Aetiology and diagnostics of paediatric hydrocephalus across Africa: a systematic review and meta-analysis

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Summary

Background We aimed to identify the aetiological distribution and the diagnostic methods for paediatric hydrocephalus across Africa, for which there is currently scarce evidence.

Methods In this systematic review and meta-analysis, we searched MEDLINE (Ovid), the Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Global Health (Ovid), Maternity & Infant Care (Ovid), Scopus, African Index Medicus (Global Index Medicus, WHO) and Africa-Wide Information (EBSCO) from inception to Nov 29, 2021. We included studies from any African country reporting on the distribution of hydrocephalus aetiology in children aged 18 years and younger, with no language restrictions. Hydrocephalus was defined as radiological evidence of ventriculomegaly or associated clinical symptoms and signs of the disorder, or surgical treatment for hydrocephalus. Exclusion criteria were studies only reporting on one specific subgroup or one specific cause of hydrocephalus. We also excluded conference and meetings abstracts, grey literature, editorials, commentaries, historical reviews, systematic reviews, case reports and clinical guidelines, as well as studies on non-humans, fetuses, or post-mortem reports. The proportions of postinfectious hydrocephalus, non-postinfectious hydrocephalus, and hydrocephalus related to spinal dysraphism were calculated using a random-effects model. Additionally, we included a category for unclear cases. Diagnostic methods were described qualitatively. To assess methodological study quality, we applied critical appraisal checklists provided by the Joanna Briggs Institute. The study was registered in Prospero (CRD42020219038).

Findings Our search yielded 3783 results, of which 1880 (49·7%) were duplicates and were removed. The remaining 1903 abstracts were screened and 122 (6·4%) full articles were sought for retrieval; of these, we included 38 studies from 18 African countries that studied a total of 6565 children. The pooled proportion of postinfectious hydrocephalus was 28% (95% CI 22–36), non-postinfectious hydrocephalus was 21% (95% CI 13–30), and of spinal dysraphism was 16% (95% CI 12–20), with substantial heterogeneity. The pooled proportion of hydrocephalus of unclear aetiology was 20% (95% CI 13–28).

Interpretation Our findings suggest that postinfectious hydrocephalus is the single most common cause of paediatric hydrocephalus in Africa. For targeted investments to be optimal, there is a need for consensus regarding the aetiological classification of hydrocephalus and improved access to diagnostic services.

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Introduction

Hydrocephalus is a disease that can require surgical treatment and lifelong follow up and care. Without timely detection and treatment, hydrocephalus can cause severe neurological deficiencies that affect quality of life and survival.[1] Hydrocephalus is one of the most common neurosurgical diseases affecting children worldwide,[2–4] with an estimated 400 000 new paediatric cases every year.[2] Previous research has shown an association between low country income level and incidence of hydrocephalus in the paediatric population.[2–4] Children in Africa are among the most commonly and severely afflicted with the disease,[2] partly due to increased incidence of postinfectious hydrocephalus following neonatal sepsis[2,5] and congenital anomalies including spinal dysraphism compared with high-income regions.[2]

In addition to the great global inequalities in paediatric hydrocephalus incidence estimates, there is a large, unmet need for neurosurgical services in African countries. Although the continent accounts for 2 million (almost 15%) of the 13·8 million essential neurosurgical cases requiring an operation every year, African health-care services have access to only 488 neurosurgeons (less than 1%) of the 49 940 neurosurgeons worldwide,[6] resulting in a large gap in access to care for patients with paediatric hydrocephalus. Reflecting the emerging public health interest in global neurosurgery, the much needed major consensus document, *Comprehensive Policy Recommendations for the Management of Spina Bifida and Hydrocephalus in Low-and-Middle-Income Countries* (CHYSPR), which was published in 2021, calls for increased investments in children with hydrocephalus across the life course.[7]

Research in context

Evidence before this study

Paediatric hydrocephalus is a neurosurgical disease associated with significant morbidity and mortality. African children are among those with the highest burden of the disease, yet they have poor access to neuroimaging diagnostics and surgical treatment. Although previous studies describe the different aetiologies affecting children in high-income versus low-and middle-income regions, we found no study describing the region-specific variances across the African continent.

Added value of this study

To the best of our knowledge, this is the first systematic review and meta-analysis examining the aetiological distribution and diagnostic methods for paediatric hydrocephalus in Africa. We included 38 studies from 18 countries, comprising 6565 children. Our results suggest that postinfectious hydrocephalus is the single most common aetiology of paediatric hydrocephalus across the African continent. We found that postinfectious hydrocephalus is significantly associated with study site geographical location defined by latitude. Moreover, the most resource-limited countries seem to experience the highest burden of postinfectious hydrocephalus. We also found that a considerable proportion of children did not have an identifiable cause of hydrocephalus, and therefore were labelled as having an unclear aetiology.

Implications of all the available evidence

Hydrocephalus is a major public health concern in Africa. Our main findings suggest that postinfectious hydrocephalus is the single most common cause. However, input from the source literature was heterogeneous, and the reporting of hydrocephalus aetiological categorisation was highly inconsistent. To aid clinicians and policy makers in formulating contextually-tailored and evidence-based decisions, we found a need for a more coordinated effort in the categorisation of hydrocephalus as well as further elucidation of the evidence regarding the association of non-biomedical factors, such as country income level and latitude of study site, with the aetiology of paediatric hydrocephalus in Africa.

Hydrocephalus has been associated with several possible aetiologies, and diagnosis is commonly based on an evaluation of clinical signs and symptoms in combination with radiological findings. Although one of the main aetiologies of paediatric hydrocephalus in high-income countries is neonatal intracranial haemorrhage,[4] there is sparse evidence on the causative mechanisms and aetiological distribution of paediatric hydrocephalus across Africa from which clinicians and policy makers can base their decisions. Research from Mbale in Uganda suggests that inflammatory changes, characteristic of neonatal infections and previous ventriculitis, is evident in a majority of the Ugandan paediatric population with hydrocephalus. For example, one of the early reports from this setting showed that 265 (57%) of 468 children had a postinfectious aetiology.[8] Another study from this setting indicated peaks in hydrocephalus occurrence in association with environmental factors such as seasonality and rainfall.[9]

Research from different African countries report that a majority of paediatric hydrocephalus cases are a result of congenital, non-postinfectious causes.[10–13] Although the diverging aetiologies reported could reflect the heterogeneity in hydrocephalus research, it could also be that the wide range of aetiological reporting could be a result of differing contextual factors. Inarguably, research from epidemiology and climatology suggests that some countries from the African meningitis belt are more affected by bacterial meningitis than others,[14] and studies from other medical disciplines have shown an association between latitude and disease.[15–17]

Surgery through cerebrospinal fluid diversion (shunts or endoscopic third ventriculostomy with or without choroid plexus cauterisation) is still the only viable treatment option to reduce substantial morbidity and mortality from hydrocephalus.[18] However, one might hope and envision that, in the future, some forms of hydrocephalus will be preventable and curable, given that adjuvant medical therapy might replace surgical treatment. Medical therapy would be particularly valuable for children with hydrocephalus in Africa due to scarce access to radiology[19] and neurosurgical treatment.[6] For targeted preventive and treatment options to be optimal and contextually tailored,[7] there is a need for increased knowledge of the aetiology and aetiological distribution of hydrocephalus. Therefore, we did a systematic review and meta-analysis to identify the empirical evidence of the predominant aetiology and the overall aetiological distribution of paediatric hydrocephalus across Africa.

