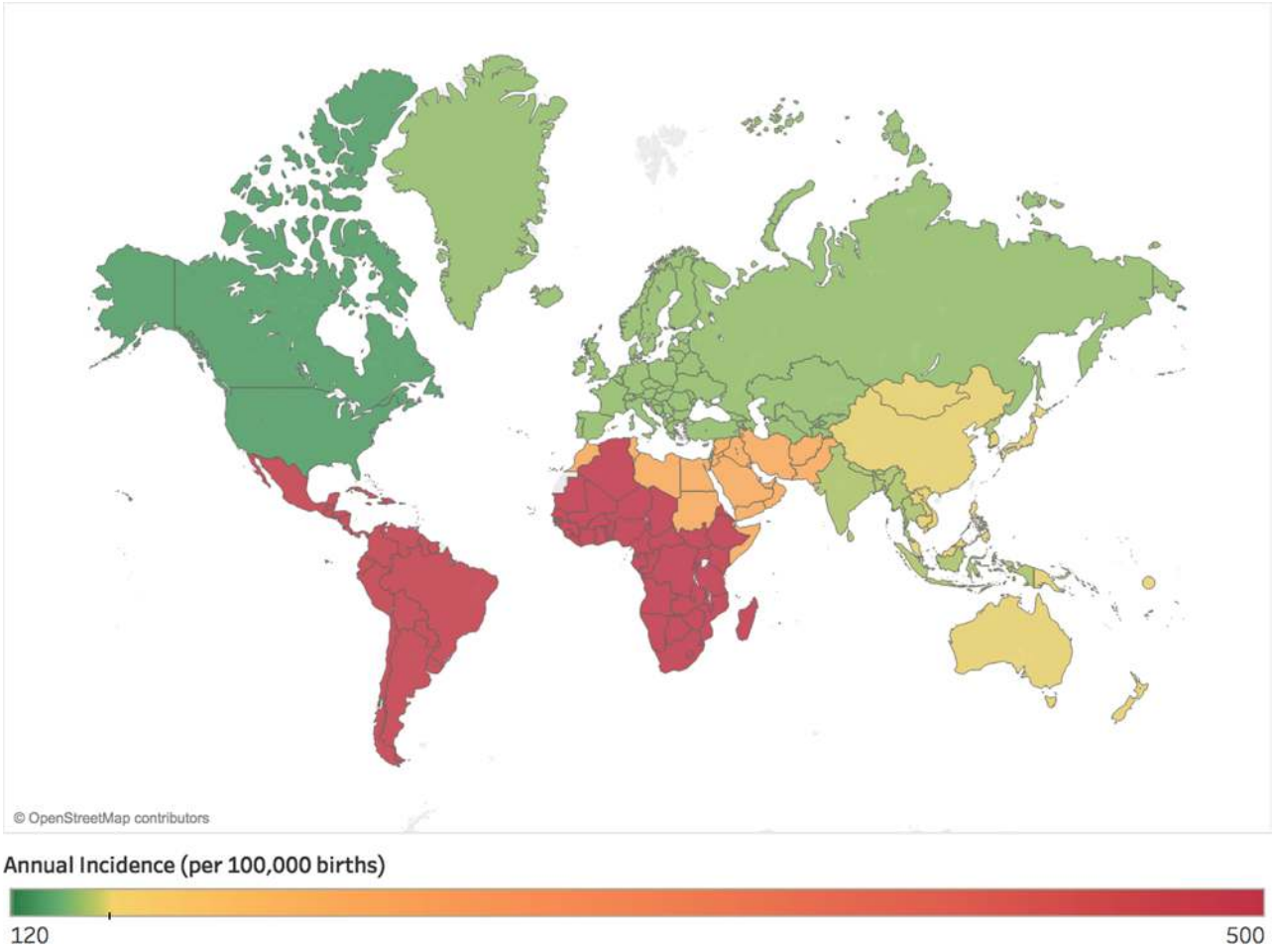

FIG. 2. Incidence of hydrocephalus by WHO region. WHO regions are shaded according to annual incidence of hydrocephalus (per 100,000 births). © OpenStreetMap contributors. Figure is available in color online only.

than in HICs (incidence: 78.7 per 100,000 live births; 95% CI 67.9–90.2) (p for interaction < 0.01) (Fig. 5, Table 2). Notably, the heterogeneity in each subgroup was high, as evidenced by the high I^2 value. After incorporating NTDs, PHH, and PIH, the annual volume of newly diagnosed hydrocephalus in LMICs was more than 20 times that in HICs (318,055 vs 12,828). For the 21 studies from LMICs, a univariate meta-regression revealed study quality (slope = –0.33, p = 0.04) to be a significant source of heterogeneity so that a higher incidence was associated with a lower study quality (Supplemental Fig. S1). No other sources of heterogeneity were identified for studies in HICs.

