



SYSTEMATIC REVIEW

REVISED **Burden of neurodevelopmental disorders in low and middle-income countries: A systematic review and meta-analysis [version 3; referees: 2 approved, 2 approved with reservations]**

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Abstract

Background: Childhood mortality from infectious diseases has declined steadily in many low and middle-income (LAMIC) countries, with increased recognition of non-communicable diseases such as neurodevelopmental disorders (NDD). There is lack of data on the burden of NDD in LAMIC. Current global burden of these disorders are largely extrapolated from high-income countries. The main objective of the study was therefore to estimate the burden of NDD in LAMIC using meta-analytic techniques.

Methods: We systematically searched online databases including Medline/PubMed, PsychoInfo, and Embase for studies that reported prevalence or incidence of NDD. Pooled prevalence, heterogeneity and risk factors for prevalence were determined using meta-analytic techniques.

Results: We identified 4,802 records, but only 51 studies met the eligibility criteria. Most studies were from Asia-Pacific (52.2%) and most were on neurological disorders (63.1%). The median pooled prevalence per 1,000 for any NDD was 7.6 (95%CI 7.5-7.7), being 11.3 (11.7-12.0) for neurological disorders and 3.2 (95%CI 3.1-3.3) for mental conditions such as attention-deficit hyperactivity disorder (ADHD). The type of NDD was significantly associated with the greatest prevalence ratio in the multivariable model (PR=2.6(95%CI 0.6-11.6) (P>0.05). Incidence was only reported for epilepsy (mean of 447.7 (95%CI 415.3-481.9) per 100,000). Perinatal complications were the commonest risk factor for NDD.

Conclusion: The burden of NDD in LAMIC is considerable. Epidemiological surveys on NDD should screen all types of NDD to provide reliable estimates.

Keywords

neurodevelopment, low and middle-income countries

Open Peer Review

Referee Status: ? ✓ ? ✓

	Invited Referees			
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		↑		
<p>REVISED</p> <p>version 2 published 22 Feb 2018</p>		? report		
		↑		
<p>version 1 published 29 Dec 2017</p>	? report	✓ report		

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REVISED Amendments from Version 2

In our Discussion, we have included fetal alcohol exposure as a risk factor that should be investigated because of its high burden in some low and middle income countries like South Africa.

See referee reports

Introduction

Neurodevelopmental disorders (NDD) are a group of disorders that typically manifest early in development and are characterised by developmental deficits that produce impairments of personal, social, academic, or occupational functioning¹. They include autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), epilepsy, intellectual disability, hearing impairments, visual impairments and motor impairments including cerebral palsy, among others. Some disorders overlap, for example in children with epilepsy, ASD occurs in 22%², ADHD in 33%², and behavioural/emotional problems in 30–50%^{3,4}. Although more than 80% of the world's births occur in low and middle-income countries (LAMIC)⁵, most of the epidemiology of NDD is based on data from developed countries^{6–8}. The lack of precise epidemiological data on NDD in poorer countries affects planning of public health interventions.

In the past decade, infant mortality has declined in many LAMIC and preventing childhood morbidity is becoming a public health priority. However, there are few studies on the epidemiology of NDD in LAMIC, where the burden could be greatest because: (i) the incidence of risk factors for NDD such as perinatal complications⁹, head injury, parasitic infections¹⁰ and nutritional deficiencies are higher in LAMIC according to the global burden of disease study¹¹; (ii) following the successful control of infectious diseases, children with neurological disability are surviving¹².

So far, no precise estimate exists for NDD in LAMIC. Available studies focus mostly on a few conditions¹³, are conducted in a small number of countries. In particular the Ten Questions Questionnaire (TQQ) has been used to determine

the prevalence of neurological impairment and disability, but this screening tool is poor at detecting NDD such as ASD and ADHD. It is unclear if the variation in estimates is due to methodological differences or is dependent upon NDD type/condition, calling for the need to review the available studies to measure the causes of variation in estimates.

To fill the knowledge gap that exists regarding the epidemiology of NDD in LAMIC, we conducted a systematic review of studies reporting prevalence and incidence of NDD. We pooled the estimates for different types of NDD and determined the causes of heterogeneity. We also described the risk factors associated with NDD among the studies included in the burden estimates.

Methods

Search strategy

We searched all articles of population studies on prevalence or incidence of NDD in the electronic databases MEDLINE and EMBASE, African Index Medicus and CINHL databases. Our last search was conducted on 31/06/2017.

We included references from identified articles that met the inclusion criteria. The main search terms were (“neurodev*” and “prevalence”) or (“neurodev*” and “incidence”) with limits (humans, journal article) in MEDLINE and EMBASE (Table 1). We used recommendations of National Health Service Centre for Reviews and Disseminations to develop a search strategy where the review question was broken down to search terms.

Two authors (MAB and SK) reviewed the titles and abstracts of articles obtained from online searches. We reviewed full texts of eligible articles from this initial evaluation stage. Reporting of findings followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines¹⁴.

Inclusion and exclusion criteria

All population-based studies measuring the prevalence or incidence of any of the NDD listed were included. A population denominator was an inclusion criterion for research database

