



RESEARCH ARTICLE

REVISED **Patterns of neurobehavioral functioning in school-aged survivors of neonatal jaundice and hypoxic-ischemic encephalopathy in Kilifi, Kenya: A cross-sectional study**

[version 3; peer review: 1 approved, 1 approved with reservations, 5 not approved]

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Abstract

Background: Studies in high-income countries have reported that school-aged children who survive neonatal jaundice (NNJ) and hypoxic-ischemic encephalopathy (HIE) develop long-term neurocognitive problems. However, less is known about the patterns of functioning in school-aged survivors of NNJ and HIE in sub-Saharan Africa. This study examined patterns of functioning in school-aged children who survived NNJ and HIE in Kilifi, Kenya.

Methods: This is a cross-sectional study that included 107 survivors of NNJ/HIE (64 with NNJ, 43 with HIE), aged 6-12 years, admitted to Kilifi County Hospital on the Kenyan Coast. The Gross Motor Function Classification System (GMFCS), Adapted Communication Profile, Raven's Coloured Progressive Matrices (RCPM) and an epilepsy screening tool were used to assess gross motor function, communication function, intellectual functioning, and epilepsy, respectively.

Results: Most of the survivors of NNJ (95.2%) and HIE (95.3%) had no impairments in gross motor functioning. A small percentage of the children in the NNJ and HIE groups had profound problems in their communication (4.7% and 4.7%); expressive communication function (4.7% and 4.7%); social functions (3.1% and 2.3%); receptive communication (4.7% and 2.3%); and communicative effectiveness (4.7% and 2.3%). Cognitive impairment was reported in 10.9% and 11.9% for NNJ and HIE survivors, respectively. Active epilepsy was

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detected in 1.6% of survivors of NNJ and 2.3% of survivors of HIE. A subgroup of severe NNJ and HIE survivors without co-occurring conditions had the worst intellectual and active epilepsy outcomes. All children had normal hearing and visual functioning except one participant who presented with mild visual acuity problems.

Conclusions: Most school-aged children who survive with NNJ and HIE have normal motor and communication function; however, one in ten are likely to present with lowered intellectual functioning compared to the normative sample.

Keywords

Neonates, jaundice, hypoxic-ischemic encephalopathy, cognition, motor, communication, disability, sub-Saharan Africa



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REVISED Amendments from Version 2

In this version, we have provided additional information about the clinical characteristics of participants with cognitive impairment and active epilepsy. We have also provided the cognitive and epilepsy outcomes of a subgroup of participants with severe neonatal jaundice (TSB \geq 250 μ mol/l) and those with a diagnosis of hypoxic-ischemic encephalopathy without any co-occurring neonatal conditions. Lastly, we have provided a supplementary table with a clinical diagnosis and the TSB levels of the participants with severe neonatal jaundice.

Any further responses from the reviewers can be found at the end of the article

Introduction

Neonatal jaundice (NNJ) and hypoxic-ischemic encephalopathy (HIE) are common insults during the neonatal period. These insults have both short-term and long-term impacts on children's functioning¹⁻⁸. The global incidence of severe NNJ is estimated at 9.9 per 10,000 live births among children⁹. Africa has the highest burden of severe NNJ with incidence rates of 667.8 per 10,000 live births (95% CI 603-738)⁹. HIE is caused by different factors, such as uterine rupture, placenta abruption, cord prolapse, maternal hypotension, and obstructed labour, which either impair the supply of blood and oxygen to the brain before, during or immediately after the birth of the baby^{10,11}. The incidence of HIE globally is estimated at 1.5 per 1000 live births (95% CI 1.3-1.7)¹², and it is associated with poor neurocognitive outcomes^{4,5,13-17}.

The overall burden of NNJ and HIE in neonates admitted to Kilifi County Hospital in Kenya increased between 1990 and 2008 significantly by 6% and 11%, respectively¹⁸. They were the second and third most common neonatal conditions after sepsis (13%)¹⁸. In 2015, 32% of neonatal mortality was caused by HIE and birth trauma in Kenya¹⁹.

Studies in high-income countries have reported that school-aged children who survive NNJ and HIE develop adverse long-term neurocognitive outcomes^{4,6,16,20-30}, although long-term outcomes of NNJ tend to be less severe. However, to the best of our knowledge, there are no studies on long-term neurocognitive outcomes in school-aged children who survived NNJ and HIE in sub-Saharan Africa (SSA) despite the high burden of NNJ and HIE in this context. This study investigated the patterns of functioning in school-aged children who survived NNJ or HIE in Kilifi, Kenya.

Methods**Study design**

This is a cross-sectional study that examined the neurobehavioral patterns of functioning of school-aged children (6–12 years) who survived NNJ and HIE.

Study site

This study was conducted at the Centre for Geographic Medicine Research-Coast (CGMR-C) located in Kilifi County, at the North Coast of Kenya. The study used the Kilifi Health

and Demographic Surveillance System (KHDSS) to identify and recruit a well-defined cohort of school-aged children who were admitted to the Kilifi County Hospital in the first 28 days of life with NNJ or HIE and for whom neonatal data were available. Participants were recruited and assessed from September to December 2017. Assessments were carried out by trained research assistants under the supervision of a psychologist (DM) at the CGMR-C neuro-assessment unit, during which participants were accompanied by their mother or a primary caregiver in the absence of the mother.

Participants and procedures

We utilized the KHDSS to identify and trace survivors. Participants were recruited in the study if they had a diagnosis of NNJ or HIE during the first 28 days of life; were aged between 6 to 12 years at the time of follow-up; parental consent was obtained; and they were living within the area covered by the KHDSS. Participants were excluded if they did not consent to the study. None of the participants in this study had a diagnosis of both NNJ and HIE. Some of the participants had sepsis and preterm birth as a secondary diagnosis. For NNJ, 23 had neonatal sepsis, and 6 were preterm, and for HIE, 5 had sepsis, and 2 were preterm. However, based on another study that we conducted, sepsis did not appear to aggravate the developmental outcomes of children with neonatal jaundice and sepsis³¹.

Diagnosis

The diagnosis of NNJ was based on clinical laboratory measurement of total serum bilirubin (TSB) as well as medical history and examination during the first 28 days of life. NNJ was defined as a TSB level of >85 μ mol/l recorded to the clinical notes at admission. Severe hyperbilirubinemia was defined as TSB of >250 μ mol/l. All the children with NNJ were admitted to KCH and were treated with phototherapy. Phototherapy was considered if they had any visible jaundice anywhere on the body on day one or TSB >260 μ mol/l on day two¹¹. HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone¹¹. Severe disability was defined as the impairment in body structure which results in significant loss and difficulty for a participant to perform a task³¹. A medical officer with a bachelor's degree in medicine and surgery made the diagnosis of NNJ and HIE and this was often discussed with consultant paediatricians who had been trained in Kenya or the United Kingdom.

Screening tools

A set of screening tools were used to describe the level of functioning and patterns of disability among participating children. Anthropometric data (weight, height, head circumference, and Mid Upper Arm Circumference) were obtained based on the World Health Organization (WHO) standards³². Screening assessments were done for gross motor functioning, communication functioning, intellectual disability, and epilepsy. The participants were screened for hearing and visual acuity using a pure-tone audiometry machine-Kamplex model R17A AUD Type 3³³ and the Snellen and E-Chart, respectively. For

audiometric testing, first, we talked to the participants while walking towards the sound-proof assessment room to assess how well they are hearing. We then inspected their ear canals using an otoscope. We then instructed the participants to push the button when they hear a sound through the headphones and tested to see if the instructions were clear. We started at 1000 Hz and decreased the level by 10dB until no response was obtained. We then increased the level by 5 Db steps until a reply was captured again. We did these steps until the lowest level at which the participant responded was received. We continued with this procedure at 2000 Hz, 4000 Hz, 500 Hz, 250 Hz, and 125 HZ for both ears. Almost all the participants had normal hearing and vision functioning except one who had mild vision problems.

The Gross Motor Function Classification System (GMFCS) was used to measure gross motor functioning. The GMFCS tool was devised by Peter Rosenbaum and colleagues to determine the level that best describes a participant's current abilities and limitations in gross motor function³⁴. The GMFCS classifies children into 5 levels: Level I, the child can walk to various places and climb stairs without using rails and can jump and run with ease, although some children might have limitations in motor coordination while performing such gross motor functions; Level II, the child has limitations in outdoor activities; Level III, the child needs support to move; Level IV, the child needs technological assistance to move; Level V, the child's movement is completely restricted, and they need complete assistance to move. The caregiver is asked to choose the best description of their child, which shows the child's level of gross motor functioning. The GMFCS has good interrater agreement [κ 0.76 to 0.88; intraclass correlation coefficient (ICC) ranging from 0.89 to 0.95]³⁵.

Communication functioning was assessed using the Adapted Communication Profile³⁶. This tool captures the child's language abilities through a caregiver report. The caregiver is asked questions about the child's communication abilities and asked to indicate the level of problems his/her child has for

the subscales social communication functions, receptive communication functions, and communication effectiveness, and this is rated using scores of 0= not a problem, 1= a bit of a problem, and 3= a big problem. The scores are then summed for each participant. The Adapted Communication Profile is contextually relevant and has previously been used with children in Kilifi³⁷; however, its psychometric properties in Kenya are yet to be established.

The Raven's coloured progressive matrices (RCPM)³⁸ was administered to assess intellectual functioning. The RCPM is made up of a series of patterns with a missing part, which the participant completes by choosing from several options. The multi-choice items require abstract reasoning. This test has been validated and previously used in children in Kilifi, Kenya³⁹ and has good internal consistency (Cronbach alpha = 0.81) and test-retest reliability (ICC = 0.77)³⁹. The test has good construct validity in the Kenyan population⁴⁰.

The epilepsy screening tool⁴¹ was used to screen for epilepsy in this study sample. This tool was validated using a three-stage screening methodology for detecting active epilepsy in Kilifi, Kenya⁴¹. Active epilepsy was defined as two or more unprovoked seizures occurring within the last 12 months⁴², or on anti-epileptic treatment.