Methods

Search strategy

For this systematic review and meta-analysis, and in line with the Pediatric Hydrocephalus Systematic Review and Evidence-Based Guidelines Task Force,[20,21] we searched MEDLINE (Ovid) and the Cochrane Database of Systematic Reviews (Wiley). We also searched the following electronic databases to capture all relevant continent-specific studies published on the topic: Embase (Ovid), Global Health (Ovid), Maternity & Infant Care (Ovid), Scopus, African Index Medicus (Global Index Medicus, WHO) and Africa-Wide Information (EBSCO). The search was done by an academic librarian (HS). All databases were searched from inception, and date of last search was Nov 29, 2021. Complete search strategies,

including search terms, are presented in the appendix (pp 3–5). The searches were not restricted by language or publication year. All references were imported into Endnote version X9 and duplicates were removed before exporting them to the software-screening tool, Rayyan.[22]

Selection criteria

Two review authors (CGA and AHP) independently screened all titles and abstracts resulting from the search according to predefined inclusion and exclusion criteria. The inclusion criteria were original studies reporting on the aetiological distribution of hydrocephalus within the paediatric population (aged ≤18 years) in any African country. Description of diagnostic tools applied was not an inclusion criterion. If the study reported on a mixed population, it was included only if separate results existed for the target population. Our working definition of hydrocephalus was radiological evidence of ventriculomegaly or associated clinical symptoms and signs of the disorder. Due to the sparsity of diagnostic tools in many low-resource settings, we accepted surgical treatment as a surrogate indicator for the diagnosis of hydrocephalus. We incorporated all forms of hydrocephalus (communicating, non-communicating, congenital, and acquired). Exclusion criteria were studies only reporting on one specific subgroup or one specific cause of hydrocephalus (eg, only congenital forms of hydrocephalus). We also excluded conference and meetings abstracts, grey literature, editorials, commentaries, historical reviews, systematic reviews, case reports, and clinical guidelines, as well as studies on non-humans, fetuses, or post-mortem reports. Disagreements about inclusion versus exclusion were resolved through discussion between CGA and AHP; a third member of the research team (PKE) served as a mediator. We made efforts to avoid inclusion of duplicate data, and in cases in which more than one paper reported on the same cohort of children, we included the study that had information on the largest group of children. Data were patient-level. The University of Oslo Library (Oslo, Norway) assisted in finding full text results. In cases in which the library was not able to obtain full text, we contacted the authors by email.

Data extraction

One of the authors (CGA) extracted data into an Excel (version 2016) spreadsheet according to prespecified variables (appendix p 6). All included studies and the Excel spreadsheet were reviewed and validated for correctness by another team member (PDK). Studies in which there was no information on mean or median age, but rather age was reported as age groups,[11, 23–27] we approximated a mean age (appendix p 6). We added country income level (based on World Bank Group analytical classifications from calendar year of publication),[28] and region according to African Union. Finally, we added latitude of study site city (appendix pp 7–8).

See **Online** for appendix

For the **Latitude of study site city** see www.gps-coordinates.net

Assessment of methodological study quality

Two review authors (CGA and EU) independently applied critical appraisal checklists provided by the Joanna Briggs Institute (Adelaide, SA, Australia) according to relevant study design, including the checklist for cohort studies (six studies), randomised control trials (one study), cross-sectional studies (one study), and case-control studies (one study). For the single-armed observational studies (retrospective and prospective designs), we applied the case series checklist (29 studies). We divided the papers into low, intermediate, or high methodological study quality on the basis of thresholds for each category that were agreed on by CGA and EU. Scoring for cohort studies was: 0–3=low quality, 4–7=intermediate quality, and 8–11=high quality; scoring for randomised control trials was: 0–4=low quality, 5–8=intermediate quality, and 9–13=high quality; scoring for cross-sectional studies was: 0–2=low quality, 3–5=intermediate quality, and 6–8=high quality; scoring of case-control studies was: 0–3=low quality, 4–7=intermediate quality, and 8–10=high quality; and scoring for case series was: 0–4=low quality, 5–8=intermediate quality, and 9–12=high quality. A score was only assigned when the answer to the question in the checklist was either "yes" or "not applicable". Scores were not assigned if the answer was "no" or "unclear". Low methodological study quality was not an exclusion criterion. A complete list of quality appraisals of all included studies is in the appendix (pp 9–13).

Categorisation of aetiologies

Studies from CURE Children's Hospital of Uganda categorised aetiologies as either postinfectious hydrocephalus, non-postinfectious hydrocephalus, or myelomeningocele;[8,29] this was a pragmatic distinction that we have modified and applied to our study. The modification includes the latter group that we have named spinal dysraphism. This new group includes hydrocephalus associated with myelomeningocele, as well as hydrocephalus associated with other forms of spina bifida and Arnold Chiari malformation. Additionally, we created a group we called "unclear". Only cases with a positively identified non-infectious congenital or acquired cause (eg, aqueduct stenosis, Dandy–Walker malformation, tumour, or haemorrhage) were embedded in our non-postinfectious hydrocephalus category. Cases labelled as congenital or non-postinfectious with no further subclassification of aetiologies were categorised as unclear, together with cases identified as idiopathic, other, unknown, etc. The rationale for applying this method relates to efforts in striving to maintain conservativism in our estimates. For a classification of all reported aetiologies across the various studies, see appendix (pp 14–18).

Data analysis

The primary objective of our study was to identify the empirical evidence of the predominant aetiology and the overall aetiological distribution of paediatric hydrocephalus across Africa. The secondary objective was to identify the methods applied to diagnose hydrocephalus and determine possible aetiology of hydrocephalus in children across Africa. All studies included in the systematic review were included in the meta-analysis. To calculate an overall proportion of paediatric hydrocephalus, we used a random effects meta-analysis of single proportions according to the DerSimonian-Laird method estimator for τ^2.[30] We used the Freeman-Tukey double arcsine transformation (FK method) to stabilise the within-study variance by using the binomial distribution[31] considering the inverse variance method and the Clopper-Pearson CI for individual studies.[32] This method might give misleading results when applied using the inverse of FK with the back transformation, and logit has been proposed an alternative transformation method.[33] An extra analysis using a generalised linear mixed model (more specifically, a random intercept logistic regression model) can be used for the meta-analysis of proportion.[34] In the logit method, we used the maximum-likelihood estimator for τ^2 and the Clopper-Pearson CI for individual studies.