Table 1. Search terms.

```
((epidemiology) OR (prevalence) OR (incidence) OR (burden)) AND
((neurodevelopmental disorder*) OR (behav* problem*) OR (behav* disorder*) OR (cogniti* impairment*)
OR (language difficult*) OR (learning disabilit*) OR (Hearing difficult*) OR (hearing impairment*) OR
(visual impairment*) OR (psychotic disorder*) OR (hyperkinetic*) OR (psychiatric disorder*) OR (ataxia)
OR (motor impairment*) OR (psychomotor disorder*) OR (attention deficit and hyperactivity disorder*)
OR (autis*) OR (epilepsy) OR (cerebral palsy)) AND
((Children) OR (infant) OR (kids) OR (teen*) OR (adolescent*)) AND
((risk factor*) OR (factor*) OR (predisposing factor)) AND
((low income countr*) OR (low-income countr*) OR (middle income countr*) OR (middle-income
countr*) OR (developing countr*) OR (developing nation*) OR (Africa) OR (south America) OR (asia) OR
(resource poor countr*) OR (third world)) AND
"humans"[MeSH Terms] AND
("0001/01/01"[PDAT] : "2017/06/31"[PDAT])
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studies. We only considered studies with a sample population of <19 years or if results were stratified by age, and a population denominator for sample <19 years was provided. We excluded studies that were not conducted in a LAMIC as defined by the current World Bank Classification of Economies¹⁵. We also excluded reviews, editorials, letters, commentaries, case series and case reports, abstracts without full texts and special-group studies, e.g., prevalence of cerebral palsy in children with a history of birth trauma, or duplicate populations. In addition, we report the findings from studies that used the TQQ, since this is the longest established screening tool and most widely reported.

Procedures

We collected all the relevant study level information required for analysis using a data extraction template designed and piloted *a priori* by the authors. MAB and SK extracted data independently. We resolved disagreements by consensus. For included studies, we recorded information on the NDD under investigation, author, year of publication, country, study design, study population, data collection and ascertainment method (medical records or questionnaires [with physical examination] in population-based studies), age, number of cases, and the prevalence/incidence estimate. The quality of all the studies that met the inclusion criteria was investigated using the Joanna Briggs Institute Prevalence Critical Appraisal Tool¹⁶.

Statistical analysis

We tabulated crude prevalence estimates expressed per 1,000 persons and the incidence expressed per 100,000 persons per year in summary tables along with their 95% confidence intervals (95%CI), stratified according to the region where the study was conducted. Where an eligible study did not report the prevalence of NDD, we derived the prevalence through dividing the total cases reported by the total sample studied, and then expressed per 1,000 population. We obtained a range using the 5th and 95th percentiles as $m \pm 1.96\tau$, where τ is the standard deviation. The computed prevalence was then utilised in the meta-analysis approach described below. We collected data on incidence as reported in a study. To estimate pooled prevalence estimates and assess for heterogeneity, we log-transformed observed prevalence and fitted random effects models to these estimates using the “metan” command in STATA v 13.1 (StataCorp., TX). The random effects model approach is robust where there is significant heterogeneity across study estimates. It uses information on prevalence and study size. It assumes that the outcomes being estimated in the different studies are not identical, but follow a lognormal distribution, allowing for among-study variation¹⁷. We then back-transformed the log estimates to the original scale to obtain prevalence estimates the confidence intervals around the estimates.

We used forest plots¹⁸ to visualize heterogeneity among studies. Using the Cochran chi-square (χ^2) test, we examined the null hypothesis that the observed heterogeneity was due to sampling error. We anticipated heterogeneity because of methodological differences so we quantified the degree of heterogeneity across studies using the statistic I^2 , from the random effect meta-analysis model. I^2 describes the percentage of the variability in estimates that is due to true differences in prevalence

rather than sampling error^{19,20}. A value >50% is considered as substantial heterogeneity.

We investigated six study level covariates for their association with prevalence estimates: the quality score of the study, continent of the study, the year, the domain studied, the method of case identification (clinical diagnosis or screening only) and the study setting (rural/urban). We examined the influence of these variables on study prevalence using both univariate and multivariable random effects meta-regression models fitted using the “metareg” command in STATA. This approach assumes two additive components of variance, one representing the variance between studies and the other the variance within studies (i.e., error variance). The proportion of heterogeneity explained by each of the covariates was estimated by comparing the between-studies component of variance in the null model (τ_0^2) with the estimate of τ^2 for the model including covariates ($(\tau_0^2 - \tau^2)/\tau_0^2$).

Results

Details of eligible studies

Electronic database search yielded 4,802 articles of which 51 studies on a total population sample size of 2,925,139 included in the meta-analysis (Figure 1). Majority of the studies were from Asia-Pacific region (n=27 (52.9%)) and Africa (n=16 (31.4%)), with six (11.8%) from Latin America and two (3.9%) from two or more continents. Table 2 summarized the study characteristics of included studies.

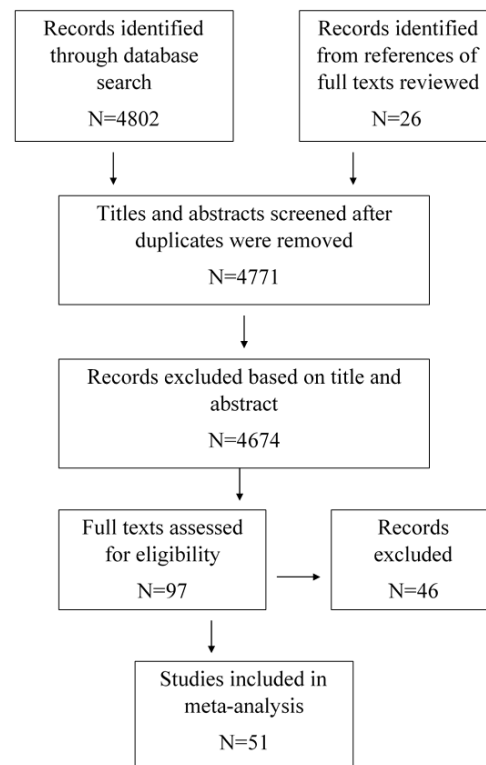


Figure 1. A summary of the study selection process.

Table 2. Summary of study characteristics for studies included in the meta-analysis.

Author	Year of publication	Country	Study setting	Domain studied	Total sample	Overall prevalence
Wagner RG ²¹	2014	South Africa		Epilepsy	36816	2
Bevilacqua MC ²²	2013	Brazil	Urban	Hearing impairment	218	1.4
Ngugi AK	2013	Kenya	Rural	Epilepsy	129069	3
Ngugi AK	2013	Multisite	Mixed	Epilepsy	308028	9.4
Ebrahimi H ²³	2012	Iran	Urban	Epilepsy	568	15.8
Caca I ²⁴	2013	Turkey		Visual impairment	21062	493.4
Arruda MA ²⁵	2015	Brazil		Attention deficit hyperactivity disorder, emotional and behavioural problems	1830	51
Burton KJ ²⁶	2012	Tanzania		Epilepsy	38523	2.9
Basu M ²⁷	2011	India	Urban	Visual impairment	3002	152.2
Prasad R	2011	Brazil		Attention deficit hyperactivity disorder	4423	199
Raina SK ²⁸	2011	India		Cerebral palsy	3966	2.27
Czechowicz JA ²⁹	2010	Peru	Urban	Hearing impairment	355	64.8
Tasci Y ³⁰	2010	Turkey		Hearing impairment	16975	2.2
Winkler AS ³¹	2009	Tanzania	Rural	Epilepsy	7399	11.2
Saldir M ³²	2010	Turkey	Urban	Mild neurological dysfunction, cerebral palsy	169	165.7
Perera H ³³	2009	Sri Lanka		Autism	374	10.7
Khan NZ ³⁴	2009	Bangladesh	Rural	Behaviour problems	499	146
Mung'ala-odera V ³⁵	2008	Kenya	Rural	Epilepsy	10218	10.7
Wong VC ³⁶	2008	China	Urban	Autism spectrum disorder	1174322	1.6
Velez van meerbeke A ³⁷	2007	Colombia	Urban	Neurodevelopmental delay disorders	2043	30.8
Zeidan Z ³⁸	2007	Sudan	Urban	Blindness	29048	1.4
Del brutto OH ³⁹	2005	Ecuador	Rural	Epilepsy	1083	5.5
Ersan EE ⁴⁰	2004	Turkey		Attention deficit hyperactivity disorder, oppositional defiant disorder	1425	81
Serdaroglu IU ⁴¹ A	2004	Turkey		Epilepsy	46813	8
Wong V ³⁶	2004	China		Epilepsy	1103	4.5
Mousa Thabet AA ⁴²	2001	Gaza		Behavioural/emotional problems	959	481.8
Couper J ⁴³	2002	South Africa	Rural	Learning disability, cerebral palsy, perceptual disability, seizure disorder	2036	17
Bulgan T ⁴⁴	2002	Mongolia		Visual impairment	416	.2
Zainal M ⁴⁵	2002	Malaysia		Visual impairment	8504	10.3
Onal AE ⁴⁶	2002	Turkey		Epilepsy	903	8.9
Rao RS ⁴⁷	2002	India	Rural	Hearing impairment	855	119
Liu XZ ⁴⁸	2001	China		Hearing impairment	34157	6.6
Olusanya BO ⁴⁹	2000	Nigeria	Urban	Hearing loss	359	139
Liu J ⁵⁰	2000	China		Cerebral palsy	385185	1.5
Liu JM	1999	China	Urban	Cerebral palsy	388192	1.6
Brito GN ⁵¹	1999	Brazil	Urban	Attention deficit hyperactivity disorder	402	32
Hackett RJ ⁵²	1997	India	Urban	Epilepsy	1172	22.2
Morioka I ⁵³	1996	China	Rural	Hearing impairment	282	198.6

Author	Year of publication	Country	Study setting	Domain studied	Total sample	Overall prevalence
Okan N ⁵⁴	1995	Turkey		Neurological disorders	5002	66
Mulatu MS ⁵⁵	1995	Ethiopia	Urban	Psychopathology	611	270
Rwiza HT ⁵⁶	1992	Tanzania		Epilepsy	11023	6.6
Koul R ⁵⁷	1988	India		Epilepsy	26419	3.2
Osuntokun BO ⁵⁸	1987	Nigeria	Urban	Epilepsy	10978	6
Bash KW	1987	South Africa	Rural	Motor impairment	1022	14.7
Taha AA ⁵⁹	2015	Egypt	Both	Hearing loss	555	20.9
Wamithi S ⁶⁰	2015	Kenya	Urban	Attention deficit hyperactivity disorder	240	6.3
Durkin MS ⁶¹	1992	Multiple	Rural	Epilepsy	22125	
Yoshito Kawakatsu ⁶²	2012	Kenya	Rural	Neurological impairments*	6362	29
Shahnaz HI ⁶³	2012	Pakistan	Rural	Neurological impairments	176364	5.5
Biritwum RB	2001	Ghana	Rural	Neurological impairments	2550	6.7