Study size

As per the KHDSS records by December 2017, of the 280 cases with NNJ admitted between 2005 and 2012, 17 (6.1%) children died before discharge, 15 (5.4%) died after discharge, while 67 (23.9%) had migrated from the KHDSS and their survival could not be determined. Of the 378 neonates who were admitted with HIE between 2005 and 2012, 117 (31.0%) died before discharge, and 16 (4.2%) died after discharge. However, 79 (20.9%) had migrated from the KHDSS, and their survival could not be determined.

The recruitment, and assessment processes are indicated in [Figure 1](#). Out of the 658 survivors of NNJ and HIE, 347

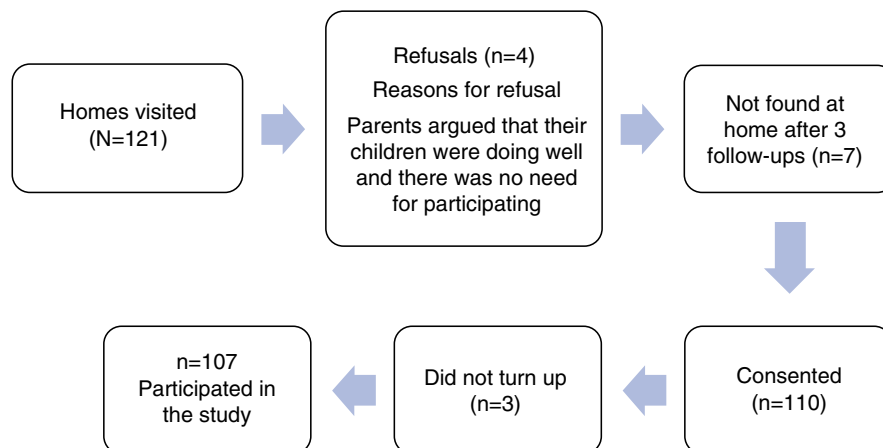


Figure 1. Participants visited, recruited, and assessed.

survivors were identified, 121 were followed up and visited at home for recruitment, and 107 participants aged 6–12 years were included in this study.

Statistical analysis

Data were collected, entered, and managed using REDCap, an electronic data capture tool hosted at the CGMR-C, and analysed using STATA (version 15)⁴³. The anthropometric variables Weight-for-Age (WAZ) and Height-for-Age (HAZ) were standardized using WHO Anthro plus⁴⁴. An abnormal nutritional status (stunted growth or underweight) was considered if the z-scores obtained from WHO Anthro plus were below -2 standard deviation (SD). The WAZ and HAZ scores of these children were compared to the WAZ and HAZ scores for children in the general population obtained in a study conducted in 2003 with 184 children aged 8 to 11 years. Descriptive statistics such as means, medians, and percentages were used to describe sample characteristics and to summarize gross motor, language, and intellectual functioning and history of epilepsy. The cognitive and epilepsy outcomes of these children were compared to the normative data obtained from a study conducted in 2016 with 11,223 children aged 6 to 9 years randomly selected from the Kenyan community to estimate the burden of neurological impairments⁴⁵. Cognitive impairment was defined as total Ravens Z-scores below -2 SD. The 95% confidence interval (CI) were calculated using the Clopper-Pearson exact method. We conducted a sub-analysis of NNJ survivors with TSB \geq 250 μ mol/l and without any co-occurring neonatal conditions and survivors of HIE without co-occurring neonatal conditions and determined their cognitive and epilepsy outcomes compared to the normative group.

Results

Demographic characteristics of participants

In this study, of the 107 included participants, 64 survived NNJ (31 females and 33 males) and 43 survived HIE (29

females and 14 males). The median age at admission was 3 [interquartile range (IQR) = 0–8] days. The current median age of the participants was 10 [interquartile range (IQR) = 5–12] years. The median TSB values of the NNJ survivors was 245 (IQR = 144– 322) μ mol/l. These participants had normal anthropometric measures; none of the participants were underweight or had stunted growth. All participants had normal hearing and visual functioning except one who had visual acuity problems. The mean WAZ was -1.3 (SD = 0.9), -1.0 (SD = 1.6), and -1.2(SD = 1.1) while the mean HAZ was -1.1 (SD = 1.1), -0.8 (SD = 1.5), and -1.3(SD = 1.1) for NNJ, HIE and for the general population, respectively. Table 1 presents a summary of these results (see underlying data⁴⁶). There were no significant differences in the WAZ [F (2, 196) = 0.5, P = 0.623] and HAZ [F (2, 285) = 2.6, P = 0.077] scores between the cases and the general population.

Neurobehavioral functioning

Gross motor functioning. As indicated in Table 2, almost all survivors of NNJ (95.2%) and HIE (95.3%) had level I gross motor functioning while 4.8% and 4.7% survivors of NNJ and HIE respectively had level II functioning, as assessed by the GMFCS.

Language functioning. Most of the children who survived NNJ and HIE did not have any problems in communication functioning (Table 2). Of the survivors of NNJ, 4.7%, 3.1%, 3.1%, 4.7%, and 4.7% had profound problems in their communication modes, expressive communication functions, social communication functions, receptive communication, and communicative effectiveness, respectively. Of the survivors of HIE, 4.7%, 4.7%, 2.3%, 2.3%, and 2.3% had a significant problem in their communication modes, expressive communication functions, social communication functions, receptive communication and communicative effectiveness, respectively (Table 2).

Table 1. Demographic characteristics of participants.

	N= 107	NNJ n (%) = 64 (59.8)	HIE n (%) = 43 (40.2)
Sociodemographic characteristics			
Age (years), Median [IQR]	10 [5-12]	10 [6-12]	8 [5-12]
Sex, n (%)			
Female	45 (68.9)	31 (53.2)	29 (31.1)
Male	62 (42.1)	33 (46.8)	14 (36.1)
Anthropometric data, Mean (SD)			
Mid upper arm circumference (cm)	17.5 (2.5)	17.7 (2.7)	17.2 (2.0)
WAZ	-1.1 (1.3)	-1.3 (0.9)	-1.0 (1.6)
HAZ	-1.0 (1.3)	-1.1 (1.1)	-0.8 (1.5)

Note. NNJ- neonatal jaundice; HIE- hypoxic-ischemic encephalopathy; WAZ- weight-for age; HAZ- height-for-age; IQR-Interquartile Range; n-number of participants

Table 2. Patterns of functioning in children who survived NNJ and HIE.

	NNJ	HIE
Type of functioning	N (%) N= 64	N (%) N= 43
GMFCS Levels of functioning		
Level I	59 (95.2)	41(95.3)
Level II	3 (4.8)	2 (4.7)
Level III	0 (0.0)	0 (0.0)
Level IV	0 (0.0)	0 (0.0)
Level V	0 (0.0)	0 (0.0)
Communication Functioning n (%)		
Communicative modes		
Not a problem	58 (90.6)	40 (93.0)
A bit of a problem	1 (1.6)	1 (2.3)
A big problem	3 (4.7)	2 (4.7)
Expressive communication functions		
Not a problem	60 (93.8)	41 (95.3)
A bit of a problem	1 (1.5)	0 (0.0)
A big problem	3 (4.7)	2 (4.7)
Social communication functions		
Not a problem	59 (92.2)	41 (95.3)
A bit of a problem	3 (4.7)	1 (2.3)
A big problem	2 (3.1)	1 (2.3)
Receptive communication functions		
Not a problem	60 (93.8)	42 (97.7)
A bit of a problem	1 (1.5)	0 (0.0)
A big problem	3 (4.7)	1 (2.3)
Communicative Effectiveness		
Not a problem	60 (93.8)	42 (97.7)
A bit of a problem	1 (1.5)	0 (0)
A big problem	3 (4.7)	1 (2.3)
Intellectual functioning		
Raven Total scores Median (IQR)	12.8 (9.5-16.5)	13.0 (10.0-18.0)
Cognitive impairment n (%)		
Yes	7 (10.9)	5 (11.6)
No	57 (89.0)	38 (88.4)
History of epilepsy		
Presence of active Epilepsy		
Yes	1 (1.6)	1 (2.3)
No	62 (96.9)	38 (90.5)

Note. NNJ- neonatal jaundice; HIE- hypoxic-ischemic encephalopathy; GMFCS- Gross Motor Function Classification System; n-number of participants; IQR- Interquartile Range

Intellectual functioning

The median IQ score based on performance on the RCPM was 12.8 (*IQR* = 9.5 - 16.5) for children who survived NNJ and 13.0 (*IQR* = 10.0 - 18.0) for the HIE group. As shown in [Table 2](#), 10.9% of the children in the NNJ group and 11.6% of the children in the HIE group had a cognitive impairment. The prevalence of cognitive impairment in survivors of NNJ [10.9% (95%CI = 4.5 - 21.2)] and HIE [11.6% (95% CI = 3.9 - 25.1)] was twenty times higher than in the normative group [0.5% (95% CI = 0.3 - 0.6)], $p < 0.001$ ([Table 3](#)).

History of epilepsy

As shown in [Table 2](#), 1.6% of survivors of NNJ and 2.3% of survivors of HIE had active epilepsy. There was no significant difference in the prevalence of active epilepsy in survivors of NNJ [1.6% (CI = 0.0 - 8.4)] and HIE [2.3% (CI = 0.0 - 12.3)] versus the normative group [0.5% (CI = 0.4 - 0.6)], $p > 0.050$ ([Table 3](#)).

Clinical characteristics of participants with cognitive impairment and active epilepsy

The mean WAZ was -1.9 (SD = 2.0) and -2.0 (SD = 2.1) while the mean HAZ was -2.2 (SD = 1.0) and -0.6 (SD = 2.9) for the

survivors of NNJ and HIE who had cognitive impairment and active epilepsy, respectively. The median TSB levels for NNJ participants with cognitive and epilepsy problems was 416 [*IQR*= 227-607]. Of the participants who had cognitive and epilepsy problems one survivor of NNJ and two survivors of HIE had sepsis while one survivor of NNJ was preterm as shown in [Table 4](#).