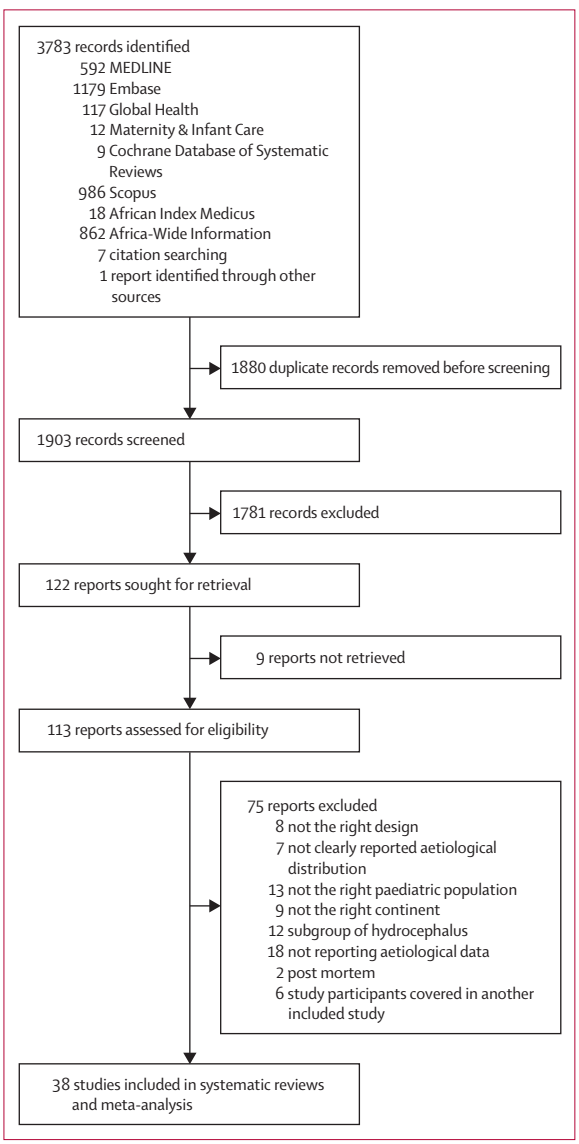

Figure 1: **PRISMA flow chart**

The effect size is reported as an overall proportion from studies that reported a single proportion, using a 95% CI and a two-tailed p value. Heterogeneity between studies was assessed with the Cochran's Q test and its magnitude evaluated by the I^2 statistics, which describe the proportion of total variation due to heterogeneity rather than chance. Variation was considered to be high when I^2 is 75% or larger.[35] To investigate potential sources of heterogeneity, we did subgroup analyses and stratified our data according to overall methodological study quality (low, intermediate, or high), country income level (low-income country, lower-middle-income country, or upper-middle-income country) and publication year (before 2000 or after 2000). We extended the analysis by a random effects meta-regression to examine associations between the observed proportion of hydrocephalus from every study and the following study characteristics: mean or median age of patients in the study, the sex of participants, methodological study quality (low *vs* intermediate or high), country income level (low-income country *vs* lower-middle-income country or upper-middle-income country) and latitude of city in which the study took place. The estimate of τ^2 in the presence of a covariate compared with the estimate when the covariate is omitted allows the proportion of the heterogeneity variance explained by the covariate to be calculated.[36] P values less than 0·05 were considered significant. Publication bias was evaluated visually by the funnel plot and further assessed using the Egger test of asymmetry applied on the funnel plot.[37] Due to the presence of substantial heterogeneity, we did not adjust for publication bias.[38]

Additionally, we did a sensitivity analysis to investigate the influence of each study to the overall results by omitting each in turn from the meta-analysis and calculating the degree to which the magnitude and significance of the overall proportion changed.[39] The diagnostic methods for paediatric hydrocephalus across Africa are presented qualitatively and in tabular form.

The statistical analyses were done using Stata version 17.0 and R–Package–Meta. A protocol in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[40] was registered on PROSPERO (CRD42020219038).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Disease categories					Demographics			Study features	
	Postinfectious hydrocephalus	Non-postinfectious hydrocephalus	Spinal dysraphism	Unclear	Total (N)	Participant age, months	Boys	Girls	Design	Quality
Beck and Lipschitz (1969)[41]	4	9	56	97	166	..	..		Unclear	Low
Seligson and Levy (1974)[13]	4	129	20	0	153	4	..		Retrospective	Low
Peacock and Currer (1984)[42]	158	106	65	111	440	..	..		Retrospective	Low
Sibanda et al (1991)[43]	24	9	18	40	91	12·4	..		Retrospective	Low
Okoro and Ohaegbulam (1992)[25]	41	20	0	89	150	17·5*	85 (57%)	65 (43%)	Retrospective	Low
Abena Obama et al (1994)[24]	33	6	12	18	69	5·8*	30 (43%)	39 (57%)†	Retrospective‡	Low
Adeloye and Khare (1997)[44]	35	13	14	6	68	..	..		Unclear	Low
Nzeh et al (2004)[45]	6	27	5	0	38	..	..		Retrospective	Low
Mweshi et al (2010)[27]	95	0	11	25	131	5·2*	80 (61%)	51 (39%)	Retrospective	Intermediate
Sanoussi et al (2010)[46]	49	10	31	6	96	11·5	46 (48%)	50 (52%)	Prospective	Intermediate
Tapsoba et al (2010)[47]	23	22	7	1	53	8·8	32 (60%)	21 (40%)	Cross-sectional	Intermediate
Idowu et al (2011)[12]	24	71	42	0	137	7·3	73 (53%)	64 (47%)	Prospective	High
Djientcheu et al (2011)[48]	6	32	5	3	46	6·9	22 (48%)	24 (52%)	Prospective	Intermediate
Warf et al (2012)[29]	578	0	110	212	900	9·2	..	..	Retrospective	High
Adjenou et al (2012)[49]	31	23	1	0	55	19·0	33 (60%)	22 (40%)	Prospective	Intermediate
Uche et al (2013)[10]	35	120	43	0	198	32·4	86 (43%)	112 (57%)	Retrospective	Intermediate
Marchie and Ayara (2013)[50]	10	0	13	27	50	2·0	25 (50%)	25 (50%)	Prospective	Intermediate
Salem-Memou et al (2014)[51]	3	52	12	3	70	29·0	52 (74%)	18 (26%)†	Retrospective	Low
Lane et al (2014)[52]	118	0	18	24	160	11·3	83 (52%)	77 (48%)§	Retrospective	High
Salvador et al (2014)[23]	52	16	0	54	122	4·5*	61 (50%)	61 (50%)	Prospective	Intermediate
Ojo et al (2015)[53]	5	0	9	20	34	4·3	16 (47%)	18 (53%)	Prospective	High
Bankole et al (2015)[11]	4	0	8	10	22	9·2*	16 (73%)	6 (27%)†	Retrospective	Intermediate
Biluts and Admasu (2015)[54]	23	28	63	0	114	10·1	61 (54%)	53 (46%)¶	Prospective	Low
Biluts and Admasu (2016)[55]	15	61	42	4	122	11·2	67 (55%)	55 (45%)	Retrospective	Intermediate
Yusuf et al (2017)[56]	7	18	14	19	58	3·0II	33 (57%)	25 (43%)	Retrospective	Low
Santos et al (2017)[57]	28	23	20	54	125	3·5II	70 (56%)	55 (44%)§	Prospective	High
Laeke et al (2017)[58]	12	21	52	28	113	7·2	68 (60%)	45 (40%)§	Retrospective	Low
Mathebula et al part 1** (2018)[59]	5	0	0	70	75	12·0II	35 (47%)	40 (53%)	Retrospective,	Low
Mathebula et al part 2** (2018)[59]	2	0	0	9	11	0·8II	2 (18%)	9 (82%)	Retrospective	Low
Cairo et al (2018)[60]	66	0	11	39	116	13·6	56 (48%)	60 (52%)	Retrospective	Intermediate
Leidinger et al†† (2018)[61]	25	15	9	14	63	6·7	32 (51%)	31 (49%)	Prospective	High
Mbabazi-Kabachelor et al (2019)[62]	191	13	15	29	248	7·9‡‡	150 (60%)	98 (40%)§	Prospective	High
Lepard et al site 1 (2020)[63]	469	0	73	188	730	4·0II	..		Prospective	High
Lepard et al site 2 (2020)[63]	25	0	24	47	96	4·0II	..		Prospective	High
Moreno Oliveras et al†† (2020)[64]	26	22	14	34	96	9·3	49 (51%)	47 (49%)	Retrospective	Low
Henderson et al (2020)[65]	99	51	65	84	299	..	..		Prospective	Intermediate
Kalangu et al site 1 (2020)[66]	18	47	3	0	68	9·0II	33 (49%)	35 (51%)	Prospective	High
Kalangu et al site 2 (2020)[66]	3	74	5	12	94	6·4II	21 (22%)	73 (78%)	Prospective	High
Kalangu et al site 3 (2020)[66]	5	32	9	1	47	36·0II	30 (64%)	17 (36%)	Prospective	High
Salem-Memou et al (2020)[67]	20	52	30	24	126	5·0	55 (44%)	71 (56%)†	Retrospective	Intermediate
Reynolds et al (2020)[68]	226	51	32	69	378	5·5II	183 (49%)	193 (51%)§§	Retrospective	Intermediate
Wubie et al (2022)[26]	40	151	117	29	337	28·6*	197 (58%)	140 (42%)	Retrospective	High
Total sum (N)	2643	1324	1098	1500	6565	..	1882 (52%)	1647 (48%)	..	..