Singhi P ⁶⁴	2007	India	Rural	Neurological impairments	1763	4.3
Ilyas Mirza ⁶⁵	2008	Pakistan	Rural	Neurological impairments	1789	248

* These included epilepsy, cognition, hearing, motor and visual impairments.

Critical appraisal of study quality

The median quality score for all the 51 eligible studies was 80% (IQR 66.7-90.0) as summarized in [Table 3](#). Of the 51 studies, 9 (20%) fulfilled all the criteria for high quality in observational studies, with the remainder being of acceptable quality. Of these 9 studies, 6 had all the 10 criteria presents while for 3 studies, the last criteria (“Were subpopulations identified using objective criteria”) was not applicable. The range of the median age (where available) was 0.7–19.0 years. The median percentage female participants in the study was 48.5% (IQR 47.8-50.1) and they were not under-represented, compared to males ($p=0.903$).

Estimates of overall prevalence and heterogeneity

The pooled prevalence is reported for all the 51 studies. The pooled prevalence per 1,000 from the random effects model for any NDD was 7.5 (95% CI=7.4–7.6) ([Figure 2](#)), 3.2 (95%CI 3.1-3.3) for mental disorders and 11.3 (95% CI 11.2-11.5) for neurological disorders. We repeated the pooled prevalence for high quality studies (quality score >80) and found a prevalence of 7.6 (95%CI 7.5-7.6) per 1,000 and for studies where cases were clinically confirmed vs those where only screening tools were used to identify cases and the prevalence among clinically confirmed cases was 14.8 (95% CI=14.6-15.0) vs 4.0 (95% CI=3.9-4.1) for those which used screening tools only. We calculated the pooled prevalence of studies that used the same screening tools. Only the TQQ had a sufficient number of studies to calculate the pooled prevalence which was 11.9 per 1000 population (95% CI=10.7-13.0).

The random effect model for all studies was associated with a very high between-study heterogeneity ($p = 0.000$, $I^2=99.9\%$). Some studies plotted outside the funnel outline in the meta-funnel analysis ([Figure 3](#)) suggesting publication, reporting and selection bias.

Factors explaining variation in documented overall prevalence

We assessed several factors in the univariable and multivariable models and six appeared to explain the highest variation in the documented median prevalence in terms of prevalence ratios. The type of NDD (whether a mental disorder or neurological disorder) was significantly associated with the greatest prevalence ratios in the multivariate analysis, (PR=2.6 (0.6-11.6, $p<0.05$)). [Table 4](#) summarizes these findings.

Prevalence per 1000 of individual domains of neurodevelopmental disorders

Most studies were on epilepsy, $n=16$ (35%), followed by hearing impairment, $n=8$ (17%), visual impairment, $n=5$ (11%) and ADHD, $n=5$ (11%). Behavioural/emotional problems had the highest prevalence of 362 per 1,000 (95% CI=337.0-387.0) (based on 2 studies), while one study on mental disorders reported a prevalence of 232 (95% CI=199.0-268.0) per 1,000. ADHD had a prevalence of 61 (95% CI=54-69), epilepsy 8 (95% CI=7.8-8.2) and ASD 0.6 (95% CI=0.5-0.6) per 1000 ([Table 5](#)).

Incidence of neurodevelopmental disorders

Three studies reported the incidence of epilepsy with a mean annual incidence of 447.7 (95% CI 415.3-481.9) per 100,000^{31,35,56}. The study characteristics of all studies included in the meta-analysis are reported on [Table 2](#).

Regional distribution of neurodevelopmental disorders

The studies were distributed as follows: Africa $n=16$ (31.4%) (77.6%), Asia-Pacific $n=19$ (37.3%), Western-European $n=7$ (13.7%), Latin-America $n=7$ (13.7%), Multisite $n=2$ (3.9%).

Asia-Pacific had the highest number of domains studied ($N=8$, 73%) followed by Africa ($N=6$, 55%) then Latin America ($N=3$, 27%). Latin America had the highest pooled overall prevalence

Table 3. Critical appraisal of study articles using the Joanna Briggs Critical Appraisal Tool for Observational Studies.

Author	Year	Was the sample representative of the target population?	Were study participants recruited in an appropriate way?	Was the sample size adequate?	Were the study subjects and setting described in detail?	Is the data analysis conducted with sufficient coverage of the identified sample?	Were objective, standard criteria used for measurement of the condition?	Was the condition measured reliably?	Was there appropriate statistical analysis?	Are all important confounding factors/subgroups/differences identified and accounted for?	Were subpopulations identified using objective criteria?	Quality
Wagner RG	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	100
Bevilacqua MC	2013	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	70
Ngugi AK	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Ngugi AK	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Ebrahimi H	2012	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Unclear	Unclear	Yes	50
Caca I	2013	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	80
Arruda MA	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Burton KJ	2012	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not applicable	88.9
Basu M	2011	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Yes	70
Raina SK	2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Czechowicz JA	2010	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	80
Tasci Y	2010	Yes	Yes	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Not applicable	66.7
Winkler AS	2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Not applicable	88.9
Saldir M	2010	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	Not applicable	77.8
Perera H	2009	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Not applicable	66.7
Khan NZ	2009	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	88.9
Mung'ala-Odera V	2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Wong VC	2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	90
Velez van Meerbeke A	2007	No	No	Unclear	No	Unclear	Yes	Yes	Yes	Unclear	Yes	40
Zeidan Z	2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	80
Del Brutto OH	2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	100
Ersan EE	2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	90
Serdaro?Lu A	2004	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	80

Author	Year	Was the sample representative of the target population?	Were study participants recruited in an appropriate way?	Was the sample size adequate?	Were the study subjects and setting described in detail?	Is the data analysis conducted with sufficient coverage of the identified sample?	Were objective, standard criteria used for measurement of the condition?	Was the condition measured reliably?	Was there appropriate statistical analysis?	Are all important factors/subgroups/differences identified and accounted for?	Were subpopulations identified using objective criteria?	Quality
Wong V	2004	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	80
Mousa Thabet AA	2001	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Yes	Unclear	Yes	60
Couper J	2002	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	80
Bulgan T	2002	No	No	Unclear	No	Unclear	Yes	Yes	Unclear	Unclear	Yes	30
Zainal M	2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	90
Onal AE	2002	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	80
Rao RS	2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Not applicable	77.8
Liu XZ	2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Not applicable	88.9
Olusanya BO	2000	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Not applicable	77.8
Liu J	2000	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear	Yes	Unclear	Not applicable	22.2
Liu JM	1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	100
Brito GN	1999	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Yes	Unclear	Yes	60
Hackett RJ	1997	Unclear	Yes	Unclear	No	Unclear	Yes	No	Unclear	No	Not applicable	22.2
Morioka I	1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Okan N	1995	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Not applicable	66.7
Mulatu MS	1995	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	90
Rwiza HT	1992	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	70
Koul R	1988	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	70
Osuntokun BO	1987	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	70
Bash KW	1987	yes	yes	yes	yes	unclear	yes	yes	yes	yes	Not applicable	88.9
Taha AA	2010	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	80
Wamithi S	2015	No	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	60
Durkin MS	1992	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Not applicable	60

Each domain was marked using either "Yes", "No", "Unclear" or "Not/Applicable".

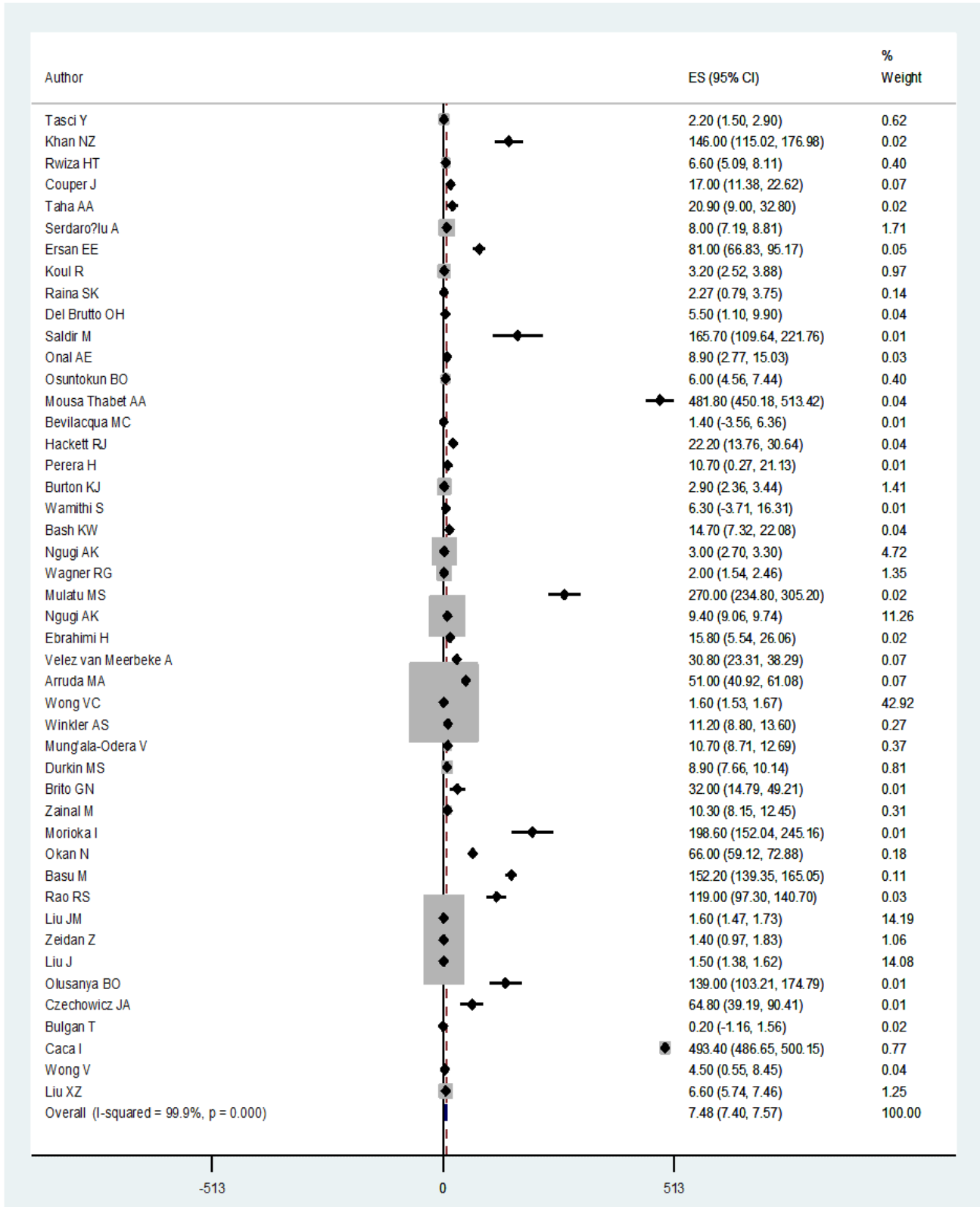


Figure 2. A forest plot showing the pooled median overall prevalence of all neurodevelopmental disorders in the included studies.

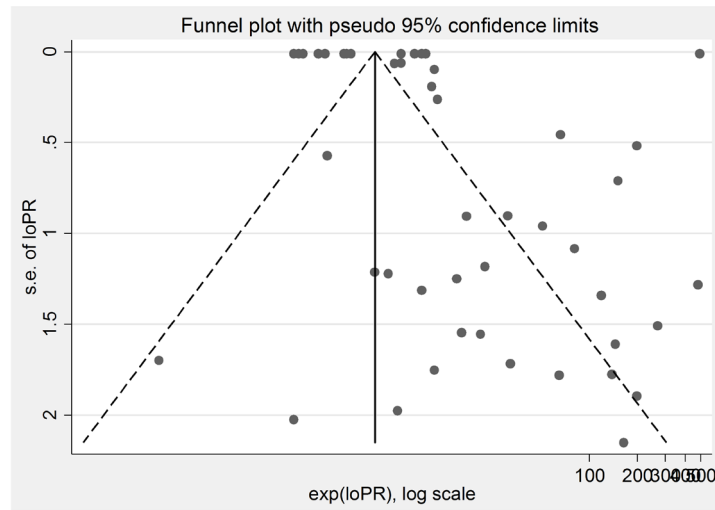


Figure 3. A funnel plot showing bias in published studies.

Table 4. Heterogeneity and factors contributing to heterogeneity.

Factor	Univariable analysis			Multivariable analysis		