Cognitive and epilepsy outcome in subgroup NNJ and HIE participants versus normative group

We conducted a sub-analysis with 15 survivors of NNJ (see supplementary table 1) whose TSB levels were measured at admission and was ≥ 250 $\mu\text{mol/l}$ and did not have any co-occurring neonatal conditions and 34 survivors of HIE without any co-occurring neonatal conditions and compared them to the normative group.

The prevalence of cognitive impairment in the sub-group of survivors of NNJ was 13.3% (95% CI = 1.7 - 40.5), and HIE 5.9% (95% CI = 0.7 - 19.7) compared to a prevalence of 0.5% (95% CI = 0.3 - 0.6) in the normative group ([Table 5](#)). The prevalence of active epilepsy in survivors of NNJ was 6.7% (CI = 0.7 - 31.9) and HIE 2.9% (CI = 0.1 - 15.3) versus the normative group 0.5% (CI = 0.4 - 0.6)].

Table 3. Cognitive and epilepsy outcome in NNJ and HIE cases versus normative group.

Outcome	NNJ cases (N=64)	Normative data (N=11,232)	Statistical tests	HIE cases (N=43)	Normative data (N=11,232)	Statistical tests
Cognitive impairment	7	51	($\chi^2(1) = 136.8$ $P < 0.001$)	5	51	($\chi^2(1) = 108.1$ $P < 0.001$)
Active epilepsy	1	54	($\chi^2(1) = 1.5$ $P = 0.215$)	1	54	($\chi^2(1) = 3.0$ $P = 0.083$)

Note. NNJ- neonatal jaundice; HIE- hypoxic-ischemic encephalopathy.

Table 4. Clinical characteristics of participants with cognitive impairment and active epilepsy.

	NNJ n = 7	HIE n = 5
Clinical characteristics		
Anthropometric data, Mean (SD)		
Mid upper arm circumference (cm)	15.2 (1.6)	16.2 (1.9)
WAZ	-1.9 (2.0)	-2.4 (2.1)
HAZ	-2.2 (1.0)	-0.6 (2.9)
Bilirubin Median [<i>IQR</i>]	416 [227-607]	-
Other problems n(%)		
Sepsis	1(14.3)	2 (40)
Preterm	1(14.3)	0(0)

Table 5. Cognitive and epilepsy outcome in subgroup NNJ and HIE participants versus normative group.

Outcome	NNJ cases (N=15)	Normative data (N=11,232)	Statistical tests	HIE cases (N=34)	Normative data (N=11,232)	Statistical tests
Cognitive impairment	2	51	($\chi^2(1) = 52.9$ $P < 0.001$)	2	51	($\chi^2(1) = 21.3$ $P < 0.001$)
Active epilepsy	1	54	($\chi^2(1) = 11.8$ $P = 0.001$)	1	54	($\chi^2(1) = 4.2$ $P = 0.040$)

Note. NNJ- neonatal jaundice; HIE- hypoxic-ischemic encephalopathy.

Discussion

This study investigated the patterns of neurobehavioral functioning in children who survived NNJ and HIE in Kilifi, Kenya. The results of this study show that most of the children who survived NNJ and HIE had normal vision, hearing, motor functioning, communication functioning, and no seizure disorder on screening tests. However, compared to the normative sample, the NNJ and HIE participants had poorer intellectual functioning. A sub group of survivors of severe NNJ and HIE without any co-occurring conditions had worse intellectual and active epilepsy outcomes compared to the normative group.

Patterns of functioning of neurobehavioral school-aged children who survived NNJ

The findings of this study suggest that most children who survived NNJ had normal vision, hearing, motor functioning, and communication functioning but had poorer intellectual functioning compared to the normative sample. A sub-group of NNJ with TSB ≥ 250 $\mu\text{mol/l}$ and without any co-occurring conditions severe intellectual and active epilepsy outcomes compared to the normative group.

Our study found that children who survived NNJ have normal hearing and visual functioning. This finding contradicts the results of a study by Martínez-Cruz *et al.*⁴⁷ who evaluated the frequency of sensorineural hearing loss (SNHL) in children aged 2 to 10 years with a history of exchange transfusion⁴⁷. The authors reported a high frequency (15%) of SNHL in survivors of NNJ. However, the children in that study were also reported to have a substantial risk of comorbidities such as cerebral palsy (20%) and epilepsy (20%), unlike in our study where 1.6% of the NNJ survivors had active epilepsy. The difference in the prevalence of epilepsy in these two studies could be because of difference in the severity of NNJ. Unlike in the current study where severe hyperbilirubinemia was defined as TSB of ≥ 250 $\mu\text{mol/l}$, the participants in Martínez-Cruz and colleagues' study had severe NNJ defined as an increase in bilirubin by >0.5 mg/dL and >0.3 mg/dL per hour in term and preterm infants, respectively, and required exchange transfusion. Therefore, the SNHL could be a result of the loss and alterations of neurons caused by the motor disorders and deposition of bilirubin in the nuclei involved in the auditory pathway. Similar to the findings of Kara

*et al.*⁴⁸ who evaluated children aged 3 to 5 years who survived NNJ, the current study did not find any visual abnormality in survivors of NNJ.

Additionally, the findings of this study are consistent with results by Chen *et al.*²² who report normal motor and neurodevelopmental outcomes after three years of age in a five-year follow-up study of 128 survivors of NNJ. A few studies have reported poor long-term cognitive functions in survivors of NNJ^{26,49,50}. The results that survivors of NNJ have poor cognitive outcomes corroborate findings by Hokkanen *et al.*²⁶ who reported that at 30 years, 40% of survivors of severe NNJ had poor cognitive functions that continued from childhood to adulthood. Studies on the associations between the long-term outcomes of active epilepsy in survivors of NNJ are limited. Zhang and colleagues report that severe NNJ can induce temporal and occipital lobe seizures in infants⁵¹.

Patterns of neurobehavioral functioning of school-aged children who survived HIE

The findings of this study suggest that children who survived HIE have normal vision, hearing, motor functioning, and communication functioning, but have poorer intellectual functioning compared to the normative sample. A subgroup of survivors of HIE without co-occurring conditions had severe intellectual and active epilepsy outcomes.

The finding that survivors of HIE have normal vision and hearing functioning corroborates the results of Mietzsch *et al.*⁵² who investigated auditory function in neonates treated with hypothermia. These authors report that although peripheral acoustic functions were altered for the neonates in their study during the first week, they normalized by week 3. A follow-up of the cohort at 18 to 30 months also showed normal visual functioning in these children. In contrast to Mercuri and colleagues⁵³, who investigated the visual function in infants aged 5 to 31 months and reported multiple ocular abnormalities in children who survived HIE, our study found normal vision functioning in the survivors of HIE. However, the difference in findings could be due to the differences in the age of participants in these two studies (5 to 31 months in the Mercuri *et al.* study versus 6 to 12 years in our study) and that many of neonates

discharged following HIE in the current study died in the community.

These findings are similar to those reported by Hayes *et al.*²⁴ who did not find any motor, language, and emotional and behavioural problems impairments among 146 survivors of HIE without cerebral palsy. Similarly, Van Kooij *et al.*³⁰ and Roberson *et al.*⁵⁴ did not find significant impairment in survivors of mild HIE motor and school performance respectively compared to the control groups. Our findings corroborate findings by Toet *et al.*⁵⁵ who report that 7% of children who survived HIE had postneonatal epilepsy. However, unlike the findings of Hayes *et al.*²⁴, who did not find any cognitive impairment in their sample, our results show that survivors of HIE have poorer cognitive outcomes compared to the normative sample. The difference in results could be due to the difference in age groups in the two samples. Since the current study had an older age group, it is likely that the cognitive deficits reflect a cumulative effect. It should be noted that the cognitive outcomes for this sample (median age 10 years) were compared to normative data from a younger sample (age 6–9 years), which implies that the number of children with cognitive impairment found in our study may be an underestimation.

Lastly, it should be noted that the normal functioning reported in this study was found in a sample consisting of children who survived beyond age 6. There is a possibility that the cases with worse outcomes died before age 6 years; thus, their data are unavailable for this study. The mortality rates of children with neonatal insults in SSA are high due to limited quality care. For instance, in severe NNJ needing exchange transfusion or HIE requiring hypothermia, provision of adequate personnel, monitoring facilities, and finances are limited, unlike in high-income countries where there are available resources and personnel to provide quality care. Therefore, it is likely that most children with mild impairment survived the neonatal insults.

Moreover, the information on the attribution of neonatal insults to cause of death of children admitted to hospital in this setting is difficult due to lack of investigations. The children in this retrospective study were treated in a busy rural district hospital, and the signs for acute bilirubin toxicity were poorly recorded. The study provides evidence on the neurobehavioral patterns of children who have inadequate information at birth but are admitted to hospital and diagnosed with NNJ or HIE. Given that the challenges in medical records are very common in many settings in Low- and Middle-Income countries this question is important to answer as it addresses the day to day reality of the children in this context.

Limitations of the study

These study findings should be interpreted taking several limitations into account. First, most of the children with severe disabilities may have died before they reached the age of 6–12 years, thus this represents a survivor cohort. Given that this study was designed to screen out children with severe disability (they could not be able to carry out tasks during assessment) and only two out of the 107 participants were severely disabled, the prevalence of severe disability in the

sample was 1.9% (0.46–7.32). Data collection on severe disability was discontinued. Second, the motor and communication assessment tools used in this study were screening instruments, which may not have captured important aspects of these outcomes. Third, potential risk factors such as socioeconomic factors, maternal education and maternal mental health, and parenting factors that are likely to affect neurodevelopmental outcomes were not considered in this study. Lastly, due to inconsistencies in clinical documentation of bilirubin levels at admission and Apgar scores, it was not possible to add estimates of the severity of illness in the children we followed up and those whom we were not able to follow-up. During the period when the participants of this study were born (2005 to 2012), most of the births occurred at home and local dispensaries. Therefore, most of the children were either referred to the hospital from the dispensaries or were brought to the hospital when the caregivers noted signs of sickness in their child. Thus, it was impossible to obtain Apgar scores (generally captured at the first 1, 5, and 10 minutes of life) or cord gases for most of the children. For this reason, we are unable to indicate the degree of HIE in this sample. Moreover, there are difficulties in obtaining the gestational age of the neonates.