It should be noted that the birth rate in LMICs dramatically superseded that in HICs (> 10 fold). The higher birth incidence of NTDs in LMICs is expected, given disparities in basic perinatal care; however, the incidence of NTD is likely abated in HICs by prenatal diagnosis and elective termination.[59] The difference in global hydrocephalus figures between WHO region classification (Table 1) and income level designation (Table 2) partially reflects the absence of NTD birth rate data by income level designation for LICs. Because each WHO region was represented within the IHME data set, the global volume can be expected to more closely approximate that reflected by WHO region (approximately 383,000) rather than that by income level (approximately 330,000).

A symmetrical inverted funnel plot suggested the absence of publication bias for papers contributing to estimates of congenital hydrocephalus incidence (Supplemental Fig. S2). Both Begg's rank correlation test (p = 0.61) and Egger's linear regression test (p = 0.09) indicated no publication bias.

Surgical Incidence and Mortality

The majority of pediatric hydrocephalus cases (> 90% in most studies) were managed operatively. Conversely, most patients from NPH series were managed nonoperatively. Not every study explicitly stated the type of hydrocephalus intervention, although the majority discussing surgical intervention described shunt insertion.

Case-fatality rates (the proportion of deaths among affected individuals, over the course of the disease) ranged broadly from 4% to 87% and varied considerably by the presence/absence of concomitant congenital defects, treated/untreated status, follow-up duration, and WHO region. Most studies reported overall case-fatality figures in pediatric patients with hydrocephalus to be between 11% and 41%.