	Prevalence ratio (95%CI)	P value	Heterogeneity (%)	Prevalence ratio (95%CI)	P value	Heterogeneity (%)
Region (as defined by the United Nations regional groups)	1.2 (0.6-2.3)	0.4	0.3	0.9 (0.5-1.9)	0.9	1.6
Condition (mental or neurological)	2.9 (0.7-12.3)	0.1	4.7	2.6 (0.6-11.6)	0.0	1.6
Setting (rural, urban or mixed)	0.8 (0.4-1.4)	0.5	2.8	0.6 (0.3-1.1)	0.2	1.6
Year	1.2 (0.7-2.3)	0.8	2.2	1.1(0.5-2.3)	0.9	1.6
Quality score (%)	1.0 (0.9-1.0)	0.1	3.2	1.0 (0.9-1.0)	0.3	1.6
Case identification method (clinically confirmed vs screening tool only)	1.6 (0.5-4.8)	0.4	0.2	2.0 (0.6-7.4)	0.4	1.6

Table 5. Mean Prevalence/incidence of individual neurodevelopmental disorders.

Condition	Number of studies reporting the condition (N=46)	Total sample size N=2740728	Mean prevalence per 1000 (95% CI)	Mean Incidence per 100000 (95% CI)
ADHD	5 (10.9%)	3897 (0.1%)	60.8 (53.5-68.8)	-
Behavior problems	2 (4.3%)	1458 (0.1%)	362.1 (337.4-387.4)	-
Cerebral palsy	3 (6.6%)	777343 (28.4%)	1.6 (1.4-1.6)	-
Epilepsy	16 (34.8%)	652240 (23.8%)	8.0 (7.8-8.2)	447.7 (415.3-481.9)
Hearing impairment	8 (17.4%)	53756 (2.0%)	11.4 (10.5-12.4)	-
Motor impairments	1 (2.2%)	1022 (0.0%)	14.6 (8.2-24.1)	-
Neurological dysfunction	2 (4.3%)	5171 (0.2%)	75.2 (68.2-82.8)	-
Visual impairment	5 (10.9%)	62032 (2.3%)	177.8 (174.8-180.8)	-
Learning disabilities	1 (2.2%)	2036 (0.1%)	80.0 (68.6-92.7)	-
Neurodevelopmental delay	1 (2.2%)	2043 (0.1%)	32.8 (25.5-41.5)	-
Other mental disorders*	1 (2.2%)	611 (0.0%)	232.4 (199.5-268.0)	-

per 1,000 for all NDD of 33.4 (95% CI=28.9-38.0), whereas Africa had the least 4.4 (95% CI=4.2-4.6). Epilepsy was the most reported condition in Asia and Africa. ADHD and hearing impairments most reported in South America.

Analysis of the settings of the studies (rural or urban), findings were available for 27 (57.4%) studies of which 15 (56%) were conducted in an urban setting, 10 (37%) in rural and 2 (6%) in both settings. The overall pooled prevalence in rural areas was 6.1 (95%CI 5.7-6.4) and was 2.1 (95%CI 2.1-2.2) per 1,000 in urban areas. We provide a summary of regional findings of the prevalence of individual domains of neurodevelopmental disorders in [Table 6](#).

Risk factors for neurodevelopmental disorders

Risk factors were reported in 13/51 (28%) studies included. Perinatal complications were the most prevalent risk factors across the NDDs. They were as significant in four out of the five (80%) conditions for which risk factor data was available. The highest median odds ratio (OR=9.4 (IQR 4.9-13.8) for perinatal complications was on participants with hearing impairments. History of febrile seizures was significantly associated with epilepsy OR=2 (95%CI 1.7-10.8), hearing impairments OR=5.6 (95%CI 4.7-9.0) and mild neurological dysfunction OR=6.7 (95%CI 2.1-25.5). Environmental factors such as parental smoking and a history of febrile illness were also prevalent risk factors. [Table 7](#) summarizes other risk factors data available from eligible studies.

Discussion

This review provides an estimate of the burden of NDD and associated risk factors in LAMIC. Only 51 eligible studies reported

the epidemiology of NDD, with a wide range of prevalence or incidence estimates for each condition. This indicates that in many LAMIC, there is a paucity of data on even the most basic epidemiology of NDD, particularly of mental health disorders. The wide range of prevalence estimates even within the same regions is comparable to that found in a review by Durkin⁶¹. It may be due to methodological differences⁶⁶ perhaps because of the difficulties involved in diagnosing most NDD particularly mental disorders for which there were fewer studies. The age of the child can complicate detection of NDDs since some disorders only manifest later in life, and the tools for detecting other disorders are relatively insensitive during early life. Furthermore, since there is considerable co-morbidity between these conditions complicating the estimates of the burden. Few studies reported risk factors for NDD with perinatal complications being the commonest risk factor for all NDD and febrile seizures for neurological disorders such as epilepsy.

Most studies were from Asia-Pacific; Africa and Latin America were under-represented. Although this may have affected the overall prevalence estimate, Polanczyk *et al.* in their review on ADHD demonstrated that geographical locations do not greatly influence prevalence outcomes⁶⁶. While the pooled estimates were comparable between Asia, Africa and Latin America, there were very few studies from the latter two continents. The minimum-pooled prevalence for all NDD was 7.5 per 1000, being higher for neurological disorders (11.3/1000) than for mental disorder studies (3.2/1000). This may be because of overrepresentation of studies on epilepsy, which is more widely studied in LAMIC. The estimates for mental disorders observed in this review are unexpectedly low, perhaps because detection of mental disorders such as ADHD and ASD is

Table 6. Regional summary of spectrum of neurodevelopmental disorders.

NDD	Asia-Pacific (N=2122324)	Africa (N=277897)	Latin America (N=10354)	Mixed (N=330153)
Pooled overall prevalence of all NDD (per 1000) and their corresponding 95% CI	7.5 (7.4-7.6)	4.4 (4.2-4.6)	33.4 (28.9-38.0)	9.4 (9.0-9.7)
Mean prevalence per 1000 for individual neurodevelopmental disorders and their corresponding 95% CI				
Autism spectrum disorders	0.6 (0.5-0.6)	-	-	-
ADHD	80.7 (67.1-96.1)	62.5 (35.4-101.0)	47.9 (39.4-57.6)	-
Epilepsy	6.7 (6.1-7.3)	3.9 (3.7-4.2)	5.5(2.0-12.0)	9.4 (9.0-9.7)
Behavioural/emotional problems	362.1 (337.4-387.4)	-	-	-
Cerebral palsy	1.6 (1.5-1.6)	-	-	-
Learning disability	-	80 (68.6-92.7)	-	-
Hearing impairments	8.1 (7.3-8.9)	125.8 (105.0-149.1)	45.4 (29.9-65.8)	-
Visual impairments	333.6 (328.5-338.7)	-	-	-
Motor impairments	-	14.7 (8.2-24.1)	-	-
Other mild neurological impairments	75.2 (68.2-82.8)	-	32.8 (25.5-41.5)	-
Other psychopathologies	-	232.4 (199.4-268.0)	-	-

These results do not include studies from Turkey which is the only country in the Western European category because the studies were too few to provide a pooled estimate.

Table 7. Risk factors for neurodevelopmental disorders and the corresponding median odds ratios with interquartile ranges.

	No. of studies (total =13 studies)	Epilepsy	Hearing impairment	Mild neurological dysfunction	Cerebral palsy	Psychopathology
Congenital malformations and injuries of the head	3	2.0*	9.4 (4.9-13.8)	-	-	-
Family history	6	2.8 (1.7-4.0)	5.1 (2.9-7.3)	-	-	-
Environmental factors such as parental smoking and families with substantial psychosocial stress	4	5.5 (1.8-8.6)	0.3 (0.2-5.1)	-	-	1.7* (95% CI 2.76-7.52)
Seropositivity to cysticercosis	1	4.2* (95% CI 1.6-11.2)	-	-	-	-
Sex male	2	1.9 (1.5-2.3)	-	-	-	-
Perinatal complications	8	2.8 (2.2-10.2)	-	1.1* (95% CI 1.1-1.2)	6.5*(95% CI 4.4-9.3)	-
History of a febrile illness	5	2.0 (1.7-10.8)	5.6 (4.7-9.0)	6.7* (95% CI 2.1-25.5)	-	-
History of snoring	1	6.5* (95%CI 4.5–9.5)	-	-	-	-
Non febrile illnesses such as jaundice	2	-	5.6 (0.2-15.8)	-	-	-
Maternal complications	1	-	0.2 (0.1-0.2)	-	-	4.6* (95% CI 2.76-7.52)

*Only one study reported this finding hence we provided the confidence interval from this study

The overall median prevalence per 1000 for neurological impairments was 13.0 (IQR= 6.1-45.0) and the mean was 47.5 (95% CI=6.5-101.6). The **pooled** median prevalence estimate for neurological impairments is 11.1(95% CI=10.7-11.5)

**Snoring when caused by upper highway obstructing may be associated with poor oxygen perfusion in the brain. Subsequent brain damage may lower seizure threshold eventually leading to epilepsy.

poor in LAMIC due to lack of tools and expertise for Measuring neurodevelopment in low-resource settings⁶⁷ and also because of some children dying early before diagnosis⁶⁸. In addition, surveys conducted in very young children may not detect ADHD. Prevalence of NDD is higher in rural areas compared to urban areas; which is consistent with previous studies of epilepsy⁶⁹ suggesting that risk factors might be more common in the rural areas. There was substantial differences between studies heterogeneity in the pooled estimates. The prevalence showed substantial variation between individual NDDs, being highest for visual impairment and lowest for ASD. The high heterogeneity observed for visual impairment may be related to the variability from the number of eligible studies included compared to ASD, but also to lack of standardised assessment. Only three studies documented incidence estimates and we could therefore not pool the findings.

This review shows that the burden of NDD is not precise and is probably greater than we have estimated. For instance, a robust study from rural Kenya utilising a demographic surveillance

system on neurological impairments and disability had a much higher estimate (67/1000) than the one presented in this review¹³. The low estimates from the review demonstrate that studies of individual conditions may not provide the true burden of NDD. A comprehensive study design approach to studying all NDD is important since these conditions overlap, and may be reliably screened together with a group of questions collated in one tool⁷⁰. The comprehensive screening approach would have important public health implication since many NDD overlap and the associated sequelae may be addressed by similar interventions.