Conclusion

Based on the screening tools used, survivors of HIE and NNJ in Kilifi, Kenya, do not experience challenges in motor and communication functioning. Additionally, their nutritional status was normal. However, a substantial proportion of them are likely to have impaired cognition compared to the normative sample. Survivors of severe NNJ and HIE without any co-occurring conditions had the worst intellectual and active epilepsy outcomes. It is likely that the children who were followed up had mild impairment while those with severe outcomes did not survive. Future research will attempt to investigate these issues using more comprehensive assessment to estimate the existence of mild to moderate impairments.

Ethical statement

Ethical approval for this study was granted by the Kenya Medical Research Institute Scientific and Ethics Review Unit (SERU); protocol number KEMRI/SERU/CGMR-C/092/3470. The primary caregivers of the children were informed about the study and their written informed consent for them and their children to take part in the study was obtained. Assent was also obtained from the children who took part in the study. Additional permission was obtained from the Kilifi County Office, and the Kilifi County Director of Education as most of the participants were school going children. Confidentiality and anonymity were maintained in all stages of data management and analysis.

Data availability

Underlying data

Harvard Dataverse: Replication Data for: Patterns of neurobehavioral functioning in school-aged survivors of neonatal jaundice and hypoxic-ischemic encephalopathy in Kilifi, Kenya: A cross-sectional study. <https://doi.org/10.7910/DVN/POTZRQ>⁴⁶

This project contains the following underlying data:

- ndd_nemo_cogn_impair_ravens_ae_20190503.tab (Data used in calculating the prevalence of Cognitive and epilepsy outcome in Neonatal Jaundice (NNJ) and Hypoxic Ischemic Encephalopathy (HIE) cases versus normative group)
- NEMO analysis do file.do (STATA v15.1 analysis script)
- NEMO_Phase1_Data Readme File.txt (Readme file containing information on the related research study, terms of access, citation requirements as well as methods of processing)
- NEMO_screening_dataset_codebook_english.pdf (Variable codebook containing description, value labels and format - English Version)
- NEMO_screening_dataset_Codebook_Swahili.pdf (Variable codebook containing description, value labels and format - Swahili)
- NEMO_screening_data_subset.tab (Data collected from the participants who survived neonatal insults)
- Prevalence-nemo.do (Stata script used to calculate prevalence)
- prevalence_nemo_data_20190520.tab (Dataset used to calculate prevalence)

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

Acknowledgements

We thank the children and their primary caregivers who took part in this study. Special appreciation to the fieldworker Javan Nyale who visited the children in their homesteads and recruited them in this study; and Samuel Mwasambu and Patricia Mwangunya who assessed the children. We acknowledge permission from the Director of Kenya Medical Research Institute (KEMRI) to publish this work.

Supplementary Table 1. Clinical Diagnosis and TSB Levels of Participants.

Clinical Diagnosis	TSB Levels
Neonatal Jaundice	268
Neonatal Jaundice	442
Neonatal Jaundice	369
Neonatal Jaundice	276
Neonatal Jaundice	290
Neonatal Jaundice	315
Neonatal Jaundice	327
Neonatal Jaundice	492
Neonatal Jaundice	270
Neonatal Jaundice	341
Neonatal Jaundice	341
Neonatal Jaundice	481
Neonatal Jaundice	512
Neonatal Jaundice	390
Neonatal Jaundice	338

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Lakshmi Nagarajan

Perth Children's Hospital, Nedlands, WA, Australia

This study examined patterns of functioning in school aged children who survived neonatal jaundice and HIE in Kenya.

Interesting features reported:

- None of the participants had both NNJ and HIE: were they classified under whichever condition was more severe?
- Were they able to collect any data regarding neonatal seizures and neonatal status epilepticus, especially in the HIE cohort.
- There were less than expected numbers of preterm infants admitted.
- The assessments were only possible / done on 107 (of 658) participants aged 6-12 years of age who had survived and still lived in the catchment area.
- Was a cause of death able to be identified in those who died after discharge or even in those who died in hospital?
- The results of the assessments are exceptionally good: Only 10—12% had cognitive impairment, < 5% had problems in communication, 2.5% had epilepsy prevalence.
- Outcomes in survivors seem much better than expected.
- Was a neurological examination documented at or near discharge?
- Mortality in hospital for HIE quite high.
- The discussion must address the interesting features outlined and the question of why the outcomes are so much better than in MIC and HIC and better than expected in LIC as well.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

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

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neonatal neurology, Epilepsy, Child neurology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 21 November 2024

<https://doi.org/10.21956/wellcomeopenres.21902.r110974>

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Alan Horn 

University of Cape Town, Rondebosch, Western Cape, South Africa

Shakti Pillay 

Groote Schuur Hospital, Cape Town, South Africa

COMBINED REPORT from Prof Alan Horn and Dr Shakti Pillay

Thank you for the opportunity to review this ambitious research.

This study evaluates the neurobehavioral outcomes of school-aged survivors of neonatal jaundice (NNJ) and hypoxic-ischaemic encephalopathy (HIE) in Kilifi, Kenya, using a cross-sectional design. While the research addresses highly relevant and underexplored topics in a resource-limited, high-

burden setting, the study is fundamentally undermined by significant methodological, conceptual, and analytical flaws which prevent it from being published in its current form and as a single paper. The authors' research questions contain within them, other important research questions, which could be reframed into two separate papers, namely, i) to determine the school-age outcomes of severe neonatal jaundice (SNJ); and ii) to determine the school-age outcomes of HIE, according to grade at presentation. Additionally, the methods of participant identification and follow up may be a useful basis for further studies.

SUMMARY OF CORE SHORTCOMINGS

The diagnostic criteria for NNJ and HIE are inadequately defined and fail to align with internationally recognised standards. Critical neonatal variables, such as gestational age, severity stratification, and standardised treatment protocols for both conditions, are notably absent. Furthermore, the inclusion of preterm babies in the HIE cohort introduces substantial misclassification bias, as prematurity-related neurological impairments differ from those caused by hypoxic-ischaemic injury. The decision to combine NNJ and HIE—two distinct conditions with divergent aetiologies and long-term consequences—into a single analysis further obscures meaningful interpretation, especially considering no baby had both pathologies. The study is also weakened by survivor bias, reliance on inadequate neurodevelopmental assessments, and underpowered subgroup analyses, all of which severely compromise the validity and generalisability of the findings.

DETAILED REVIEW

Methodological Flaws

1. Diagnostic Criteria: Neonatal Jaundice (NNJ) and Hypoxic-Ischaemic Encephalopathy (HIE)

a. Inflated NNJ Prevalence:

The threshold for diagnosing NNJ (total serum bilirubin (TSB) > 85 $\mu\text{mol/L}$) is significantly lower than international standards, which overestimates the prevalence of NNJ and includes cases unlikely to have clinical significance. This could explain the high proportion of survivors with normal motor and communication outcomes.

b. Inadequate Definition of Severe Neonatal Jaundice (SNJ):

SNJ is not adequately defined. Internationally, SNJ is typically defined by exchange transfusion thresholds (TSB \geq 428 $\mu\text{mol/L}$) or bilirubin encephalopathy. Only one of the 21 studies in the systematic review by [Slusher, et al. \(2017¹\)](#) (BMJ Paediatrics Open 2017;1:e000105) defined SNJ at the level similar to that suggested by the authors (TSB \geq 256 $\mu\text{mol/L}$), a level not associated with poor outcome. In addition, the low threshold of 250 $\mu\text{mol/L}$ for severe hyperbilirubinemia lacks the necessary contextual details, such as day of life and gestational maturity, which must be considered when interpreting TSB levels to determine clinical significance ([Wu et al., \(2015²\)](#) JAMA Pediatr. 2015;169(3):239-246). Standardised guidelines, such as those from the American Academy of Pediatrics (AAP), use age-specific thresholds for clinical interventions. This deviation from internationally accepted guidelines undermines the clinical relevance of the findings.

c. Underreporting of Severe Cases:

Limited clinical documentation of TSB levels at critical time points (e.g., hours after birth) may have resulted in underreporting of true severe hyperbilirubinaemia, affecting the study's relevance for understanding kernicterus and other severe outcomes.

d. Global Comparability Issues:

The study does not contextualise the local incidence of SNJ in Kilifi against international standards. The low TSB thresholds used in this study invalidate comparisons with other studies, which apply higher thresholds based on international guidelines.

e. Inadequate Definition of HIE: The study diagnoses HIE solely on clinical parameters (e.g., convulsions, poor motor tone). It should include standardised grading or severity systems such as Sarnat staging and/or amplitude-integrated EEG (aEEG). It should also include objective measures of acute peripartum hypoxia e.g., Apgar scores and cord blood gases. The lack of these details reduces diagnostic accuracy and reproducibility. The definition of HIE should be in line with published norms. [Molloy EJ, *et al.*, (2018³) *Pediatr Res.* 84(5), 574 (2018); Workineh Y, *et al.*, (2020⁴) *Heliyon.* 6(4), e03793; 10.1016/j.heliyon.2020.e03793 (2020); Horn AR, *et al.*, (2013⁵) *J Perinat Med.* 41(2), 211–7 (2013)] The authors should contextualise the local incidence of HIE in Kilifi against this standardised definition to provide global relevance and comparability.

f. Misclassification bias in HIE cohort: The inclusion of preterm babies in the HIE cohort introduces heterogeneity, since neurological impairments in premature babies often arise from conditions unrelated to hypoxic-ischaemic injury. This complicates the interpretation of neurodevelopmental outcomes.

g. Inadequate Terminology: The term “patterns of functioning” is overly broad and lacks specificity. The term “neurological impairment” is more precise and conveys greater clinical relevance (Abuga JA *et al.*, (2022⁶) *PLOS Glob Public Health* 2(2): e0000151). Using precise terminology would improve the clarity and impact of the findings.

h. No Discussion on use of Therapeutic Hypothermia for HIE: The study does not indicate if therapeutic hypothermia (cooling) was used, which is important to contextualise the findings.