Age data are mean, median, N, or n (%). Disease categorisation is detailed in the appendix (pp 14–18). *Age approximated. †Calculated from gender ratio. ‡The study includes one retrospective and one prospective part; the retrospective part is longest, and hence it has been listed as a retrospective study. §Specific numbers provided only for boys. ¶Numbers inconsistently presented in individual studies. IIAge reported as median. **The article consists of two different parts (retrospective review and household); we have assumed that the cases in the household survey are not included in the retrospective review. ††Studies are from the same hospital and have an overlapping time period, and so might include some of the same cases. ‡‡Age provided as mean for two separate groups of children (7·4 months and 8·4 months), and so we have applied 7·9 months as a middle age between these two groups. §§Study provides these numbers (% and n) which adds up to 376 (meaning two participants are missing).

Table 1: **Main characteristics in all included studies**

Results

Our search yielded 3783 results, of which 1880 (49·7%) were duplicates and were removed. We screened the remaining 1903 titles and abstracts, of which we excluded 1781 (93·6%) studies that did not fulfil our inclusion criteria. Of the 122 reports sought for retrieval from the screening period, email requests were sent concerning nine articles; four authors reverted back and the paper did not fulfill inclusion criteria and hence were not retrieved for full-text review. The other five were excluded after two emails with no response. CGA searched the reference lists of all included studies for relevant titles, and one

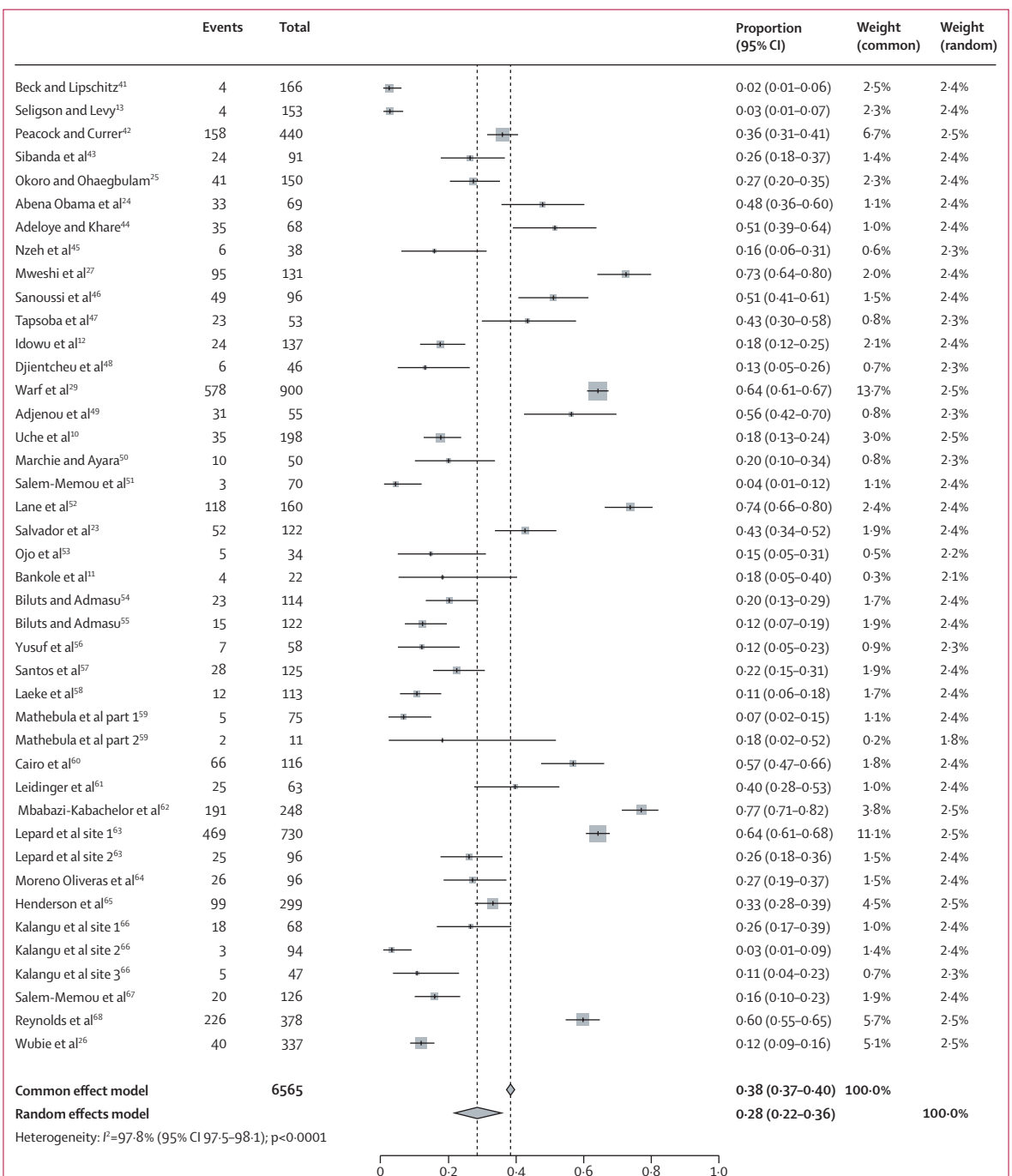

Figure 2: **Forest plot of meta-analysis of studies reporting on frequency of postinfectious hydrocephalus**
The Mathebula study had two designs (review and household survey). The Kalangu study was at three centres (Harare, Zimbabwe; Oshakati, Namibia; and Lubumbashi, Democratic Republic of the Congo). The Lepard study was at two centres (Mbale, Uganda and Lagos, Nigeria).

study was added.[54] Further, EU provided a list of potentially relevant studies that were found from the conference proceedings from the annual scientific meetings of related national and regional scientific organisations, such as the West African College of Surgeons, The Nigerian Academy of Neurological Surgeons, as well as their affiliate journals, which resulted in the inclusion of one additional study.[59] Of the resulting 113 papers, 75 (66·4%) were excluded (appendix pp 19–20) and 38 (33·6%) were included (figure 1[69]). In total, the 38 studies included data from 6565 children from 18 African countries (appendix p 23). The median age was 7·9 months (IQR 5·0–11·5). The median frequency of boys was 51·5% (IQR 47·9–59·3) (table 1).

Four studies included cases from more than one centre within the same city.[26,43,49,68] However, two studies were multicentre studies including different countries, one included three centres[66] and another included two centres.[63] Additionally, one study included two parts and two different study settings.[59] These three studies have been listed according to number of study settings, and hence, the meta-analysis included 42 study items from 38 papers.[10–13,23–27,29,41–68] The included studies were first published between 1969 and 2021, and except for five studies written in French,[24,47,49,51,67] all were written in English. Although countries from all African regions are included, the western African region was most frequently represented (13 study items), followed by the southern region (12 study items), the eastern region (12 study items), the central region (four study items), and the northern region (one study item). The majority of countries were defined as low-income (21 study items), followed by lower-middle income (19 study items), and then upper-middle income (two study items).

There was no uniform way of reporting the aetiological distribution in the included studies, and the level of comprehensiveness and precision was incongruous. Although some studies made distinctions between congenital or primary versus acquired or secondary hydrocephalus, others made additional distinctions between communicating or non-communicating and were more detailed (eg, some reported on the intracerebral site of obstruction regarding the flow of cerebrospinal fluid). In accordance with the prespecified classification of methodological study quality within the 42 study items, 15 studies had methods rated as low quality, 14 studies had methods rated as intermediate quality, and 13 studies had methodological study quality rated as high.