The study showed disproportionately many studies of neurological impairments which may have skewed the overall pooled estimates. While some neurological impairments overlap with NDD⁷¹⁻⁷³ a substantial proportion of common NDDs such as ADHD and emotional problems present without neurological comorbidities. The multivariate meta-regression analysis showed that neurological studies might have influenced the estimates, compared to mental disorder studies. Visual impairments, which are easier to detect, were the commonest NDD, per-

haps also contributing to the high prevalence of neurological impairments⁷⁴. The paucity of mental disorder studies in these poor regions of the world may be related to the challenges in identifying these conditions such as lack of child and adolescent psychiatrists^{75,76}. In ADHD for instance, studies relied on reports from teachers and parents to make diagnosis⁵¹. It is difficult to translate these reports into valid and reliable case definitions because of the varying definitions of “normal behaviour” in different societies. However with the current success in local adaptation of tools for assessing behavioural⁷⁷ and developmental disorders⁷⁸ quality studies on mental disorder conditions such as ADHD and ASD should be possible in poor regions of the world.

The low prevalence of mental disorders is likely contributed by ASD. The prevalence of ASD is much lower than the burden documented in literature, suggesting possible under recognition of ASD in LAMIC particularly Africa. A recent review of ASD in sub-Saharan Africa found only one study on the prevalence of ASD⁷⁹. On the contrary, other mental disorders may be easily recognised and assessed, for example, behavioural/emotional problems were reported in 36%, ADHD in 6% and other mental disorders in 23%, albeit all were based on less than five studies. It is likely that there are sporadic low-quality studies in LAMIC that are not published or are placed in unindexed journals, based on the evidence of publication bias from the funnel plots. More robust studies on mental disorders in children are needed in LAMIC. The identification of NDD in poor regions is becoming easier following the advent of cheap and easy assessment approaches including the mental health gap action program intervention guide⁸⁰. Tools such as WHO’s Ten Questions Screen can be used to screen those to be prioritised for diagnosis of NDD^{35,81,82}.

Few studies reported several risk factors (Table 4). Perinatal complications²¹ and family history of febrile seizures^{26,35,46,83} were common across a different number of NDD, particularly epilepsy. The role of perinatal complications in the risk of neurological conditions is recognised in previous studies⁸³ and improvement in obstetric services may be helpful. Family history of seizures was associated with neurological disorders in rural Kenya¹³. Family history of seizures may represent genetic susceptibility or shared environmental factors for NDD, the later is supported by the high incidence of febrile infections in these regions. While environmental factors such as parental smoking are important in mental health problems in children, few NDD studies from LAMIC investigated this factor. Gene-environment interactions should be explored as the risk for NDD in these poor regions of the world. Some of the risk factors mentioned have a higher incidence in LAMIC than in high-income countries, and could have an additive interaction effect with each other^{84–86} which probably explains the higher burden of NDD in the former parts of the world. Other risk factors such

as fetal alcohol exposure which has been shown to have a high burden in some LAMIC^{87,88} and which result in neurodevelopmental impairments such as intellectual disability were not explored in the included studies and should be examined in future studies.

Limitations

There were methodological differences and lack of use of standardized measures to assess NDD in most studies. To mitigate the effect of methodological differences on the prevalence estimates, we conducted a sub-analysis of prevalence estimates for studies that used the same methods of case ascertainment. Additionally, the pathophysiology of individual NDD varies widely and this limits the generalizability of intervention strategies. For example, whereas biomedical interventions such as medications and surgery may be more helpful in neurological impairments, alternative interventions such as behavioural therapy may be more helpful for mental health disorders. Subjective methods such as reports from teachers and parents were used to assess for the presence of impairments. This limits the reliability of the estimates provided in this study. The effect of sex on NDD could not be explored since prevalence results were not aggregated based on sex, despite evidence of male/female propensity in some NDDs such as ASD. We did not separate crude from adjusted estimates therefore the estimates we have provided may still be under estimates. Currently, there is no standard validated tool for assessing quality of evidence presented in observational studies hence, although we appraised the studies included in our meta-analysis, there may still be methodological limitations. Studies on neurological impairments such as epilepsy, which have lower prevalence than other mental disorders in other parts of the world, were overrepresented in the sample and that influenced the overall prevalence estimate. The estimates of ASD were lower than reports from high-income countries, which may have lowered the overall estimates of NDD. Lack of data on the severity of the NDDs limits the clinical implications of this study. Although NDD manifests early in development, delayed diagnosis in many LMIC may have delayed detection of these disorders at the time of the study. Some countries may have transitioned to high-income countries based on the World Bank classification of Economies and this may change the estimates provided in this study. For the studies where prevalence was not reported, we calculated it as a proportion cases over the total study sample. This method may have resulted in underestimation of the prevalence since there was no background information to adjust calculated prevalence for attrition and sensitivities of screening tools.

Conclusions

This review indicates that the burden of NDD in LAMIC is considerable, but there is lack of reliable epidemiological data on some NDD such as ASD which may underestimate the true burden of NDD in LAMIC. Screening for all NDD in

epidemiological surveys is recommended to provide reliable estimates for planning purposes e.g. to inform resource allocation towards the rehabilitation of affected children. Mental disorders such as ADHD and ASD were rarely reported, and more studies particularly in Africa and Latin America are required to provide reliable estimates since neurological conditions such as epilepsy usually have conserved estimates compared to mental disorders. The risk factors investigated were few with the role of perinatal complications and history of febrile seizures being consistent with previous studies. Studies considering all potential risk factors are required to inform preventive interventions aimed at mitigating the risk factors for neurodevelopmental disorders.

Data availability

Final dataset for the systematic review is available on OSF: <http://doi.org/10.17605/OSF.IO/9E2WY>⁸⁹

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Competing interests

No competing interests were disclosed.

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Supplementary material

Supplementary File 1: PRISMA checklist.

[Click here to access the data.](#)

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Open Peer Review

Current Referee Status:



Version 3

Referee Report 08 June 2018

doi:[10.21956/wellcomeopenres.15516.r33282](https://doi.org/10.21956/wellcomeopenres.15516.r33282)