2. Unclear Rationale for Combining HIE and NNJ

a. The study combines NNJ and HIE outcomes into a single analysis, despite participants not having both conditions. NNJ and HIE have divergent aetiologies, mechanisms, and long-term consequences. Combining these cohorts dilutes the specificity of the analysis and hinders meaningful interpretation.

b. The data should be presented as two separate papers - one focusing on NNJ and the other on HIE. This approach would allow for greater clarity and more targeted insights.

3. Data Collection: Missing Neonatal and Perinatal Data

a. Missing Essential Perinatal and Neonatal Variables: Critical data (as reported in the reference outcome study (Abuga JA *et al.*, (2022⁶) *PLOS Glob Public Health* 2(2): e0000151)

such as gestational age, birth weight, Apgar scores, and the presence of neonatal complications (e.g., sepsis, growth restriction) are missing. These variables are essential for stratifying severity and understanding aetiologies. The study's focus on NNJ survivors treated with phototherapy should include an analysis of other factors, such as gestational age and neonatal morbidities, to adjust for confounders.

b. Lack of Treatment Protocols: The study fails to provide detailed descriptions of treatment protocols for NNJ and HIE at Kilifi County Hospital. Was intensive phototherapy, exchange transfusion (ET), or ventilatory support available? How were seizures identified and treated? The absence of this information hinders interpretation of findings in the context of local clinical practices and limits the study's relevance.

c. Adverse Events Between Discharge and Assessment: Adverse events occurring after discharge (e.g., sepsis, collapse, trauma) that could significantly affect neurological outcomes are not documented. These events should be captured and analysed to provide a more comprehensive understanding of their impact on long-term neurodevelopmental outcomes.

4. Survivor and Selection Bias

a. Survivor Bias: The study examines a "survivor cohort," excluding children with severe disabilities and those who died. This introduces survivor bias, underestimating the true burden of NNJ and HIE on neurodevelopmental outcomes.

b. Missing Mortality Data: Despite a reported 31% mortality rate in HIE cases, mortality outcomes are not analysed, leaving a significant gap in the understanding of disease burden.

c. Loss-to-Follow Up: High attrition rates due to migration or unknown survival status compromise the study's generalisability.

5. Inadequate Neurodevelopmental Assessments

a. Use of Screening Tools: The study includes some screening tools which have not been validated as diagnostic assessments in the context limiting the detection of subtle impairments – the assessments should align closely with existing normative data (see 7a below)

b. Missing Domains: Critical domains such as behavioural and emotional functioning, which are often affected in survivors of NNJ and HIE, are not evaluated.

c. Normative Data Issues: Cognitive outcomes are compared to younger normative data (6–9 years), despite the study cohort's older age range (6–12 years). This mismatch introduces bias and likely underestimates deficits.

6. Statistical and Contextual Limitations

a. Underpowered Subgroup Analyses: Subgroup analyses (e.g., for severe NNJ and isolated HIE) are underpowered, with small sample sizes and wide confidence intervals

rendering conclusions unreliable.

b. Lack of Socioeconomic Context: Key contextual factors, such as maternal education, socioeconomic status, and healthcare access, are not analysed, even though they are well-established determinants of neurodevelopmental outcomes.

c. Ambiguous Terminology: The results use vague descriptors like “a bit of a problem” and “a big problem.” Severity should be categorised using standardised classifications (e.g., mild, moderate, severe) to ensure clarity and comparability.

Results

a. Normative Data Reference Issues: The authors state that cognitive and epilepsy outcomes were compared to normative data obtained from a study conducted in 2016 (Reference 45). However, Reference 45 could not be found by the reviewers. It is assumed that the intended reference was (Abuga JA *et al.*,(2022⁶), PLOS Glob Public Health 2(2): e0000151. If so, the reference should be corrected please, and it should be noted that the data were collected in 2015, not 2016. Additionally, (Abuga JA *et al.*,(2022⁶), reported motor, hearing, and vision outcomes, which should also be included in the study's comparisons to provide a more comprehensive analysis.

b. Missing Normative Data from the 2015 Cohort: The tables do not include normative data from the 2015 cohort, which limits the ability to contextualise and interpret the outcomes. Outcomes should be compared to this cohort to enhance the robustness of the analysis and improve the study's relevance.

Typographical Issues

a. The last sentence of the "Participants and Procedures" paragraph lacks a full stop. Similarly, the last sentence of the "Diagnosis" paragraph also lacks a full stop.

b. Inconsistent Spelling Conventions: The manuscript alternates between UK and US English spellings (e.g., "labour" vs. "neurocognitive outcomes" and "hypoxic-ischemic" vs. "paediatricians").

c. Spelling error: “**peripherical**” acoustic function. Correction: Replace with “**peripheral**”.

d. Spelling error: “**coleguaes**” (in “Zhang and coleguaes report”). Correction: Replace with “**colleagues**”.

e. Spelling error: Prevalence-nemo.do (Stata script used to “**calcuarte**”). Correction: Replace with “**calculate**”.

CONCLUSION

While the research question is relevant, these critical shortcomings prevent the manuscript from making a meaningful or actionable contribution to the field. We therefore recommend rejection, as the study requires a comprehensive methodological and analytical redesign to meet the standards of rigor and impact necessary for publication.

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Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

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

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 25 October 2024

<https://doi.org/10.21956/wellcomeopenres.21902.r107546>

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Raj Prakash

Maternal and Child Health , Institute of Health Research, University of Bedfordshire, Luton, England, UK

Thank you very much. The study is a promising attempt to look into the complexities of management of neonatal population in LMCI setting with low resources.

- This study was done in 2017, and it is almost 7 years since then. Is there any specific reason for this delay in indexing. Because the relevance will change as this is a very dynamic area and even in LMICs the NICUs and neonatal care are improving.
- The major limitation of this study is the population sample. For example, we will not consider a term baby with TSB 100 on day 2 as having jaundice and we will not start phototherapy (based on NICE chart UK). Similarly, baby with TSB level 300 on day 4 need not require phototherapy. The study considers NNJ > 85 at admission. My doubt is whether all these babies are normal babies without actual jaundice. Did the authors used any standard definition of NNJ, e.g.: WHO /NICE/NICDH or National guideline.

Same with HIE- HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone.

This could be due to meningitis, sepsis, neonatal seizure due to any cause including metabolic problems.

I understand the difficulty of recording APGARs etc. in the low resource settings. Authors did not use any standard definition of perinatal asphyxia/ HIE e.g.: WHO/ national guideline.

- Is there any explanation that survivors of HIE without any co-occurring conditions had worse intellectual and active epilepsy outcomes compared to the normative group?

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

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

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neonatal Medicine

I confirm that I have read this submission and 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.

Reviewer Report 25 September 2024

<https://doi.org/10.21956/wellcomeopenres.21902.r94602>

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Brigitte Vollmer

University of Southampton, Southampton, England, UK

The authors present descriptive data from a cross-sectional study, examining school-age outcomes of survivors of neonatal HIE and neonatal jaundice from a cohort sub-Saharan Africa (Kilifi, Kenya). This is an interesting dataset, but I have several concerns about this manuscript and would be grateful if the authors could clarify the following questions:

It is surprising that none of the HIE survivors has developed cerebral palsy. I am wondering whether children who developed CP were excluded, or whether, in fact, none of the children had moderate-severe HIE and only case with mild HIE were in this sample? The authors mention in the methods that "HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone". If this was the case it will be possible to classify into mild, moderate, severe HIE, perhaps using the modified Sarnat score. This would provide a better idea of the sample characteristics and all more accurate interpretation of the somewhat surprising findings in the HIE sample.

The authors used the GMFCS as a measure of gross motor function. It will be important to add a sentence to say that this is a measure that is ONLY validated for CP and should only be used in children who have a diagnosis of CP (although it has been used by other authors in the same way as in this study, but this is, strictly speaking, not correct). The reference given for the GMFCS is incorrect, it refers to the GMFM, which is a different measure. It is also important to note that the good consistency of the GMFCS described in ref 35, applies to CP and here mainly to more severe CP, i.e. the higher GMFCS levels.

In the discussion, I think the authors need to carefully review and revise the section where they put their findings in context with the literature. For example, as far as I can see, the interpretation of the Hayes paper is not entirely correct.

It would be helpful if the authors could specific what they mean with HIE or NNJ "without co-occurring conditions"

Is there information on the neonatal characteristics of those lost to follow-up and how this may compare to those who were seen in this study?

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

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

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neonatal and developmental neurology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 21 September 2023

<https://doi.org/10.21956/wellcomeopenres.21902.r64802>

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Tina M. Slusher 

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² Hennepin Healthcare, Minneapolis, MN, USA

³ Bowen University Teaching Hospital, Ogbomosho, Nigeria

This version is significantly improved from the previous version and answers my questions.

Most children with KSD followed by experts like Dr. Steven Shapiro have been shown to have normal intelligence. It is of course very hard to test intelligence in children with KSD as these children are basically "trapped in a body that does not work" but have and are expected to have normal intelligence. If the authors would add that there is controversy and some experts in the field disagree with your conclusion about lowered intellectual function, this would be a valuable addition.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My primary area of research is severe neonatal jaundice, its preventions, diagnosis, treatment and follow-up. I also have interest in breast feeding in LMICs and bubble CPAP/respiratory support beyond the neonate.

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

Version 2

Reviewer Report 21 May 2020

<https://doi.org/10.21956/wellcomeopenres.17282.r38105>

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Deirdre Murray 

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The manuscript is improved as more detail regarding the diagnosis of hyperbilirubinaemia is included. However the main issue is unresolved. The authors are focusing on two very separate neonatal conditions (Hyperbilirubinaemia and HIE) but ignoring others (sepsis, IUGR, preterm birth). I think this paper should either be a detailed follow up of all jaundiced neonates (including those with severe outcome) or a detailed follow up of HIE. At present it is not answering either question well and the co-existing factors are confusing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Perinatal brain injury, hypoxic ischaemic encephalopathy, neurodevelopment outcome.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for

reasons outlined above.