The pooled proportion of postinfectious hydrocephalus was 28% (95% CI 22–36) with high heterogeneity (I^2=97·8% [95% CI 97·5–98·1]; p<0·0001) according to our random effects model (figure 2). The funnel plot visually indicated publication bias (appendix p 24), and this was supported by the Egger test (p=0·0010). According to the prespecified subgroup analysis, the stratified pooled estimates showed a lower proportion of postinfectious hydrocephalus in low-quality studies compared with intermediate-quality or high-quality studies, and a higher proportion in studies from low-income countries versus lower-middle-income countries or upper-middle-income countries (table 2). Extending the analyses with meta-regression, results from the univariable model identified a negative association between the proportion of postinfectious hydrocephalus and the presence of studies of low methodoligical quality versus studies of intermediate or high methodological quality (p=0·018), a positive association between postinfectious hydrocephalus and low-income countries

	N	Postinfectious hydrocephalus		Non-postinfectious hydrocephalus		Spinal dysraphism		Unclear	
		Proportion (95% CI)	I^2 (%)	Proportion (95% CI)	I^2 (%)	Proportion (95% CI)	I^2 (%)	Proportion (95% CI)	I^2 (%)
All studies	42	0·28 (0·22–0·36)	97·8	0·21 (0·13–0·30)	98·6	0·16 (0·12–0·20)	93·6	0·20 (0·13–0·28)	97·1
Methodological study quality									
Low	15	0·18 (0·11–0·28)	94·8	0·24 (0·11–0·39)	97·3	0·17 (0·09–0·26)	95·2	0·28 (0·12–0·86)	98·8
Intermediate	14	0·36 (0·25–0·48)	95·9	0·20 (0·08–0·35)	97·6	0·15 (0·09–0·22)	92·4	0·16 (0·07–0·27)	96·1
High	13	0·33 (0·19–0·49)	97·8	0·19 (0·05–0·40)	99·2	0·15 (0·10–0·25)	92·7	0·17 (0·08–0·29)	96·3
Country income level*									
Upper middle	2	0·16 (0·00–0·58)	98·4	0·51 (0·05–0·96)	99·0	0·10 (0·03–0·21)	86·3	0·19 (0·09–0·32)	86·8
Lower middle	19	0·20 (0·12–0·28)	96·8	0·22 (0·09–0·38)	98·3	0·17 (0·12–0·22)	88·6	0·26 (0·13–0·42)	98·0
Low	21	0·38 (0·29 -0·49)	97·7	0·18 (0·09–0·29)	98·4	0·16 (0·10–0·23)	95·7	0·16 (0·09–0·24)	96·1
Publication year									
1969–99	7	0·24 (0·10–0·42)	97·3	0·21 (0·06–0·48)	98·3	0·15 (0·07–0·26)	94·7	0·28 (0·10–0·50)	98·1
2000–21	35	0·29 (0·21–0·38)	97·7	0·21 (0·12–0·31)	98·6	0·16 (0·12–0·21)	93·5	0·19 (0·11–0·27)	96·7

*Income level is based on World Bank Group analytical classifications from calendar year of publication.

Table 2: **Estimate of the proportion of each category of hydrocephalus found with stratification on study quality, income level, and publication year using the random effects model**

versus lower-middle or upper-middle income countries (p=0·0035), and a decreasing proportion of postinfectious hydrocephalus with increasing distance from the equator (p=0·014; table 3; figure 3).

A multivariable meta-regression model indicated that these three variables together accounted for 25% of the between-study heterogeneity (data not shown). In the subgroup of studies published after 2000, the results were similar (appendix p 25). The influential analysis showed a stable pooled estimate whichever study was omitted from the meta-analysis (appendix p 26).

The pooled proportion of non-postinfectious hydrocephalus was 21% (95% CI 13–30) with high heterogeneity (I^2=98·6% [95% CI 98·4–98·7]; p<0·0001) according to our random effects model (figure 4). The funnel plot visually indicated publication bias (appendix p 27), and this was supported by the Egger test (p=0·015). The subgroup analysis showed a lower proportion of non-postinfectious hydrocephalus in studies from low-income countries than in studies from lower-middle-income countries or upper-middle-income countries (table 2). In univariable meta-regression analysis, we found that age was significantly associated with the proportion of non-postinfectious hydrocephalus (p=0·012; table 3), indicating an increasing proportion of non-postinfectious hydrocephalus with increasing mean age of patients in the study (figure 3), accounting for 13% of the between-study heterogeniety (data not shown). In the subgroup of studies published after 2000, the results were similar (appendix p 28). The influential analysis showed a stable pooled estimate whichever study was omitted from the meta-analysis (appendix p 29).

	β coefficient	SE (β)	p value
Postinfectious hydrocephalus			
Mean age of patients in study, months	−0·0057	0·0050	0·2482
Frequency of boys, %	0·0024	0·0041	0·5630
Latitude of study place, °	−0·0112	0·0046	0·0138
Study quality, low *vs* intermediate or high	−0·1814	0·0765	0·0178
Income level*, low *vs* lower middle or upper middle	0·2080	0·0712	0·0035
Non-postinfectious hydrocephalus			
Mean age of patients in study, months	0·0164	0·0065	0·0122
Frequency of boys, %	0·0006	0·0055	0·9114
Latitude of study place, °	0·0056	0·0067	0·4041
Study quality, low *vs* intermediate or high	0·0517	0·1124	0·6457
Income level*, low *vs* lower middle or upper middle	−0·0781	0·1070	0·4656
Spinal dysraphism			
Mean age of patients in study, months	0·0016	0·0500	0·6709
Frequency of boys, %	0·0049	0·0033	0·1410
Latitude of study place, °	−0·0032	0·0035	0·3564
Study quality, low *vs* intermediate or high	0·0213	0·0585	0·7158
Income level*, low *vs* lower middle or upper middle	−0·0018	0·0560	0·9747
Unclear			
Mean age of patients in study, months	−0·0134	0·0057	0·0189
Frequency of boys, %	−0·0071	0·0051	0·1642
Latitude of study place, °	0·0086	0·0058	0·1330
Study quality, low *vs* intermediate or high	0·1339	0·0962	0·1640
Income level*, low *vs* lower middle or upper middle	−0·1146	0·0927	0·2162

*Income level based on World Bank Group analytical classifications from calendar year of publication.

Table 3: **Meta-regression model between the proportion of each category of hydrocephalus found and the different study-level and patient-level variables in univariable analyses using the 42 study items**

The pooled proportion of spinal dysraphism was 16% (95% CI 12–20) with high heterogeneity (I^2=93·6% [95% CI 92·1–94·7]; p<0·0001) according to our random effects model (figure 5). Publication bias was not found by the Egger test (p=0·28; appendix p 30). A stratification analysis showed no meaningful difference between subgroups, and none of the covariates considered were associated with the proportion of spinal dysraphism. The results were similar in the subgroup of studies published after 2000 (appendix p 31). The influential analysis showed a stable pooled estimate whichever study was omitted from the meta-analysis (appendix p 32).

The pooled proportion of hydrocephalus of unclear aetiology was 20% (95% CI 13–28), with high heterogeneity (I^2=97·1% [95% CI 96·6–97·5]; p<0·0001) according to our random effects model (table 2). In the subgroup of studies published after 2000, the pooled proportion of hydrocephalus of unclear aetiology was 19% (95% CI 11–27), with high heterogeneity (I^2=96·7% [95% CI 96·1–97·3]; p<0·0001).