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In 2006 the World Health Organization published its first global report on neurological diseases.¹ In this publication they noted that, as a direct result of decreased mortality from infectious disease, there was a rising burden of neurological disorders worldwide. This new awareness for neurological diseases arose from the herculean work done and made public by the Global Burden of Disease Study in 2000. The importance of tackling neurological disorders was reemphasized by the follow-up Global Burden of Disease Study published in 2015.² While these studies did not differentiate between neurological and neurodevelopmental conditions, they emphasized the growing importance of these disorders worldwide. For example, the prevalence of epilepsy for all ages has increased by 39.2% between 1990 and 2015.² However, while these studies were informative in better understanding the burden of neurological disease as a whole, the global impact of neurodevelopmental disorders (NDD) could, at best, only be inferred from these studies (the conditions reported included Alzheimer's disease, Parkinson's disease, migraine headaches, multiple sclerosis, stroke and epilepsy). Yet, and somewhat paradoxically, as infant mortality rates continue to decrease worldwide (by close to 50% since 1990³) it is likely that the burden of NDD is growing. Indeed, a large proportion of childhood deaths occurs in the neonatal period (first 28 days of life). As the number of children who survive the neonatal period increases it is likely that NDD, as a result of challenges survived during this critical period, will increase in frequency. It is therefore essential to gain a better understanding of the magnitude and distribution of children affected by NDD. We cannot hope to start addressing this problem until we better understand the scope it represents. The epidemiology of NDD in low and middle-income countries (LAMIC) is currently largely inferred from high income countries. Yet it is not clear how accurate these inferences are as the socioeconomic realities of LAMIC are very different from those of high income countries. As LAMIC are gradually emerging from a medical system geared primarily at acutely managing infectious illnesses, the burden of NDD is becoming more and more obvious. It is clear that medicine in these countries is undergoing a slow but fundamental shift toward managing the comorbidities of infants and children surviving medical conditions that would previously have been fatal. As this shift occurs, reevaluating the actual incidence and prevalence of NDD in LAMIC will be of critical importance in shaping therapeutic and interventional priorities. It is within this context that Bitta et al. undertake a metanalysis of available literature reviewing the incidence and prevalence of NDD in LAMIC⁴.

The authors start by defining NDD "neurodevelopmental disorders ... typically manifest early in development and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning"⁴. These disorders include e both neurological (epilepsy,

intellectual disability, hearing and visual impairments, and cerebral palsy) and neuropsychiatric disorders (autism spectrum disorders (ASD) and ADHD). This meta-analysis is conducted using the best possible tools for this sort of systematic review of the literature. It follows the Joanna Briggs Critical Appraisal tool⁵ developed in 2014 by Munn et al. The authors were inclusive in a search that queried four large databases, including the African Index Medicus. They used a broad search strategy with a large number of inclusive terms to capture as much of the relevant literature as possible. The papers they reviewed were all conducted in LAMIC, had a population base less than 19 years old, (or were stratified by age, allowing for extraction of the less than 19 years old individuals) and only full research articles were included (reviews, case reports, etc. were excluded). 51 studies were found to meet the selection criteria. Of those 9 met the “high quality” criteria with the remainder meeting the “acceptable quality” criteria. The articles reviewed were published between 1987 and 2015. 16 studies were from the African continent, 5 from the Americas (mostly Brazil), 27 from Asia and 2 were from multiple sites. 10 of the 51 studies were designed to capture neuropsychiatric disorders, while the rest were geared toward neurological disorders (with 16 studies designed to study the epidemiology of epilepsy). The authors immediately note an important caveat, that many of the studies used the Ten Question Questionnaire (TQQ) tool. The TQQ has fairly good specificity for NDD, but according to one study⁶, it has low sensitivity (70 to 80% except for epilepsy where the sensitivity was 100%) and very low positive predictive value (11 to 33%). Furthermore, this tool may not capture the actual number of patients with neuropsychiatric disorders such as ASD and ADHD.

The results of this meta-analysis are noteworthy for several reasons. First and foremost is the very large variability between different regions of the world. The reported overall prevalence of NDD in Latin America 33.4/1000, but in Africa 4.4/1000 and in Asia 7.5/1000. This difference most likely points to the fundamental limitations to such studies in LAMIC where it is likely that NDD are underreported. Indeed, it is intriguing that the prevalence of NDD is highest in Latin America and lowest in Africa, yet Sub-Saharan Africa has the highest rates of poverty, neonatal mortality and malnutrition.³ One explanation might be that Sub-Saharan Africa is still dealing with such high mortality rates that they are not yet experiencing the full onslaught of NDDs, as many of the children most at risk for NDDs do not survive infancy. Another major issue relates to the ability to report NDDs in low-income countries. This was nicely highlighted in a recent meta-analysis on the burden of severe neonatal jaundice⁷. This study highlights the difficulty in obtaining such data in LAMICs. Despite numerous hospital-based studies highlighting the magnitude of the problem of severe neonatal jaundice in LAMICs, there were only 4 LAMICs that had population-based results. It is also instructive to compare the rates of NDDs reported in this systematic analysis to the available data for developed countries. Prevalence rates for many NDDs are readily available from the Centers for Disease Control and Prevention (see table). It is rather surprising to note how similar the numbers from the USA are to those reported in this study, notably for ADHD, cerebral palsy, epilepsy, learning disability and neurodevelopmental delays. This is likely a result of many different factors, including the difficulty at gathering this information in LAMICs, but also the differences in medical care. As noted above, improved medical care paradoxically associates with increased numbers of patients with NDDs (for example premature infants less than 30 weeks' gestation are unlikely to survive in LAMIC, but are at highest risk for NDDs in high-income countries where survival of these infants is becoming routine). It is also important to note the 10-fold higher rate of reported behavioral problems and hearing impairments. Why behavioral problems might be higher in LAMICs is not readily apparent but worth exploring. As pointed out by Galler et al, while most children now survive, early malnutrition is associated with continued neurodevelopmental deficits including behavior problems.⁸ Also worth noting is the higher prevalence of hearing impairments. One could postulate that infectious diseases such as CMV and rubella and the high incidence of severe neonatal hyperbilirubinemia in many LAMICs may contribute to the higher prevalence of hearing loss noted in this review.⁹⁻¹¹

What becomes clear on reading this meta-analysis is that much more data is needed to start understanding the scope of the problem of NDDs in LAMIC. Furthermore, while greater numbers are needed, one might argue that information as to the etiology of these disorders will be as important, if not more, in forming an actionable impression. In summary, this study is comprehensive and well conducted. It is inclusive in its criteria while abiding by the best practices of systematic reviews. Yet, the results are confounding. They leave the reader perplexed and wanting to know more. And this is perhaps the most important point that this study makes and we whole heartedly agree with the author's concluding statements "The burden of NDD in LAMIC is considerable. Epidemiological surveys on NDD should screen all types of NDD to provide reliable estimates."

Table 1: Comparison of NDD prevalence in LAMIC and USA

For an annotated version of the manuscript please click [here](#).

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Pediatric Global Health; Severe Neonatal Jaundice; Respiratory Failure in LMICs

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 21 May 2018

doi:[10.21956/wellcomeopenres.15516.r33128](https://doi.org/10.21956/wellcomeopenres.15516.r33128)



Zulfiqar A Bhutta

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This is an interesting and potentially important systematic review of literature from Low and Middle Income Countries (LMICs) on the burden of neurodevelopmental disorders. As described in the methods, the authors specifically sought population representative studies to derive prevalence and incidence data.

Although the authors seem to have thrown the net wide, the search strategy and the terms therein does appear to be limited and one wonders therefore as to the completeness and hence, representativeness of the review. I looked for studies from Pakistan and while the one recent study by my group in Sindh was included, two important cohort studies from Punjab were absent¹⁻². One wonders if help from a qualified librarian was sought in developing the search (and associated MeSH terms)?