Author Response 03 Aug 2023

Dorcas Magai

Dear Deirdre Murray, We thank you for your comments and feedback to improve our manuscript. Below, you will find our responses addressing the comments and suggestions, and we hope that with these revisions, we have sufficiently addressed the concerns. Thank you.

1. The manuscript is improved as more detail regarding the diagnosis of hyperbilirubinaemia is included. However, the main issue is unresolved. The authors are focusing on two very separate neonatal conditions (Hyperbilirubinaemia and HIE) but ignoring others (sepsis, IUGR, preterm birth). I think this paper should either be a detailed follow up of all jaundiced neonates (including those with severe outcome) or a detailed follow up of HIE. At present it is not answering either question well and the co-existing factors are confusing.

We have given a detailed description of other co-existing neonatal conditions under participants and procedures as follows:

None of the participants in this study had a diagnosis of both NNJ and HIE. Some of the participants had sepsis and preterm birth as a secondary diagnosis. For NNJ, 23 had neonatal sepsis, and 6 were preterm, and for HIE, 5 had sepsis, and 2 were preterm. However, based on another study that we conducted, sepsis did not appear to aggravate the developmental outcomes of children with neonatal jaundice and sepsis [4].

Additionally, we have conducted a sub-analysis with NNJ and HIE participants who did not have any co-existing neonatal conditions and the results provided as follows:

We conducted a sub-analysis with 15 survivors of NNJ whose TSB levels were measured at admission and was ≥ 250 $\mu\text{mol/l}$ and did not have any co-occurring neonatal conditions and 34 survivors of HIE without any co-occurring neonatal conditions and compared them to the normative group. The prevalence of cognitive impairment in the sub-group of survivors of NNJ was 13.3% (95% CI = 1.7 - 40.5), and HIE 5.9% (95% CI = 0.7 - 19.7) compared to a prevalence of 0.5% (95% CI = 0.3 - 0.6) per 100 in the normative group (Table 5). The prevalence of active epilepsy in survivors of NNJ was 6.7% (CI = 0.7 - 31.9) and HIE 2.9% (CI = 0.1 - 15.3) versus the normative group 0.5% (CI = 0.4 - 0.6).

References

1. Bhutani, V.K. and L. Johnson, *Kernicterus in the 21st century: frequently asked questions*. J Perinatol, 2009. 29 Suppl 1: p. S20-4.
2. Smitherman, H., A.R. Stark, and V.K. Bhutani, *Early recognition of neonatal hyperbilirubinemia and its emergent management*. Semin Fetal Neonatal Med, 2006. 11(3): p. 214-24.

3. Varughese, P.M., *Kramer's scale or transcutaneous bilirubinometry: the ideal choice of a pediatrician? can we trust our eyes?* 2019.

4. Magai, D.N., et al., *Neonatal jaundice and developmental impairment among infants in Kilifi, Kenya.* *Child Care Health Dev*, 2020. 46(3): p. 336-344.


Competing Interests: No competing interests were disclosed.

Reviewer Report 31 March 2020

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Bolajoko O. Olusanya 

¹ Centre for Healthy Start Initiative (HSI-Centre), Lagos, Nigeria

² Centre for Healthy Start Initiative (HSI-Centre), Lagos, Nigeria

The authors have not addressed my earlier concerns regarding the selection criteria of these school-aged children and the essential details of their neonatal profile. This retrospective study thus remains fundamentally flawed without adequate information on the TSB levels of each participant on admission. Simply reporting the average TSB level for all the cases is not helpful, more so as the stated value (TSB <15mg/dL) expectedly does not indicate any significant risk of bilirubin-induced neurologic dysfunctions in well-babies based on the extensive evidence in the literature.

The authors may wish to consider the following options:

1. Report the current data among these school-aged children without any linkage to the limited neonatal information of the participants.

2. Undertake a future study that prospectively recruits neonates with various degrees of hyperbilirubinaemia and determine outcomes at school-age based on the severity of hyperbilirubinaemia. This will allow for a more objective analysis among children with mild to moderate jaundice (typically TSB <20mg/dL) compared to those with severe jaundice (typically TSB ≥20mg/dL).

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neonatal jaundice, Newborn hearing screening, School hearing screening, Developmental disabilities, Childhood hearing loss, Clinical epidemiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 03 Aug 2023

Dorcas Magai

Dear Bolajoko O Olusanya, We thank you for your insightful comments and feedback to improve our manuscript. We have addressed the comments and suggestions as highlighted below. With these revisions, we hope to have sufficiently addressed the concerns. Thank you.

1. A) The authors have not addressed my earlier concerns regarding the selection criteria of these school-aged children and the essential details of their neonatal profile.

We have included the selection criteria as follows:

Participants were recruited in the study if they had a diagnosis of neonatal jaundice (NNJ) or hypoxic-ischaemic encephalopathy (HIE) during the first 28 days of life; were aged between 6 to 12 years at the time of follow-up; parental consent was obtained; and they were living within the area covered by the Kilifi Health Demographic Surveillance System (KHDSS). Participants were excluded if they did not consent to the study.

1. This retrospective study thus remains fundamentally flawed without adequate information on the TSB levels of each participant on admission.

We have provided a list of bilirubin levels measured at admission for the participants included in the sub-analysis (see supplementary table). We would also like to point out that in addition to the bilirubin levels measured at admission, other participants had a clinical diagnosis.

**Supplementary Table: Clinical Diagnosis and TSB Levels of Participants
Clinical Diagnosis TSB Levels**

**Neonatal Jaundice 268
Neonatal Jaundice 442
Neonatal Jaundice 369
Neonatal Jaundice 276
Neonatal Jaundice 290
Neonatal Jaundice 315
Neonatal Jaundice 327
Neonatal Jaundice 492
Neonatal Jaundice 270
Neonatal Jaundice 341
Neonatal Jaundice 341
Neonatal Jaundice 481
Neonatal Jaundice 512
Neonatal Jaundice 390
Neonatal Jaundice 338**

1. Simply reporting the average TSB level for all the cases is not helpful, more so as the

stated value (TSB <15mg/dL) expectedly does not indicate any significant risk of bilirubin-induced neurologic dysfunctions in well-babies based on the extensive evidence in the literature.

There is considerable debate about the criteria for a safe level of bilirubin in sick neonates[1-3]. Moreover, this is a pragmatic study conducted in Kenya- one of the sub-Saharan African countries- where the risk of bilirubin is not well known on the long-term outcomes of survivors. Therefore, the study provides information on long-term outcomes, including cognition and communication, since there are few studies of children surviving these insults in SSA.

We conducted a sub-analysis of survivors of NNJ with TSB \geq 250 μ mol/l who did not have any co-occurring neonatal conditions, and the results provided as follows:

We conducted a sub-analysis with 15 survivors of NNJ whose TSB levels were measured at admission and was \geq 250 μ mol/l and did not have any co-occurring neonatal conditions and 34 survivors of HIE without any co-occurring neonatal conditions and compared them to the normative group. The prevalence of cognitive impairment in the sub-group of survivors of NNJ was 13.3% (95% CI = 1.7 - 40.5), and HIE 5.9% (95% CI = 0.7 - 19.7) compared to a prevalence of 0.5% (95% CI = 0.3 - 0.6) per 100 in the normative group (Table 5). The prevalence of active epilepsy in survivors of NNJ was 6.7% (CI = 0.7 - 31.9) per 100 and HIE 2.9% (CI = 0.1 - 15.3) per 100 versus the normative group 0.5% (CI = 0.4 - 0.6) per 100.

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1. Bhutani, V.K. and L. Johnson, *Kernicterus in the 21st century: frequently asked questions*. J Perinatol, 2009. 29 Suppl 1: p. S20-4.
2. Smitherman, H., A.R. Stark, and V.K. Bhutani, *Early recognition of neonatal hyperbilirubinemia and its emergent management*. Semin Fetal Neonatal Med, 2006. 11(3): p. 214-24.
3. Varughese, P.M., *Kramer's scale or transcutaneous bilirubinometry: the ideal choice of a pediatrician? can we trust our eyes?* 2019.

Competing Interests: No competing interests were disclosed.

Reviewer Response 05 Sep 2023

Bolajoko O Olusanya

I decline further review because of potential conflict of interest.

Competing Interests: I now have an ongoing collaboration with two of the authors of this manuscript which may be construed as a potential conflict of interest.

Reviewer Report 27 March 2020

<https://doi.org/10.21956/wellcomeopenres.17282.r38106>

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Tina M. Slusher 

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This version is much improved over the previous version I reviewed however one critical piece is still missing. To be a valid indicator of the neurodevelopmental outcome of these children we must have the actual full range of bilirubin levels and even more importantly, what were the bilirubin levels of the children who had delays or problems in any of the areas tested. 144 $\mu\text{mols/l}$ is simply not high enough to cause problems in any neonate except the extremely premature and 25% of the bilirubin levels were even lower than 144. Lower bilirubin levels are actually felt to be potentially beneficial to neonates. Researchers at my institution are actually studying that and trying to determine what bilirubin levels are actually problematic in premature neonates.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My primary area of research is severe neonatal jaundice, its preventions, diagnosis, treatment and follow-up. I also have interest in breast feeding in LMICs and bubble CPAP/respiratory support beyond the neonate.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 03 Aug 2023

Dorcas Magai

Dear Tina M Slusher, We thank you for your comments and feedback to improve our manuscript. Below, you will find our responses addressing the comments and suggestions, and we hope that with these revisions, we have sufficiently addressed the concerns. Thank you.