The results were similar in a sensitivity analysis, using the logit transformation, and do not change our conclusion (appendix p 33).

Diagnostic methods applied consisted of preoperative clinical assessments and history-taking, as well as radiographical imaging including ultrasound, CT, MRI, X-rays, and per-operative ventriculoscopy (appendix pp 21–22).

Discussion

Our findings in this systematic review and meta-analysis suggest that the pooled proportion of postinfectious hydrocephalus is reported as a frequent aetiology of paediatric hydrocephalus across African countries (28% of cases). The pooled proportion of positively identified non-infectious cases of congenital and acquired hydrocephalus was 21%, and the pooled proportion of cases arising from spinal dysraphism was 16%. We also found an unclear cause in 20% of children with hydrocephalus. It therefore seems reasonable to believe that postinfectious hydrocephalus could be the single

most common cause of paediatric hydrocephalus in Africa, given that it was more common than spinal dysraphism, and given the heterogeneity of the non-postinfectious hydrocephalus category.

We found that latitude of study site, income level of the country, and methodological study quality contributed to heterogeneity in the proportion of cases categorised into the postinfectious hydrocephalus group. First, the finding that there was a significant negative association between the latitude of the study site and proportion of postinfectious hydrocephalus is interesting and relevant. Although studies from the field of cardiology,[15] allergology,[17] and neurology[16] have shown that latitude could be associated with disease, this association has not previously been described in the hydrocephalus literature. One previous study from CURE Children's Hospital of Uganda showed an association between postinfectious hydrocephalus and seasonality or rainfall.[9] As latitude is a marker for rainfall and temperatures,[15] our finding thus builds on and extends beyond existing evidence, suggesting that postinfectious hydrocephalus is significantly associated with study site latitude across the African continent.

Second, our findings suggest that the pooled proportion of postinfectious hydrocephalus is associated with economic status of the country, representing significantly more cases in low-income countries than in lower-middle-income or upper-middle-income countries across Africa. This finding mirrors previously published global estimates[2] affirming the link between income level of country and the proportion of postinfectious cases of hydrocephalus. These two non-biomedical findings—that geographical and socioeconomic factors are associated with postinfectious hydrocephalus—underline the importance of addressing the management of paediatric hydrocephalus holisticly. This research should act as a catalyst for future preventive measures aimed at improving maternal and neonatal quality of care to reduce the risk of peripartum and neonatal infections.

Third, we found that postinfectious hydrocephalus was significantly more common in studies with methodological study quality rated as being of intermediate or high quality than those rated as being of low quality. This finding could be related to intermediate-quality or high-quality studies having more comprehensive protocols for the classification of postinfectious hydrocephalus, as well as better access to more advanced diagnostic equipment, than low-quality studies. Regardless of reason, this finding suggests that a more distinct aetiological pattern, with an even higher pooled proportion of postinfectious hydrocephalus, might have been revealed if studies of low methodological quality were excluded from the review. This is an interesting finding, and it emphasises the need for more high-quality research on the topic.

Illustrative of the high-quality research needed on this topic is emerging evidence from CURE Children's Hospital of Uganda in Mbale, Uganda, that has identified the presence of a microbial pathogen (*Paenibaccillus thiaminolyticus Mbale* strain) with postinfectious hydrocephalus in their paediatric population[70,71] through

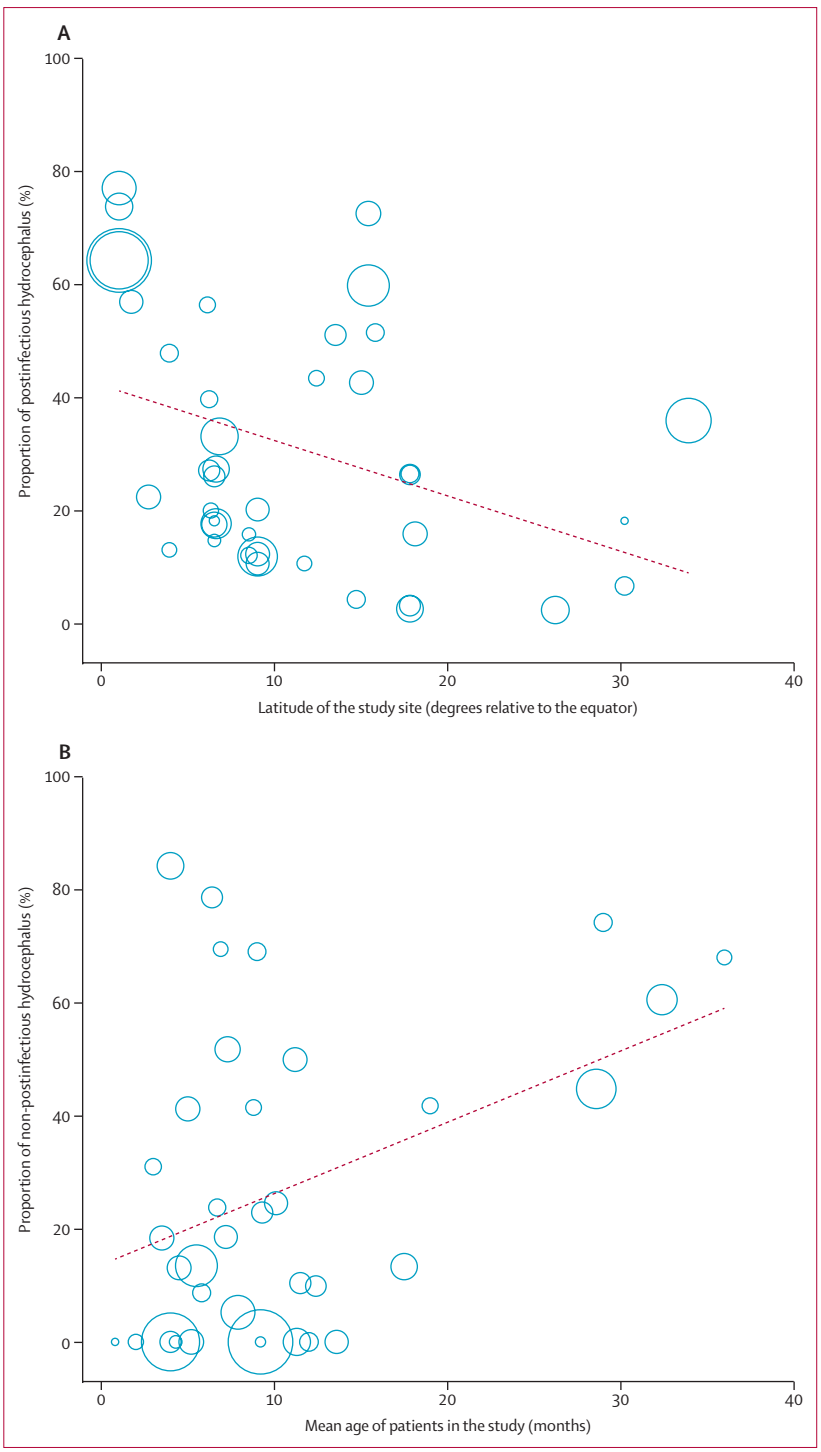

Figure 3: **Bubble plots of a meta-regression of the proportion of postinfectious hydrocephalus versus latitude of the study site (A) and proportion of non-postinfectious hydrocephalus versus mean age of patients in the study (B)**
The size of the circle indicates the precision of each estimate.