The study sample sizes vary greatly from less than 200 to several thousand, and a legitimate question would pertain to the inclusion of such small sample sizes in the analysis; these couldn't be representative population samples. Some comment on these small studies would be warranted.

The other source of data might be from the Cohorts group, as well as recent follow up studies by the Saving Brains consortium, and one wonders if an overture was made?

Finally, it would have helped to see a comparison with the GBD estimates for LMICs to compare envelopes as well as major diagnoses.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 15 March 2018

doi:[10.21956/wellcomeopenres.15516.r31921](https://doi.org/10.21956/wellcomeopenres.15516.r31921)



Carl C. Bell

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Much better as it takes into account probably the biggest contributor (fetal alcohol exposure) to Neurodevelopmental Disorders in childhood.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Referee Report 28 February 2018

doi:[10.21956/wellcomeopenres.15269.r31063](https://doi.org/10.21956/wellcomeopenres.15269.r31063)



Carl C. Bell

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I guess my comments were too subtle to get a response and I did approve the article, however the consideration of fetal alcohol exposure in the continents studied still did not get any mention. I suspect I should have been more diligent in my comments, but it appears I get another chance to comment.

May *et al*¹ found "In this low SES, highly rural region, FAS occurs in 93–128 per 1000 children, PFAS in 58–86, and, ARND in 32–46 per 1000. Total FASD affect 182–259 per 1000 children or 18–26%."

Adnams CM. The determinants of Intellectual Disability and related mental illness in Africa presented at 3RD Annual Malawi Mental Health Research Research and Development Conference in 2013 (I realize this was not published and technically may not have been grist for the mill in the paper) noted the problem of Intellectual Disabilities, considered by DSM-5 to be a neurodevelopmental disorder, in the continent of Africa.

A publication on Intellectual Disability is available by Maulik PK, *et al*² which examines the prevalence of ID in some of the continents the authors of the article under consideration are studying. It is my sense that Intellectual Disability is often a neurodevelopmental disorder and a common etiologic factor of this disorder is fetal alcohol exposure.

Lange S *et al*³ lists six studies done in South Africa and gives prevalence of FASD using WHO regional and global mean prevalence of FASD.

There is another study on FASD in Malawi which I cannot locate at the moment, but I guess, to reiterate, I continue to have a concern that the issue of Fetal Alcohol Spectrum Disorders were not considered in this study.

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Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 08 Mar 2018

Mary Bitta, KEMRI-Wellcome Trust Research Program, Kenya

Dear Dr Bell

Thank you very much for pointing out the absence of fetal alcohol exposure as a risk factor for neurodevelopmental disorders in our study. We acknowledge that fetal alcohol exposure is an important risk factor for some NDD such as intellectual disability. We have now included this in our discussion on risk factors and have included the references that you suggested.

Regarding the study by Maulik PK, some of the individual studies in the review which met our

inclusion criteria have been included in our analysis.

Kind regards

Mary

Competing Interests: I declare no competing interests

Version 1

Referee Report 29 January 2018

doi:[10.21956/wellcomeopenres.14705.r30191](https://doi.org/10.21956/wellcomeopenres.14705.r30191)



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I read the article and find it wanting but that is from no fault of the authors, rather it is a fault of the lack of good epidemiologic data that is out there about China, Africa, and South America. The author's make good points about the need for better surveillance of the problem of neurodevelopmental disorders. They should be looking at issues of autism, intellectual disability, ADHD, speech and language disorders, specific learning disorders, and motor disorders which are the usual problems, but it occurs to me that they should also be looking for fetal alcohol exposure as in some places it is a serious problem that leads to the usual 6 previously mentioned. There is even evidence emerging that fetal alcohol exposure leads to epilepsy. Unfortunately, the epidemiologic data in the three continents of interest was not very robust.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 29 January 2018

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People with neurodevelopmental disorders (NDD) experience not only the health consequences of the condition, but also limits to social and economic participation, stigma and marginalisation. Addressing them through prevention strategies, screening programs for early detection, comprehensive interventions, equity of access to services and legislative and policy environments about rights and opportunities reduces the burden on individuals and families, but these are not distributed evenly throughout the world. Most evidence about population prevalence has been generated in high-income nations.

This systematic review with meta-analyses sought to establish the burden of neurodevelopmental disorders (NDD) in low- and middle-income countries and to identify factors associated with these. This has important potential to assist understanding of whether conditions are predominantly attributable to biological factors, and so occur at similar prevalence in all nations, or reflect external factors that vary among countries including health systems, access to health services and essential medicines, public health infrastructure, and human and gender-based development indicators.

The systematic review has been conducted and reported with considerable technical proficiency. There are however aspects of the conceptualisation, methods, analyses and interpretation which in our opinion warrant re-consideration:

1. It is not clear that the definition of NDD provided is widely used or accepted, it is drawn from a single study, and not a more authoritative source. There is little debate that conditions like cerebral palsy, autism spectrum disorders and epilepsy have neurological origins. However, to include 'behaviour problems' which are well known to reflect experiences, including of maltreatment, reduces conceptual clarity.
2. The inclusion criteria are quite well described, but need more precision to enable replication. The definition provided is that NDDs 'manifest early in development'. It is of particular concern, given the aim, that no age criterion was used and so, while purporting to report burden among children and adolescents, it is not clear that studies were limited to or had to report disaggregated data for participants of this age to be included.
3. All systematic searches for evidence from LAMIC have to include the names of each country and cannot assume that studies have used the World Bank Classification of Economies in reporting their data. In our opinion it is essential that this is corrected
4. The studies included in the review are not listed as references (a serious oversight) and so we cannot assume in checking them that we have identified the same papers. However, to claim that they are all of 'neurodevelopmental disorders' appears inaccurate. As examples, the study of 'hearing impairment' by Czechowicz et al in Peru concluded that the most common cause among children was untreated infections. The study of 'visual impairment' (Zainal et al) was a national survey in Malaysia, included participants up to the age of 96 years, and concluded that untreated cataract among older adults was the major contributing factor. Antisocial behaviour, aggression and fearfulness among children in Gaza (Mousa Thabet et al) were attributed to living in a war zone.
5. The related central concern is that the overall prevalence is reported as though it relates to one disorder. Most studies were of a single condition, but others reported combined prevalence

estimates for several NDDs (for example, Arrda et al; Couper et al). The pooled prevalence is therefore difficult to interpret. The meta-regression with this outcome therefore makes little sense. In our opinion consideration should be given to removing the meta-analysis.

6. Given the age ranges reported in the few studies that we selected to read, we do not know how the authors reached the conclusion that *The median age of participants was 10.4 years, with an interquartile range (IQR) of 8.8-10.8 years and a full range 0.7–19.0 years*. This needs to be explained clearly.
7. The inclusion criterion is that there is a ‘population denominator’, so it is unclear how in studies in which prevalence is not reported, it is calculated on the basis of proportion of cases in the sample. Please explain what biases this might have introduced.