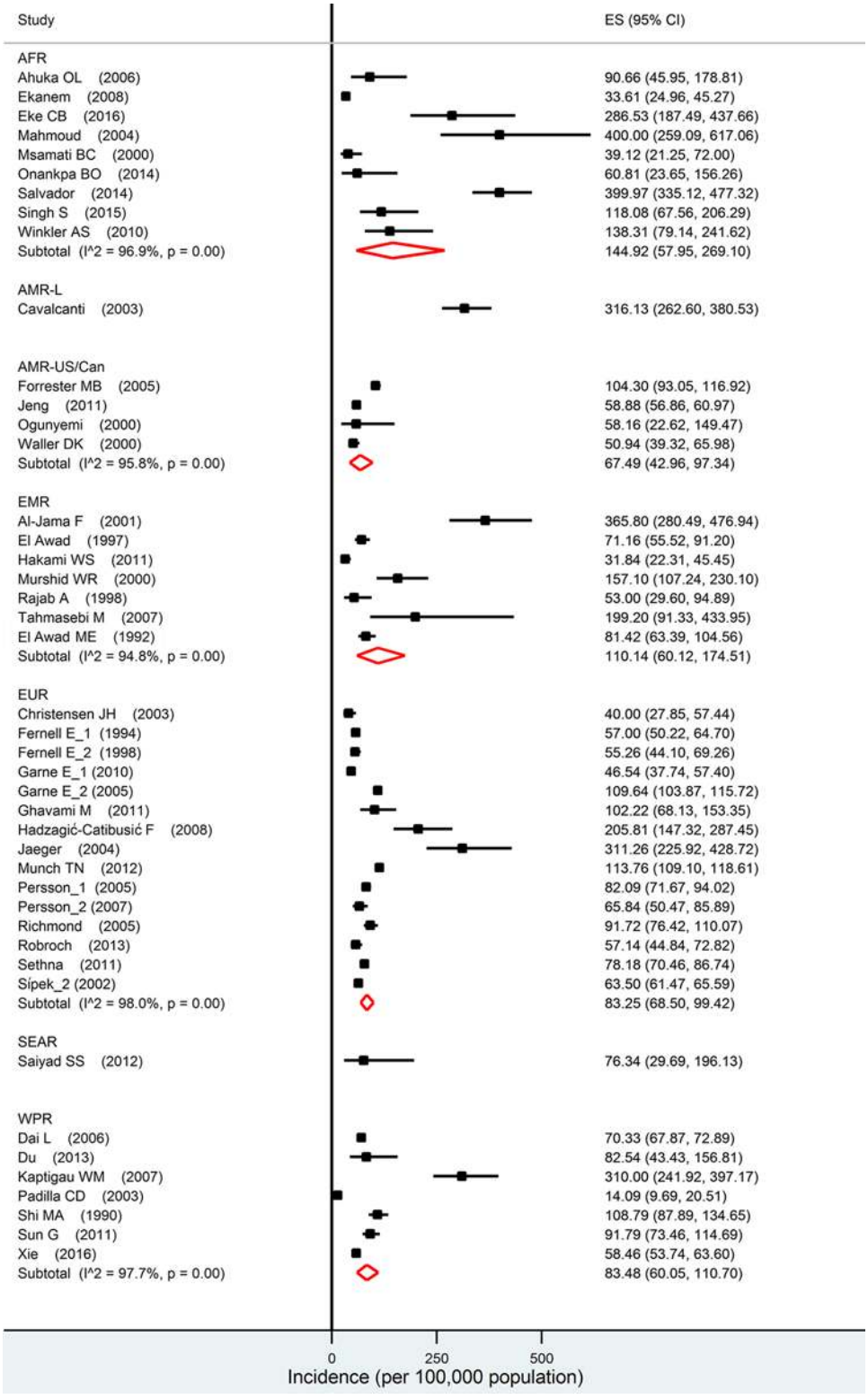

FIG. 3. Forest plot of the incidence of congenital hydrocephalus by WHO region; random-effects model. Effect size (ES) values represent the number of cases of hydrocephalus per 100,000 births (95% CI). *Diamonds* represent the pooled estimate of the incidence for each subgroup (width denotes 95% CI). Weights are from the random-effects analysis using the method of DerSimonian and Laird. Heterogeneity by WHO region: AFR (I^2 = 96.9%, p for heterogeneity < 0.01; 9 studies); AMR-L (I^2 = not applicable; 1 study); AMR-US/Can (I^2 = 95.8%, p < 0.01; 4 studies); EMR (I^2 = 94.8%, p < 0.01; 7 studies); EUR (I^2 = 98.0%, p < 0.01; 15 studies); SEAR (I^2 = not applicable; 1 study); and WPR (I^2 = 97.7%, p < 0.01; 7 studies); p for interaction comparing the different subgroups < 0.01. Figure is available in color online only.

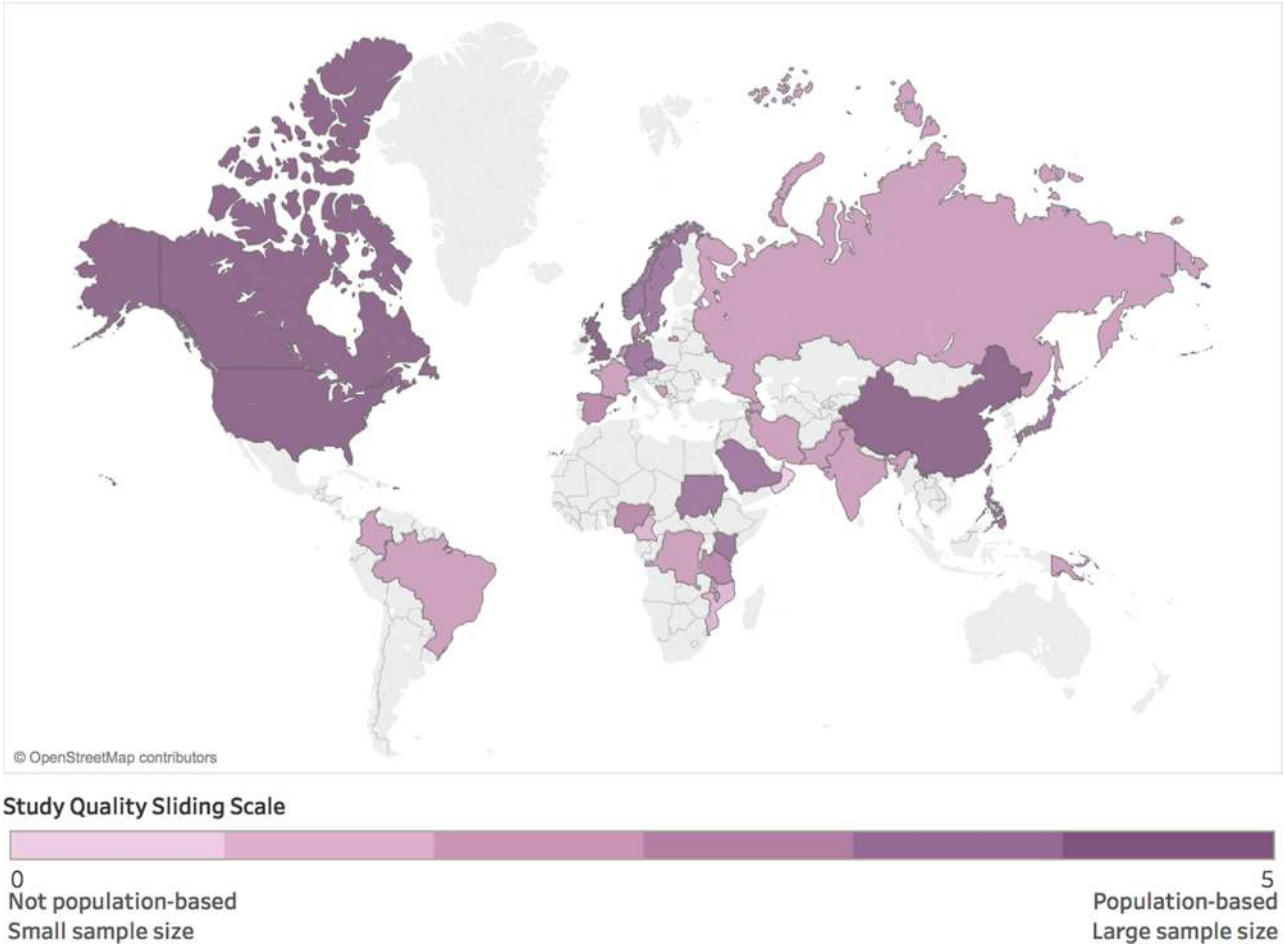

FIG. 4. Geographic representation of source data. The global map indicates countries from which hydrocephalus data were derived. Countries are shaded according to study quality along a spectrum, where 0/5 is shaded light purple and 5/5 is shaded dark purple. In countries with more than a single paper, the highest study quality was used for shading purposes. © OpenStreetMap contributors. Figure is available in color online only.