1. This version is much improved over the previous version I reviewed however one critical piece is still missing.

To be a valid indicator of the neurodevelopmental outcome of these children we must have the actual full range of bilirubin levels

We have now included this information. See supplementary table 1 below:

Supplementary Table: Clinical Diagnosis and TSB Levels of Participants

Clinical Diagnosis TSB Levels

Neonatal Jaundice 268

Neonatal Jaundice 442

Neonatal Jaundice 369

Neonatal Jaundice 276

Neonatal Jaundice 290

Neonatal Jaundice 315

Neonatal Jaundice 327

Neonatal Jaundice 492

Neonatal Jaundice 270

Neonatal Jaundice 341

Neonatal Jaundice 341

Neonatal Jaundice 481

Neonatal Jaundice 512

Neonatal Jaundice 390

Neonatal Jaundice 338

1. and even more importantly, what were the bilirubin levels of the children who had delays or problems in any of the areas tested.

We have published the clinical characteristics of participants who had cognitive impairment and active epilepsy, and the results presented as follows: The mean WAZ was -1.9 (SD = 2.0) and -2.0 (SD = 2.1), while the mean HAZ was -2.2 (SD = 1.0) and -0.6 (SD = 2.9) for the survivors of NNJ and HIE who had cognitive impairment and active epilepsy, respectively. The median TSB levels for NNJ participants with cognitive and epilepsy problems was 416 [IQR= 227-607]. Of the participants who had cognitive and epilepsy problems, one survivor of NNJ and two survivors of HIE had sepsis, while one survivor of NNJ was preterm, as shown in Table 4.

1. 144 $\mu\text{mol}/\text{l}$ is simply not high enough to cause problems in any neonate except the extremely premature and 25% of the bilirubin levels were even lower than 144. Lower bilirubin levels are actually felt to be potentially beneficial to neonates. Researchers at my institution are actually studying that and trying to determine what bilirubin levels are actually problematic in premature neonates.

There is considerable debate about the criteria for a safe level of bilirubin in sick neonates [1]

Moreover, this is a pragmatic study conducted in Kenya- one of the sub-Saharan African countries- where the risk of bilirubin is not well known on the long-term outcomes of survivors. Therefore, the study provides information on long-term outcomes, including cognition and communication, since there are few studies in children surviving these insults in SSA.

We conducted a sub-analysis of survivors of NNJ with TSB $\geq 250 \mu\text{mol}/\text{l}$ and did not have any co-occurring neonatal conditions and the results provided as follows:

We conducted a sub-analysis with 15 survivors of NNJ whose TSB levels were measured at

admission and was ≥ 250 $\mu\text{mol}/\text{l}$ and did not have any co-occurring neonatal conditions and 34 survivors of HIE without any co-occurring neonatal conditions and compared them to the normative group. The prevalence of cognitive impairment in the sub-group of survivors of NNJ was 13.3% (95% CI = 1.7 – 40.5), and HIE 5.9% (95% CI = 0.7 – 19.7) per 100 compared to a prevalence of 0.5% (95% CI = 0.3 – 0.6) in the normative group (Table 5). The prevalence of active epilepsy in survivors of NNJ was 6.7% (CI = 0.7 – 31.9) and HIE 2.9% (CI = 0.1 – 15.3) versus the normative group 0.5% (CI = 0.4 – 0.6) per 100.

References

1. Bhutani, V.K. and L. Johnson, *Kernicterus in the 21st century: frequently asked questions*. J Perinatol, 2009. 29 Suppl 1: p. S20-4.
2. Smitherman, H., A.R. Stark, and V.K. Bhutani, *Early recognition of neonatal hyperbilirubinemia and its emergent management*. Semin Fetal Neonatal Med, 2006. 11(3): p. 214-24.
3. Varughese, P.M., *Kramer's scale or transcutaneous bilirubinometry: the ideal choice of a pediatrician? can we trust our eyes?* 2019.
4. Magai, D.N., et al., *Neonatal jaundice and developmental impairment among infants in Kilifi, Kenya*. Child Care Health Dev, 2020. 46(3): p. 336-344.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 12 August 2019

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Jean-Baptiste Le Pichon 

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⁹ Bowen University Teaching Hospital, Ogbomosho, Nigeria

In this cross-sectional retrospective study, the authors set out to investigate the neurodevelopmental outcome of infants born with neonatal jaundice and hypoxic ischemic encephalopathy in low-resource setting and for that the authors are to be commended. This information is urgently needed if we are to get the appropriate resources, infra-structure and governmental support to eliminate or at least significantly decrease these diseases and the long-term consequences for children who survive these insults as neonates. This article is especially noteworthy in that the study team includes experts in neurodevelopment from the Kenya Medical Research Institute (KEMRI).

However, there are several significant issues with the study that significantly impact the interpretation of the results. First, it is unclear how the authors define neonatal jaundice and hypoxic ischemic encephalopathy. Notably, a serum bilirubin of 85 micromoles/liter would not be expected to cause any problems except perhaps for the extremely low-birth weight infants. Even 250 micromoles/liter would rarely be expected to cause motor or developmental problems. Furthermore, the complete absence of any children with deafness along with the lack of other markers of severe neonatal jaundice such as the need for exchange transfusion or even phototherapy make it unlikely that the population included in this study were at risk for neurodevelopmental delay from neonatal jaundice. The only possible marker of acute bilirubin encephalopathy they recorded is death. While death certainly is a marker of severe neonatal jaundice, it can be the result of multiple other pathological processes. Unfortunately, the authors do not clarify whether the death was related to jaundice or not, leaving this uncertainty open to interpretation. It follows that the lack of markers for acute bilirubin encephalopathy confounds any possible relationship between the observed (or lack thereof) neurodevelopmental problems and hyperbilirubinemia. In fact, low levels of bilirubin (as reported in this study) have been postulated to be neuroprotective not harmful. The study would have been much more meaningful had the authors looked at children who had had suffered from truly severe neonatal hyperbilirubinemia and/or acute bilirubin encephalopathy.

Diagnosis of hypoxic ischemic encephalopathy by “clinical diagnosis” at discharge is also too non-specific to have any idea of the group of neonates being discussed. The authors give no indication of the degree of hypoxic ischemic encephalopathy and thus, as with neonatal jaundice, the interpretation of a possible causal relationship with neurodevelopmental delay in school age children remains uninterpretable. In addition, the authors do not clarify the training of the clinicians making the diagnosis of HIE or how this diagnosis was validated, further complicating any possible meaningful interpretation of the observed results.

There is no comment regarding neonates who had both neonatal jaundice and hypoxic ischemic encephalopathy. Asphyxiated neonates would be expected to higher risk for acute bilirubin encephalopathy and long-term problems, but this group is not addressed by the authors.

Because of the flaws mentioned above, the study as currently presented, does not add sustainably to our understanding of the true magnitude of neurodevelopmental problems from either neonatal jaundice or hypoxic ischemic encephalopathy. The study may be meaningful if the authors add substantial clarification of their patient populations and demonstrate why the selected populations would be expected to potentially have an increased risk of neurodevelopmental problems from either neonatal jaundice or hypoxic encephalopathy.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

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

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My primary area of research is severe neonatal jaundice, its preventions, diagnosis, treatment and follow-up. I also have interest in breast feeding in LMICs and bubble CPAP/respiratory support beyond the neonate.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 27 Feb 2020

Dorcas Magai

Response to Reviewer Comments

Reviewer 1: Tina Slusher

1. Notably, a serum bilirubin of 85 micromoles/litre would not be expected to cause any problems except perhaps for the extremely low-birth weight infants. Even 250 micromoles/litre would rarely be expected to cause motor or developmental problems. Furthermore, the complete absence of any children with deafness along with the lack of

other markers of severe neonatal jaundice such as the need for exchange transfusion or even phototherapy make it unlikely that the population included in this study were at risk for neurodevelopmental delay from neonatal jaundice.

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according to the guidelines used by the clinicians for the final diagnosis. *HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone (WHO, 2013) (See page 5)*

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5. In addition, the authors do not clarify the training of the clinicians making the diagnosis of HIE or how this diagnosis was validated, further complicating any possible meaningful interpretation of the observed results.

- We have amended and provided the required information about the training of the clinicians. *A Medical officer with a bachelor's degree in medicine and surgery made the diagnosis of NNJ and HIE and this was often discussed with consultant pediatricians who had been trained in Kenya or the United Kingdom (page 4).*

6. There is no comment regarding neonates who had both neonatal jaundice and hypoxic ischemic encephalopathy. Asphyxiated neonates would be expected to higher risk for acute bilirubin encephalopathy and long-term problems, but this group is not addressed by the authors.

Because of the flaws mentioned above, the study as currently presented does not add sustainably to our understanding of the true magnitude of neurodevelopmental problems from either neonatal jaundice or hypoxic-ischemic encephalopathy.

- We did not have these cases in this cohort. *None of the participants in this study had a diagnosis of both NNJ and HIE as those with a combined diagnosis were excluded from this cohort study (page 4).*

Reviewer 2: Deirdre Murray

1. The definition of hyperbilirubinaemia is very vague. They seem to have included all infants with a bilirubin level > 85. The authors do not give a time for this, beyond stating that the measurement took place in the first 28 days. The majority of infants have some level of jaundice, and will reach this level

- The bilirubin was measured on admission, since many of the neonates were born at home, it was difficult to determine the exact age in hours. Moreover, the inclusion criteria included neonates up to 30 days of age as per the definition of neonatal period as used in other studies (Newman, Xiong, Gonzales, & Escobar, 2000). However, despite the inclusion criteria of 0- 30 days, the median age of the participants at admission was 3 [interquartile range (IQR) = 0-8] days (page 6-7).

2. They state that they have done a sub analysis in the severe group, but do not tell us the numbers or the results in this group, who are actually the more interesting.

- We have provided the actual numbers of children with hyperbilirubinemia. *A sub-*

analysis was conducted with 25 participants with severe hyperbilirubinemia on all outcomes, and similar results were obtained (page 6).

3. Surprisingly with this low level of hyperbilirubinaemia the outcomes are poor which makes me wonder whether these infants had other underlying diagnoses, such as sepsis, prematurity, IUGR?