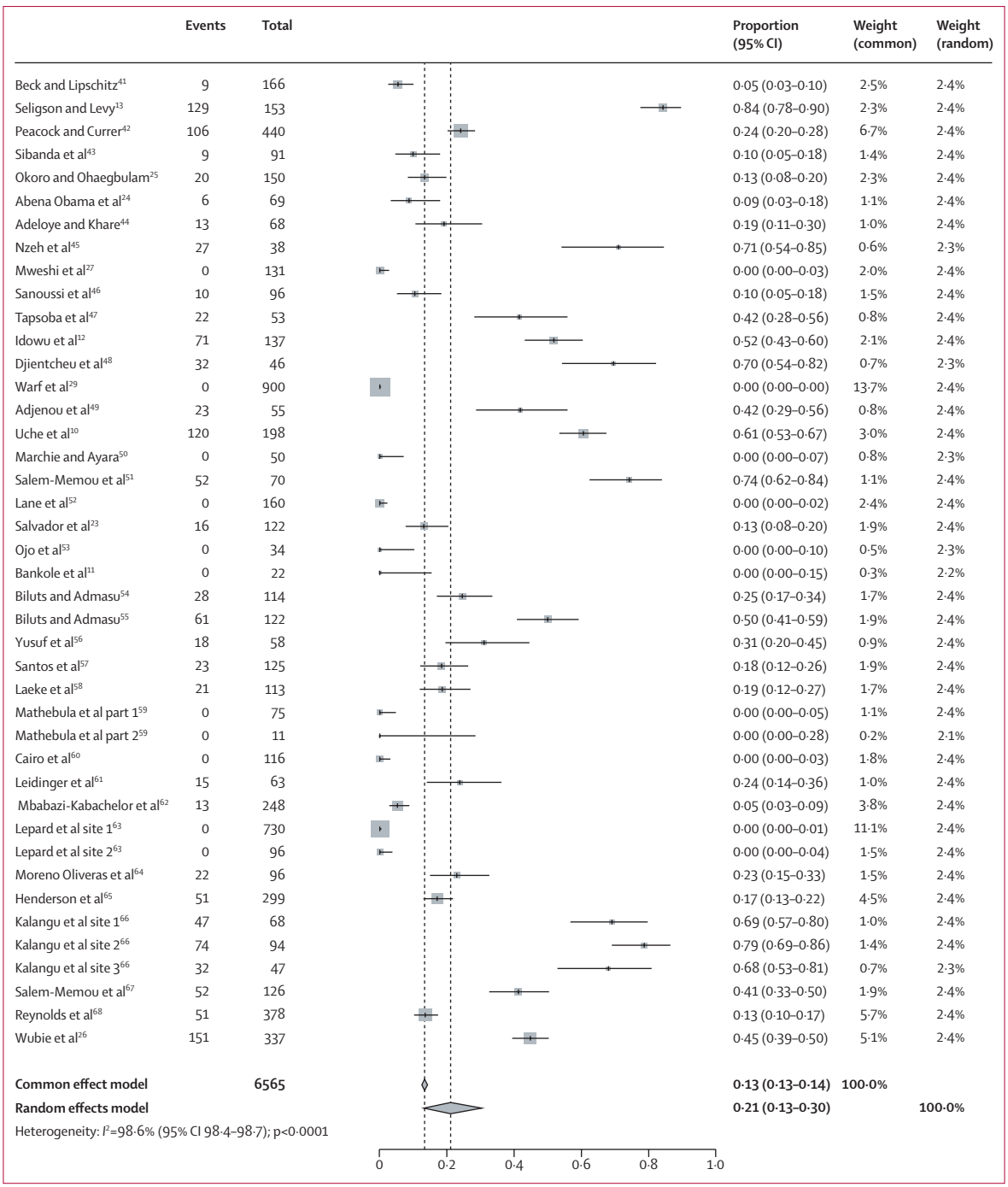

Figure 4: **Forest plot of meta-analysis of studies reporting on frequency of non-postinfectious hydrocephalus**
The Mathebula study had two designs (review and household survey). The Kalangu study was at three centres (Harare, Zimbabwe ; Oshakati, Namibia; and Lubumbashi, Democratic Republic of the Congo). The Lepard study was at two centres (Mbale, Uganda and Lagos, Nigeria).

DNA or RNA analysis of blood or cerebrospinal fluid. However, despite this neurosurgical hospital having treated thousands of children with hydrocephalus since 2001, there were previously almost entirely no signs of pathogens on standard bacterial culture.[70] Although different pathogens might be responsible for postinfectious hydrocephalus in other regions of Africa,[70,71] one could speculate that a higher burden of postinfectious hydrocephalus could have been identified had the same advanced sampling techniques been applied elsewhere in Africa. With increased knowledge on the pathogens involved in postinfectious hydrocephalus, and further

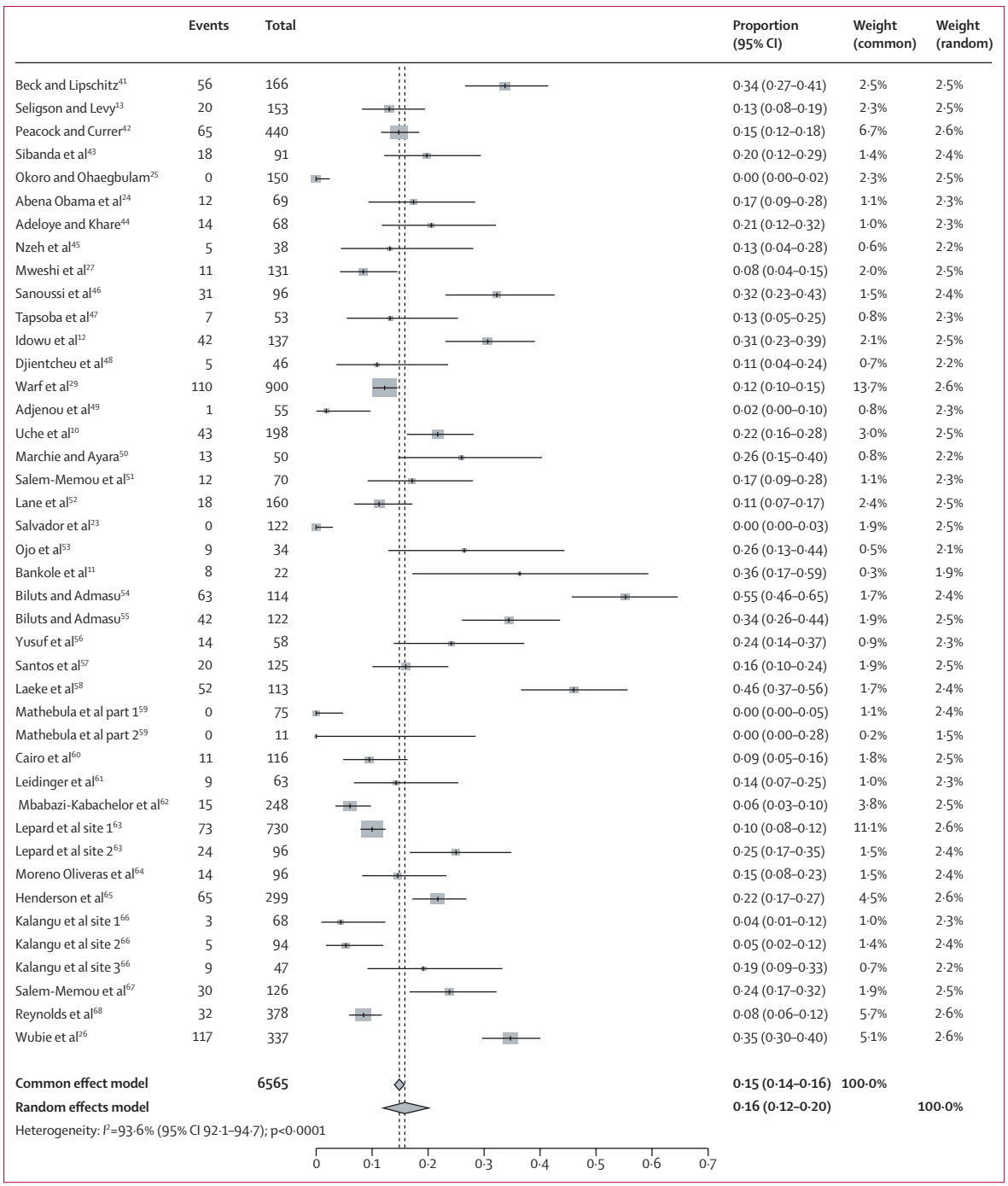

Figure 5: **Forest plot of meta-analysis of studies reporting on frequency of hydrocephalus due to spinal dysraphism**
The Mathebula study had two designs (review and household survey). The Kalangu study was at three centres (Harare, Zimbabwe; Oshakati, Namibia; and Lubumbashi, Democratic Republic of the Congo). The Lepard study was at two centres (Mbale, Uganda and Lagos, Nigeria).