Adult Hydrocephalus

To deliver as comprehensive a global picture as possible, adult hydrocephalus was also investigated (*Appendix*). Incompatible epidemiological measures of case reporting, however, precluded merging adult and pediatric figures to obtain a single estimate for all-age hydrocephalus. Nonetheless, 10 NPH and 3 non-NPH adult studies met inclusion criteria and incorporated data from 3 continents. Only 5 NPH studies provided relevant incidence figures ranging from 1.1 to 5.5 newly affected individuals per 100,000 persons.[8,47,51,55] Despite the high heterogeneity among the 4 studies, a meta-regression analysis was not possible due to the few studies in this group. An adequately powered, population-based estimate of the incidence of non-NPH adult hydrocephalus was not identified in this review.

An asymmetrical inverted funnel plot suggested the presence of publication bias for the incidence of NPH. However, both Begg's rank correlation test ($p = 0.33$) and Egger's linear regression test ($p = 0.49$) indicated no publication bias. The trim and fill method was used to recalculate the pooled incidence by imputing 2 studies to the right of the effect estimate. The analysis suggested that the imputed incidence was identical to the original pooled estimate.

Discussion

Herein, we report the largest and most comprehensive systematic review of global hydrocephalus epidemiology to date. To our knowledge, for the first time in a systematic and quantitative fashion, we have estimated the global volume of hydrocephalus. More than 1700 titles were examined to reach 78 relevant papers representing more than 40,000 patients across 34 countries. The estimate birth prevalence of pediatric hydrocephalus is greatest in AFR, AMR-L, and SEAR and lowest in AMR-US/Can. On the African continent alone, more than 180,000 new cases of childhood hydrocephalus will develop each year. Meanwhile, nearly 90,000 new cases are estimated in SEAR and WPR. The greater prevalence of NTDs and PIH in these regions, as well as the higher birth rates per capita, accounts for the greater burden of disease in these regions relative to EUR and AMR-US/Can.