8. There is a lack of definitional clarity about places. The term ‘Asia’ is used without a definition and this needs to be much more specific (e.g. South Asia, South East Asia, or Central Asia). It is not at all clear why it is thought relevant to report the findings by ‘continent’ (sometimes described in the paper as regions) when there are established regional groupings of countries, including the ones used by United Nations agencies that are widely known and would assist with generalisation.
9. It is not meaningful under a sub-heading *Regional distribution of neurodevelopmental disorders*, to report the proportions of ‘populations’ in different regions. Saying that countries are ‘under-represented’ does not explain this construct. The differences reflect the available research and not absolute numbers in these settings. Clarity should be improved.
10. In the Discussion there is little engagement with whether these estimates suggest that there are disparities in prevalence of NDD between low- and middle-, and high-income nations, but this is of key importance to the translation of this evidence, including where efforts to ameliorate this burden should be focused. This should be added.
11. Calling ‘mental disorders’ neurodevelopmental is questionable, in particular as the implications for interventions are quite different. There should be discussion of this.
12. Further clarifications include:
 - *due sampling error.... ?* due to sampling error;
 - *what are high stress families?*
 - *What is the significance of a history of snoring?*

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 12 Feb 2018

Mary Bitta, KEMRI-Wellcome Trust Research Program, Kenya

RESPONSE TO REVIEWERS

We thank the reviewers for their very helpful comments and we have provided a point by point response to each comment.

1. It is not clear that the definition of NDD provided is widely used or accepted, it is drawn from a single study, and not a more authoritative source. There is little debate that conditions like cerebral palsy, autism spectrum disorders and epilepsy have neurological origins. However, to include 'behaviour problems' which are well known to reflect experiences, including of maltreatment, reduces conceptual clarity.

Reply: We have now revised the reference cited for the definition of NDD and replaced it with the Diagnostic Statistical Manual Fifth Edition (DSM V) which is the original source of the definition. DSM V describes NDD as "A group of conditions with onset in the developmental period. The disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning."

<https://dsm.psychiatryonline.org/doi/abs/10.1176/appi.books.9780890425596.dsm01>

The inclusion criteria are quite well described, but need more precision to enable replication. The definition provided is that NDDs 'manifest early in development'. It is of particular concern, given the aim, that no age criterion was used and so, while purporting to report burden among children and adolescents, it is not clear that studies were limited to or had to report disaggregated data for participants of this age to be included.

Reply: In our inclusion criteria, we have now specified that "We only considered studies with a sample population of <19 years or if results were stratified by age, and a population denominator for sample <19 years was provided". We have also noted in the limitation section of the discussion that "These NDDs may have started early, but because of delayed diagnosis in many LMIC, they may have been detected much later at the time of the study.

2. All systematic searches for evidence from LAMIC have to include the names of each country and cannot assume that studies have used the World Bank Classification of Economies in reporting their data. In our opinion it is essential that this is corrected

Reply: We recognize the limitations of World Bank Classification of Economies criteria and have noted in the limitations section that this may have left out countries that were previously LAMIC but had transitioned into HIC during the study period.

3. The studies included in the review are not listed as references (a serious oversight) and so we cannot assume in checking them that we have identified the same papers. However, to claim that they are all of 'neurodevelopmental disorders' appears inaccurate. As examples, the study of 'hearing impairment' by Czechowicz et al in Peru concluded that the most common cause among children was untreated infections. The study of 'visual impairment' (Zainal et al) was a national survey in Malaysia, included participants up to the age of 96 years, and concluded that untreated cataract among older adults was the major contributing factor. Antisocial behaviour, aggression and fearfulness among children in Gaza (Mousa Thabet et al) were attributed to living in a war zone.

Reply: We have now added the references to the all the included studies.

4. The related central concern is that the overall prevalence is reported as though it relates to one disorder. Most studies were of a single condition, but others reported combined prevalence estimates for several NDDs (for example, Arrda et al; Couper et al). The pooled prevalence is

therefore difficult to interpret. The meta-regression with this outcome therefore makes little sense. In our opinion consideration should be given to removing the meta-analysis.

Reply: We acknowledge the difficulty in interpreting the pooled overall prevalence. Rather than stating that the pooled prevalence is for all NDD, we have now re-stated that the overall prevalence is for any NDD, to mean the presence of at least one NDD.

5. Given the age ranges reported in the few studies that we selected to read, we do not know how the authors reached the conclusion that *The median age of participants was 10.4 years, with an interquartile range (IQR) of 8.8-10.8 years and a full range 0.7–19.0 years*. This needs to be explained clearly.

Reply: We have now only reported the range of the median age reported in individual studies (where this was available).

6. The inclusion criterion is that there is a 'population denominator', so it is unclear how in studies in which prevalence is not reported, it is calculated on the basis of proportion of cases in the sample. Please explain what biases this might have introduced.

Reply: We have now noted in the limitation section that "This method may have resulted in underestimation of the prevalence since there may be no background information to adjust calculated prevalence for attrition and sensitivities of screening tools".

7. There is a lack of definitional clarity about places. The term 'Asia' is used without a definition and this needs to be much more specific (e.g. South Asia, South East Asia, or Central Asia). It is not at all clear why it is thought relevant to report the findings by 'continent' (sometimes described in the paper as regions) when there are established regional groupings of countries, including the ones used by United Nations agencies that are widely known and would assist with generalization.

Reply: We thank the reviewers for this observation. We have now revised the regional data to reflect the UN regional groupings.

8. It is not meaningful under a sub-heading *Regional distribution of neurodevelopmental disorders*, to report the proportions of 'populations' in different regions. Saying that countries are 'under-represented' does not explain this construct. The differences reflect the available research and not absolute numbers in these settings. Clarity should be improved.

Reply: We agree with the reviewer that the proportions reported only reflect the available research rather than the absolute numbers in these settings. We have now deleted this section to avoid confusion.

9. Calling 'mental disorders' neurodevelopmental is questionable, in particular as the implications for interventions are quite different. There should be discussion of this.

Reply: We thank the reviewers for this point. We have acknowledged how the widely varying pathophysiology of the individual disorders affects intervention strategies in our limitations section. In particular we note that "Non-treatment interventions may be more useful in neurodevelopmental disorders, while treatment is more helpful in mental health disorders".

10. Further clarifications include:

o *due sampling error.... ?* due to sampling error;

Reply: This was a typographical error and has been corrected.

o *what are high stress families?*

In this context we were referring to families undergoing psychosocial stress that results from factors such as poverty (and all the negative consequences of deprivation) exposure to negative life events such as natural disasters etc. In the light of this, the term high stress families has now been revised to read "families with substantial psychosocial stress".

o *What is the significance of a history of snoring?*

Reply: Snoring when caused by upper highway obstructing which may be associated with poor oxygen perfusion in the brain. Subsequent brain damage may lower seizure threshold eventually leading to epilepsy. This information is now provided in the revised manuscript.

Competing Interests: No competing interests were disclosed.