insight into routes of infection, postinfectious hydrocephalus could be treated medically in the future. Therefore, a coordinated public health approach, including a shift of focus from treatment to prevention, will require replication of the work that has been done in Mbale, Uganda in other parts of Africa, as the current surgical options, although lifesaving, have severe limitations and can lead to lifelong complications.[57,58]

In our non-postinfectious hydrocephalus group, which is a heterogeneous category with a multitude of positively identified non-infectious aetiologies, the meta-regression analysis showed a positive association with age, indicating

increasing frequency with increasing mean age of the study population. There might be several reasons for this finding, such as more challenges related to diagnosing or recognising postinfectious hydrocephalus with increasing age. Additionally, some causes within the non-postinfectious hydrocephalus category, such as tumour and trauma, could occur later in life, after infancy.

Given the heterogeneity of the non-postinfectious hydrocephalus group, it is plausible to believe that spinal dysraphism is the second single most common cause of hydrocephalus across Africa. The provision of folic acid for all women of childbearing age is an important preventive measure for spina bifida,[72] and ultimately hydrocephalus, because roughly 80% of children with spina bifida develop hydrocephalus.[73]

We found a pooled proportion of 20% of hydrocephalus cases with an unclear aetiology, which further strengthens our call for more high-quality research on the topic. In general, the hydrocephalus literature is characterised by poor consensus regarding aetiological classification and, as expected, our meta-analysis found high heterogeneity. Not only was the data itself scattered, as illustrated in our forest plot figures, reporting of the categories by included studies was not uniform, nor were they always transparently described. For example, one study from South Africa reported that high rates of infections were assessed through history-taking, but it did not specify the criteria applied.[42] Another study from Zambia described a group of children that received endoscopic third ventriculostomy and mentioned infection as causing hydrocephalus in a majority of patients, but it failed to clearly report how they arrived at this decision.[27] The heterogeneous and diverse classification of aetiology within the hydrocephalus literature in general, and within the included studies specifically, hampers and challenges any coordinated effort to adequately address the massive disease burden that paediatric hydrocephalus represents across Africa. This challenge is a clinically meaningful finding that requires attention and, to comprehensively address it, will require the establishment of national registries as a foundational step, coupled with monitoring of geographical and demographic information, to report on regions with a particularly heavy burden of hydrocephalus and associated conditions such as spina bifida, as recommended by the CHYSPR group.[7]

The criteria applied for diagnosis of postinfectious hydrocephalus in the studies from CURE Children's Hospital of Uganda include that there be no known history of hydrocephalus at birth and either a history of febrile illness (with or without accompanying seizures) before the onset of a clinically evident hydrocephalus, or imaging or endoscopic findings suggesting previous ventriculitis.[8] Moreover, the status of the aqueduct on imaging or through ventriculoscopy is a key issue in the classification methods. Many of the included studies in this review reported high numbers of aqueduct stenosis and determined this as congenital aqueduct stenosis. Because infections can cause aqueduct stenosis due to inflammation, some of these children could in fact have had a postinfectious hydrocephalus aetiology. Additionally, the terminology applied to categorise various neural tube defects, both cranial and spinal, was not homogenous.

Furthermore, the scarcity of advanced imaging facilities such as MRI hinders not only proper diagnostics and classification of aetiology, but also adequate evaluation of treatment, thereby limiting necessary information about outcomes.[74] Some studies[23,47,53,55–57,64] reported that imaging led to additional out-of-pocket costs for families and problems with damaged technical equipment, both of which reduced access to radiological investigations.

We see five main limitations to our systematic review. First, the classification of hydrocephalus into categories required simplifications that potentially weakens this evidence. Moreover, the non-postinfectious hydrocephalus group includes several diverse aetiologies (both congenital and acquired). Second, the inclusion criteria for the individual studies varied according to variables such as overall aim of the study, age of inclusion, diagnostic methods applied, and surgical treatment provided. Third, the methodological study quality of included studies was often rated as low, which makes the estimates provided less reliable. Estimating pooled proportions on the basis of studies that included some children from selected groups of study participants could provide rudimentary results. In addition to differences related to classification of hydrocephalus, other disparate non-biological differences (ie, diagnostic methods applied [ultrasound, CT, MRI, and clinical assessment or history-taking]) are factors that could contribute to variability. Fourth, our investigation is limited by publication bias, or small-study effect, which could lead to biased estimates that appear precise.[36] Fifth, a further limitation was the impossibility of controlling for small-study effects due to substantial heterogeneity.

Despite these limitations, the data provide an extensive summary of the best current evidence on this subject from Africa. A strength of the study is that we have made efforts to transparently describe the methods we applied to categorise the various aetiologies. Other strengths are that we made no restriction to language, and that we deliberately searched databases beyond MEDLINE and Embase.

To improve targeted preventive and treatment efforts, there is a need for more evidence from which clinicians, ministries of health, and other health policymakers can create context-relevant and feasible clinical guidelines, as well as political strategies to enhance care for paediatric hydrocephalus. Future research should strive to identify infectious and inflammatory causes of postinfectious hydrocephalus, such as the recent discovery of the *P thiaminolyticus Mbale* pathogen in Uganda,[70,71] and it should aim to improve our understanding of the

aetiological distribution within the non-postinfectious hydrocephalus group, and within the group of unclear causes. Moreover, research to establish guidelines for the categorisation of hydrocephalus would be an initial and important step to steer policy and practice, strengthen coordinated preventive measures, and possibly catalyse the search for definitive treatment options. The findings from our systematic review and meta-analysis suggest that improved access to diagnostic services and increased consensus regarding hydrocephalus aetiological classification should be a prioritisation for future research. There is also a need for more research on how non-biological factors, such as country income level and latitude of study site, contribute to an uneven distribution of hydrocephalus among children worldwide.

Contributors

CGA conceptualised the study, was responsible for project administration, wrote the original draft, data curation and methods (including screening, data extraction, and critical appraisal of included articles). AHP was responsible for methods (including screening articles, data extraction, and validation of data extraction) and writing (reviewing and editing). EOU was responsible for methods (including critical appraisal of included articles and validation of data extraction) and writing (reviewing and editing). PDK was responsible methods (including validation of data extraction) and writing (reviewing and editing). IS was responsible for statistical methods and analysis, drafting the statistical methods section, the results of the meta-analysis, and writing (reviewing and editing). HEF was responsible for writing (reviewing and editing). HS was responsible for the systematic literature search and writing (reviewing and editing). PKE conceptualised the study and was responsible for methodological and academic supervision, project administration, and writing (reviewing and editing).

Declaration of interests

We declare no competing interests.

Data sharing

The datasets used and analysed are available from the corresponding author upon reasonable request.

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