For the worldwide community, hydrocephalus is a tre-

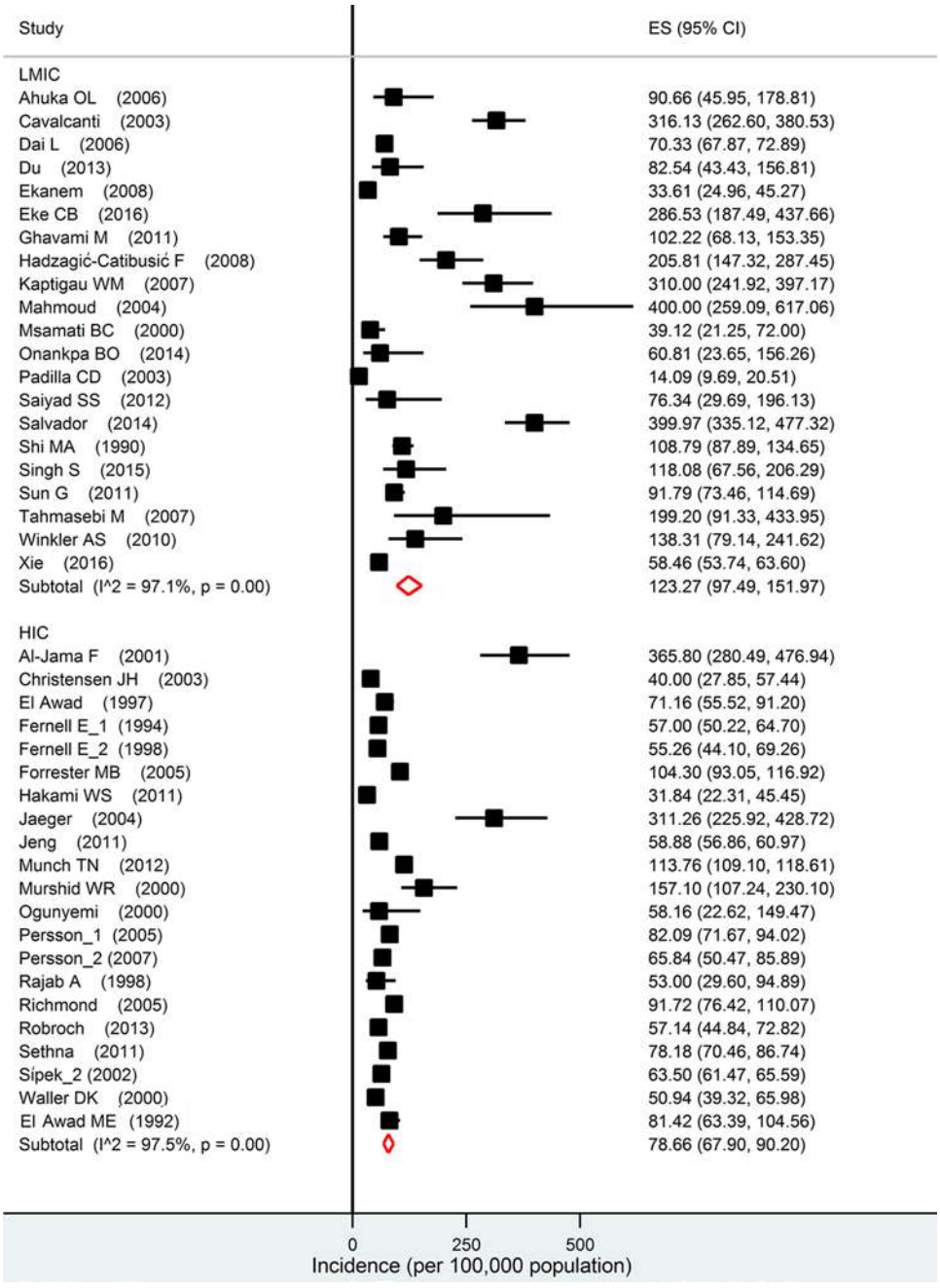

FIG. 5. Forest plot of congenital hydrocephalus incidence by World Bank income level (LMICs vs HICs); random-effects model. Effect size values represent cases of hydrocephalus per 100,000 live births (95% CI). *Diamonds* represent the pooled estimate of the incidence for each subgroup (width denotes 95% CI). Weights are from the random-effects analysis using the method of DerSimonian and Laird. Heterogeneity by income level: LMICs (I^2 = 97.1%, p < 0.01; 21 studies); HICs (I^2 = 97.5%, p for heterogeneity < 0.01; 21 studies); p for interaction comparing the different subgroups < 0.01. Figure is available in color online only.

mendously important public health concern. Not only is hydrocephalus one of the most common childhood neurological disorders, but also it is among the most common conditions treated by neurosurgeons.[82] For perspective, in 2015 an estimated 150,000 children were newly infected with HIV—less than half the number of children expected to develop hydrocephalus (http://aidsinfo.unaids.org). In disease burden calculations, the disability weight for hydrocephalus far exceeds that of tuberculosis, rheumatic heart disease, and blindness, to name a few.[70] Left untreated, hydrocephalus results in cognitive impairment, developmental delay, and often death. Yet it remains one of the most treatable conditions presenting for neurosurgical management.[48,97,99] Indeed, CSF diversion—and avoidance of sequelae associated with hydrocephalus—has been shown to be more cost-effective than antiretroviral therapy for HIV, orthopedic surgery for long-bone fractures, and even aspirin therapy for ischemic heart disease.[56]

The optimal treatment for hydrocephalus—particularly in low-resource settings—remains an intriguing topic of research, and one that is beyond the scope of this epidemiological review. While shunt insertion has represented the historical mainstay of treatment, the risk of malfunction and infection has prompted greater interest in procedures, such as endoscopic third ventriculostomy with or without choroid plexus cauterization, that might offer an alternative to shunting with fewer complications and reduced cost.[18,89,94] Whatever the optimal treatment, there is clearly an enormous worldwide volume of hydrocephalus that has been previously underrecognized.[56,61]

Prior Efforts to Obtain Global/Region Incidence Figures

Others have attempted to estimate a global or regional incidence of hydrocephalus and other CNS conditions via literature review,[92] state-sponsored health registries,[13] regional random sampling,[103] and both basic[99] and advanced mathematical modeling.[45] Wu and colleagues undertook an extraordinary effort to quantify the prevalence of childhood hydrocephalus in rural Kenya, but their random sampling technique was underpowered, and their results, by definition, were confined to the geographic region of study.[103] The IHME has become the standard bearer for population disease estimates by employing advanced statistical algorithms that control for dozens of health-influencing geopolitical and socioeconomic covariates. However, the global burden of hydrocephalus can only be roughly estimated by assuming a fraction of the congenital malformation estimates. Literature reviews, like the one undertaken here, are plagued by publication bias and vast study heterogeneity. We have attempted to strengthen our review methodology by conducting a series of meta-regression analyses that 1) acknowledge differences in methodological quality and study scope and 2) are specific for each WHO region. The result is a series of estimates specific to each region and for each World Bank income partition. Our goal is to provide figures that can be used not only for research focusing and care priority designation but also for neurosurgical advocacy and policy reforms.

Reliance on hospital-based data may lead to an overestimation of the severity of hydrocephalus experienced within a given population, as milder cases might never come to medical attention. However, when such studies attempt to extrapolate their observations onto the general population by asserting nonporous catchment, such estimates tend to underestimate the true overall disease burden. Additionally, the case estimates in Tables 1 and 2 incorporate only childhood hydrocephalus, leaving adult hydrocephalus unaccounted for. A lack of sufficient epidemiological data existed for tumor-related hydrocephalus, trauma-related hydrocephalus, and NPH, among others. Thus, the figures reported here likely represent an underestimation rather than an overestimation. Furthermore, given the lesser proportion of population-based studies emerging from LMICs, such underestimations might be more dramatic in LMICs than in HICs.

Inclusion of adult hydrocephalus in this review was deliberate, and an inability to responsibly estimate the global incidence of adult disease was discovered only after the systematic review was conducted. Thus, while the quantitative results only include childhood hydrocephalus, the aim of this study, its methodology, and its qualitative yet objective findings encompass both pediatric and adult variants. Indeed, the discovery of a paucity of population-based data on adult hydrocephalus is itself a tremendously important finding. In terms of establishing priorities for future research on hydrocephalus, this finding is perhaps even more impactful than the numeric estimations generated from the pediatric meta-analysis. While childhood hydrocephalus certainly attracts more attention among neurosurgeons globally, adult hydrocephalus too, from which many patients suffer, is a problem worldwide, despite relatively affordable and straightforward treatment. However, without a rough scope of the problem and known areas of maximal burden, it remains a problem whose solution is nearly impossible to efficiently craft.

Lastly, these estimates should not be interpreted to represent the total hydrocephalus case burden expected to require medical and/or surgical evaluation and treatment. It is well known that the initial treatment for hydrocephalus often represents just the first of several interventions during the lifetime of a patient with hydrocephalus.[43] Therefore, the global burden estimates provided here are only for the primary presentation and do not account for the multiple operations that may be necessary for individual patients after the initial treatment.

Limitations and Future Directions

The estimates outlined above are just that—estimates. However, they are estimates that are informed by the best, most up-to-date, and most diversified data available. Examination of the imperfections found within these figures is essential to understand their context and assign their value. First, the source data from which incidence figures are calculated are heterogeneous and often fragile. Differences in definition (ventriculomegaly vs symptomatic hydrocephalus), diagnostic modality (ultrasound vs CT or MRI vs clinical signs and symptoms), and age at evaluation (e.g., prenatal vs birth vs toddlerhood) all contribute to nonbiological differences in disease frequency. Similarly, drawing incidence figures and prevalence ratios from a non–population-based study design risks painting an incomplete, if not misleading, picture. Moreover, those regions where disease burden is suspected to be the greatest contain the largest proportion of hospital-based data and therefore garnered a lower methodological quality score. Because of publication bias and the need to incorporate data from resource-poor settings, we maintained a lower threshold for inclusion for papers from LMICs. This may have resulted in an over- or underestimation of incidence figures, particularly in WHO regions with a higher proportion of LMICs. Next, stated differences among individual study conclusions might reflect the study methodology and inclusion criteria as much as they might represent true differences among populations. Partitioning results by WHO region risks reliance on assumptions made regarding similarities among member countries. For example, while both Japan and Cambodia are WPR affiliates, their health-modifiable attributes, including governance, gross domestic product, and health care infrastructure, differ dramatically. The incidence of hydrocephalus in both countries

is therefore not likely to be identical. Finally, when combining the Global Burden of Disease incidence values for NTD,[45] to simplify data presentation the respective standard errors were not combined. While error propagation may therefore be present, the relative impact on overall regional estimates is minimal.

While hindering, these limitations should serve as a roadmap for future studies to not only more accurately estimate the global burden of hydrocephalus, but also do so in such a way as to maximize capacity building and resource allocation to regions in greatest need. Special attention should also be given to evaluating the burden of adult forms of hydrocephalus worldwide. These figures are expected to grow each year, as the world population also continues to grow and age. Efforts to define the etiological agents of PIH and to raise community awareness of the causes and treatments are underway in the developing world.[52,74,95,98] Estimating the global incidence is only among the initial steps. Mapping the geopolitical barriers from access to hydrocephalus care, educating the surgical workforce, and empowering local medical communities with the tools to prevent and treat the condition must become a priority.

Conclusions

Hydrocephalus is a major public health concern estimated to affect more than 380,000 new individuals annually. The volume of disease is greatest in the African, Latin American, and Southeast Asian regions and lowest in the United States and Canada. LMICs are expected to experience a case burden more than 20-fold that of HICs. Identification of region-specific causes and barriers to treatment and community-based education programs are active initiatives needing support and growth. An estimation of adult hydrocephalus burden is lacking and deserves attention. Meanwhile an international, coordinated effort toward surgical capacity building will be necessary to ensure global demand is met, particularly in resource-poor settings.

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Appendix

Search Terms

(((“epidemiology” [Subheading] OR “Epidemiology”[MeSH] OR epidemiology[tiab] OR epidemiological[tiab] OR population[tiab] OR population-based[tiab] OR inciden*[tiab] OR prevalen*[tiab] OR burden OR ratio[tiab] OR DALY[tiab] OR “disability adjusted life year*”[tiab] OR YLL[tiab] OR “years of life lost”[tiab] OR YLD[tiab] OR “years lost to disability”[tiab] or “years lost due to disability”[tiab] OR ratio[tiab] OR QALY[tiab] OR “quality adjusted life year*”[tiab]))

AND

(“Hydrocephalus”[MeSH] OR Hydrocephal*[tiab])

AND

(“Africa”[MeSH] OR “Asia”[MeSH] OR “Central America”[MeSH] OR “Developing Countries”[MeSH] OR “Geographical Locations Category”[MeSH] OR “Internationality”[MeSH] OR “Latin America”[MeSH] OR “South America”[MeSH] OR “Dominican Republic”[tiab] OR “Principe”[tiab] OR “Puerto Rico”[tiab] OR “Sao Tome”[tiab] OR “Saudi Arabia”[tiab] OR “Sierra Leone”[tiab] OR “Virgin Islands”[tiab] OR Afghanistan*[tiab] OR Africa*[tiab] OR Albania*[tiab] OR Algeria*[tiab] OR America*[tiab] OR Andorra*[tiab] OR Angola*[tiab] OR Antarct*[tiab] OR Antigua*[tiab] OR Arab Emirate*[tiab] OR Argentin*[tiab] OR Armenia*[tiab] OR Aruba*[tiab] OR Asia*[tiab] OR Atlantic[tiab] OR Australia*[tiab] OR Austria*[tiab] OR Azerbaijan*[tiab] OR Azores Islands[tiab] OR Baham*[tiab] OR Bahra*[tiab] OR Bangladesh*[tiab] OR Barbad*[tiab] OR Barbuda*[tiab] OR Barthelemy[tiab] OR Barthélemy[tiab] OR Belarus*[tiab] OR Belgi*[tiab] OR Belize[tiab] OR Bengali[tiab] OR Benin*[tiab] OR Bermuda*[tiab] OR Bhutan*[tiab] OR Bissau[tiab] OR Bolivia*[tiab] OR Bosnia*[tiab] OR Botswana*[tiab] OR Brazil*[tiab] OR Brunei[tiab] OR Bulgaria*[tiab] OR Burkina Faso[tiab] OR Burma[tiab] OR Burmese*[tiab] OR Burundi*[tiab] OR Cabo Verd*[tiab] OR Caicos[tiab] OR Cambodia*[tiab] OR Cameroon*[tiab] OR Canad*[tiab] OR Cape Verd*[tiab] OR Cayman[tiab] OR Central[tiab] OR Chad*[tiab] OR Chile[tiab] OR China[tiab] OR Chinese[tiab] OR Colombia*[tiab] OR Comoros[tiab] OR Congo*[tiab] OR Costa Rica*[tiab] OR Cote[tiab] OR Cote d’Ivoire[tiab] OR Croatia*[tiab] OR Cuba[tiab] OR Cuban[tiab] OR Cyprus[tiab] OR Czech Republic[tiab] OR Denmark[tiab] OR developing countr*[tiab] OR developing nation*[tiab] OR Djibouti[tiab] OR Dominica*[tiab] OR East[tiab] OR East Timor[tiab] OR Ecuador*[tiab] OR Egypt*[tiab] OR El Salvador*[tiab] OR Eritrea*[tiab] OR Estonia*[tiab] OR Ethiopia*[tiab] OR Europ*[tiab] OR Fiji*[tiab] OR Finland[tiab] OR France[tiab] OR French Guiana[tiab] OR Gabon*[tiab] OR Gambia*[tiab] OR Gaza*[tiab] OR Georgia*[tiab] OR German*[tiab] OR Ghana*[tiab] OR Greece[tiab] OR Grenada*[tiab] OR Grenadines[tiab] OR Guadeloupe[tiab] OR Guatemala*[tiab] OR Guinea*[tiab] OR Guyan*[tiab] OR Haiti*[tiab] OR Herzegovina*[tiab] OR Hondura*[tiab] OR Hungary[tiab] OR Iceland*[tiab] OR income[tiab] OR India[tiab] OR Indian*[tiab] OR Indonesia*[tiab] OR Iran*[tiab] OR Iraq*[tiab] OR Ireland[tiab] OR Israel*[tiab] OR Italian[tiab] OR Italy[tiab] OR Ivory Coast[tiab] OR Jamaica*[tiab] OR Japan*[tiab] OR Jordan*[tiab] OR Kazakh*[tiab] OR Kenya*[tiab] OR Kiribati[tiab] OR Kitts[tiab] OR Korea*[tiab] OR Kosovar*[tiab] OR Kosovo[tiab] OR Kuwait*[tiab] OR Kyrgyz*[tiab] OR Lao[tiab] OR Laos*[tiab] OR Laotian*[tiab] OR latin america[tiab] OR Latvia[tiab] OR Lebanes*[tiab] OR Lebanon[tiab] OR Lebanese[tiab] OR Lesotho[tiab] OR less developed countr*[tiab] OR less developed nation*[tiab] OR Liberia*[tiab] OR Libya*[tiab] OR Liechtenstein[tiab] OR Lithuania[tiab] OR lmic[tiab] OR lmics[tiab] OR low income countr*[tiab] OR low income nation*[tiab] OR Lucia[tiab] OR Luxembourg[tiab] OR Macedonia*[tiab] OR Madagascar*[tiab] OR Madeira Island[tiab] OR Malawi*[tiab] OR Malaysia*[tiab] OR Maldives[tiab] OR Mali[tiab] OR Malta[tiab] OR Marshall Island*[tiab] OR Martinique[tiab] OR Mauritania*[tiab] OR Mauriti*[tiab] OR Mexican*[tiab] OR Mexico[tiab] OR Micronesia*[tiab] OR middle income countr*[tiab] OR middle income nation*[tiab] OR Moldova[tiab] OR Moldova*[tiab] OR Monaco[tiab] OR Mongolia*[tiab] OR Montenegr*[tiab] OR Montserrat[tiab] OR Morocc*[tiab] OR Mozambique[tiab] OR Myanmar[tiab] OR Namibia*[tiab] OR Nauru[tiab] OR Nepal*[tiab] OR Nevis[tiab] OR New Zealand[tiab] OR Nicaragua*[tiab] OR Niger*[tiab] OR Nigeria*[tiab] OR North[tiab] OR Norway[tiab] OR Oman*[tiab] OR Pacific[tiab] OR Pakistan*[tiab] OR Palau[tiab] OR Palestin*[tiab] OR Panama*[tiab] OR Papua[tiab] OR Paraguay*[tiab] OR Peru*[tiab] OR Philippin*[tiab] OR Poland[tiab] OR poor countr*[tiab] OR poor nation*[tiab] OR Portug*[tiab] OR Principe[tiab]

OR Qatar*[tiab] OR Romania*[tiab] OR Russia*[tiab] OR Rwanda*[tiab] OR Saint Lucia[tiab] OR Saint Vincent[tiab] OR Samoa*[tiab] OR San Marino[tiab] OR Sao Tome[tiab] OR Senegal*[tiab] OR Serbia*[tiab] OR Seychelles[tiab] OR Sierra Leone*[tiab] OR Singapore[tiab] OR Slovakia*[tiab] OR Slovenia*[tiab] OR Solomon[tiab] OR Solomon Island*[tiab] OR Somalia*[tiab] OR South [tiab] OR Spain[tiab] OR Sri Lanka[tiab] OR Sudan*[tiab] OR Suriname*[tiab] OR Swaziland*[tiab] OR Swed*[tiab] OR Switzerland[tiab] OR Syria*[tiab] OR Taiwan[tiab] OR Tajik*[tiab] OR Tanzania*[tiab] OR Thai*[tiab] OR third world countr*[tiab] OR third world nation*[tiab] OR Timor Leste[tiab] OR Timor*[tiab] OR Tobago[tiab] OR Togo*[tiab] OR Tonga*[tiab] OR Trinidad*[tiab] OR Tunisia*[tiab] OR Turkey[tiab] OR Turkish[tiab] OR Turkmen*[tiab] OR Turks[tiab] OR Tuvalu*[tiab] OR Uganda*[tiab] OR Ukrain*[tiab] OR under developed countr*[tiab] OR under developed nation*[tiab] OR underdeveloped nation*[tiab] OR underdeveloped nation*[tiab] OR United Kingdom[tiab] OR United States[tiab] OR Uruguay[tiab] OR Uzbeki*[tiab] OR Vanuatu*[tiab] OR Vatican[tiab] OR Venezuela*[tiab] OR Viet nam*[tiab] OR Vietnam*[tiab] OR Vincent[tiab] OR West[tiab] OR West Bank[tiab] OR Yemen*[tiab] OR Zambia*[tiab] OR Zimbabw*[tiab])

NOT

("Animals"[MeSH] NOT "Humans"[MeSH])

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Conception and design: Dewan. Acquisition of data: Dewan, Rattani, Glancz. Analysis and interpretation of data: Dewan, Rattani, Mekary, Baticulon. Drafting the article: Dewan. Critically revising the article: Dewan, Rattani, Mekary, Glancz, Baticulon, Fieggen, Wellons, Park, Warf. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dewan. Statistical analysis: Dewan, Mekary, Yunusa. Administrative/technical/material support: Rattani, Baticulon. Study supervision: Wellons, Warf.

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