- We have addressed this issue in the methods section as follows: *Some of the participants had sepsis and preterm birth as a secondary diagnosis. For NNJ 23 had neonatal sepsis, and 6 were preterm. In the HIE group, 5 had sepsis, and 2 were preterm. However, based on another study that we conducted, sepsis did not appear to aggravate the developmental outcomes of children with neonatal jaundice and sepsis (Magai et al., 2020) (page 5).*

4. The follow up rate was low. they state that 347 survivors were identified and 121 were followed up. Please explain why the other 227 were not followed?

- This explanation is given under limitations in the discussion section as follows: *Given that this study was designed to screen out children with severe disability (they could not be able to carry out tasks during assessment) and only two out of the 107 participants were severely disabled, the prevalence of severe disability in the sample was 1.9% (0.46 -7.32). Data collection on children with severe disability was discontinued (page 10) as we had reached the needed sample size to determine the severity of disability in these children.*

5. They have stated in their discussion the other major limitation: the fact that it is likely that a high proportion of children; those with moderate or severe HIE are likely to have died. If the authors could focus on this as a study of outcome following HIE, reporting mortality and survival, with outcome to 10 years then this would be a very valuable article and would add significantly to the literature.

- Plans to study the mortality and survival of NNJ and HIE are underway in future studies. However, in this study, our main research question in the current study was to understand the neurobehavioral patterns of survivors of NNJ and HIE.

6. Minor points:

How did the WAZ and HAZ scores compare to the general population? Do they have this data?

- We have addressed this issue as follows: *The WAZ and HAZ scores of these children were compared to the WAZ and HAZ scores for children in the general population obtained in a study conducted in 2003 with 184 children aged 8 to 11 years (page 6). The mean WAZ was -1.3 (SD = 0.9), -1.0 (SD = 1.6), and -1.2 (SD = 1.1) while the mean HAZ was -1.1 (SD = 1.1), -0.8 (SD = 1.5), and -1.3 (SD = 1.1) for NNJ, HIE, and for the general population respectively. There were no significant differences in the WAZ [$F(2, 196) = 0.5, P = 0.623$] and HAZ [$F(2, 285) = 2.6, P = 0.077$] scores between the cases and the general population (Page 7).*

7. The first paragraph of the discussion is repeated twice in the second paragraph.

- We have revised this part and deleted the repetition as needed.

Reviewer 3: Bolajoko O Olusanya

1. The clinical profile of the participants as neonates is quite deficient and does not provide an objective basis for evaluating the risks of neurodevelopmental disorders. For example,

the operational definitions of NNJ used in the study are rarely associated with neurodevelopmental disorders. NNJ is generally benign except in children with or at risk of acute bilirubin encephalopathy (ABE). Since the authors acknowledged inconsistencies in clinical documentation of bilirubin levels at admission (and presumably on discharge also), it would have been useful to identify those who received phototherapy and/or exchange transfusion as proxies for identifying participants with severe NNJ. This is even more crucial in a developing country like Kenya where delays in receiving appropriate care are not uncommon (see Olusanya et al. (2014)¹.

- The purpose of this study was to assess more subtle impairments, such as cognitive impairment and communication since this has not been studied in children surviving these insults in sub-Saharan Africa. Our inclusion of children with TSB>85 µmols/l is based on two facts: First, this is the level at which jaundice is reliably detected in the neonate. It is the definition used by the American Academy of Pediatrics for hyperbilirubinaemia, and other authors (Avery, 2005; Ho, 1992; Kramer, 1969; Porter & Dennis, 2002). Second, there are considerable difficulties in establishing gestational age (Rijken et al., 2011; Taylor et al., 2010) and time of birth and the severity of hypoxic-ischemic encephalopathy of neonates admitted to hospitals serving rural areas in sub-Saharan Africa, where most births occur at home. Moreover, there is considerable debate about the criteria for a safe level of bilirubin in sick neonates (Bhutani & Johnson, 2009; Smitherman et al., 2006; Varughese, 2019). This is one of the few studies to provide data that suggests that few problems develop in neonates who have bilirubin levels between 85 and 250 µmol/l.

- We have amended the document to include the above information. *Phototherapy was considered if there were any visible jaundice anywhere on the body on day one or TSB> 260 µmols/l (WHO, 2013) (page 4).*

2. The study suggests that the clinical diagnosis of HIE was based on Apgar scores. Please clarify and report the criteria for HIE.

- HIE diagnosis was not based on Apgar scores. We have amended this part and included the clinical signs of HIE that were used according to WHO guidelines. *HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone (WHO, 2013) (See page 4).*

3. It is unclear why the authors opted for auditory brainstem response (ABR) in these school-aged children rather than pure-tone audiometry which is a more accurate and common measure of auditory threshold, especially in resource-limited settings. The authors need to provide details of the type of ABR and the methodology employed for hearing screening in their population.

- We have added details on the type of audiometry machine and the methodology employed: *The participants were screened for hearing and visual acuity using a pure-tone audiometry machine-Kamplex model R17A AUD Type 3 (Harlor & Bower, 2009) and the Snellen and E-Chart, respectively. For audiometric testing, first, we talked to the participants while walking towards the sound-proof assessment room to assess how well they are hearing. We then inspected their ear canals using an otoscope. We then instructed the participants to push the button when they hear a sound through the headphones and tested to see if the instructions were clear. We started at 1000 Hz and decreased the level by 10dB until no response was obtained. We then increased the level by 5 Db steps until a reply was captured again. We did these steps until the lowest level at*

which the participant responded was received. We continued with this procedure at 2000 Hz, 4000 Hz, 500 Hz, 250 Hz, and 125 HZ for both ears. Almost all the participants had normal hearing and vision functioning except one who had mild vision problems (page 4-5).

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Competing Interests: No competing interests

Reviewer Report 09 August 2019

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Deirdre Murray 

¹ Department of Paediatrics and Child Health, University College Cork, Cork, Ireland

² Department of Paediatrics and Child Health, University College Cork, Cork, Ireland

³ Department of Paediatrics and Child Health, University College Cork, Cork, Ireland

The authors deserve credit for performing this study in a developing country. Data on outcome following HIE is very sparse in Sub Saharan Africa, so this information would be very important for planning therapeutic trials. However it feels like they are addressing two very different questions in the two conditions studied. My main concerns are as follows:

The definition of hyperbilirubinaemia is very vague. They seem to have included all infants with a bilirubin level > 85. The authors do not give a time for this, beyond stating that the measurement took place in the first 28 days. The majority of infants have some level of jaundice, and will reach this level. They state that they have done a sub analysis in the severe group, but do not tell us the numbers or the results in this group, who are actually the more interesting.

Surprisingly with this low level of hyperbilirubinaemia the outcomes are poor which makes me wonder whether these infants had other underlying diagnoses, such as sepsis, prematurity, IUGR?

Similarly no grades are given for HIE. However this is understandably difficult in a retrospectively study. More detailed neonatal information regarding these infants; Apgar score, severity of encephalopathy would be more informative if available.

The follow up rate was low. they state that 347 survivors were identified and 121 were followed up. Please explain why the other 227 were not followed?

They have stated in their discussion the other major limitation: the fact that it is likely that a high proportion of children; those with moderate or severe HIE are likely to have died. If the authors could focus on this as a study of outcome following HIE, reporting mortality and survival, with outcome to 10 years then this would be a very valuable article and would add significantly to the literature.

Minor points:

How did the WAZ and HAZ scores compare to the general population? Do they have this data?

The first paragraph of the discussion is repeated twice in the second paragraph.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

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No

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Perinatal brain injury, hypoxic ischaemic encephalopathy, neurodevelopment outcome.

I confirm that I have read this submission and 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 27 Feb 2020

Dorcas Magai

Response to Reviewer Comments

Reviewer 1: Tina Slusher

1. Notably, a serum bilirubin of 85 micromoles/litre would not be expected to cause any problems except perhaps for the extremely low-birth weight infants. Even 250 micromoles/litre would rarely be expected to cause motor or developmental problems. Furthermore, the complete absence of any children with deafness along with the lack of other markers of severe neonatal jaundice such as the need for exchange transfusion or even phototherapy make it unlikely that the population included in this study were at risk for neurodevelopmental delay from neonatal jaundice.

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- We have revised this part and deleted the repetition as needed.

Reviewer 3: Bolajoko O Olusanya

- 1.The clinical profile of the participants as neonates is quite deficient and does not provide an objective basis for evaluating the risks of neurodevelopmental disorders. For example, the operational definitions of NNJ used in the study are rarely associated with neurodevelopmental disorders. NNJ is generally benign except in children with or at risk of acute bilirubin encephalopathy (ABE). Since the authors acknowledged inconsistencies in clinical documentation of bilirubin levels at admission (and presumably on discharge also), it would have been useful to identify those who received phototherapy and/or exchange transfusion as proxies for identifying participants with severe NNJ. This is even more crucial in a developing country like Kenya where delays in receiving appropriate care are not uncommon (see Olusanya et al. (2014)1.
- The purpose of this study was to assess more subtle impairments, such as cognitive impairment and communication since this has not been studied in children surviving these insults in sub-Saharan Africa. Our inclusion of children with TSB>85 $\mu\text{mols/l}$ is based on two facts: First, this is the level at which jaundice is reliably detected in the neonate. It is the definition used by the American Academy of Pediatrics for

hyperbilirubinaemia, and other authors (Avery, 2005; Ho, 1992; Kramer, 1969; Porter & Dennis, 2002). Second, there are considerable difficulties in establishing gestational age (Rijken et al., 2011; Taylor et al., 2010) and time of birth and the severity of hypoxic-ischemic encephalopathy of neonates admitted to hospitals serving rural areas in sub-Saharan Africa, where most births occur at home. Moreover, there is considerable debate about the criteria for a safe level of bilirubin in sick neonates (Bhutani & Johnson, 2009; Smitherman et al., 2006; Varughese, 2019). This is one of the few studies to provide data that suggests that few problems develop in neonates who have bilirubin levels between 85 and 250 $\mu\text{mol/l}$.

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- HIE diagnosis was not based on Apgar scores. We have amended this part and included the clinical signs of HIE that were used according to WHO guidelines. *HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone (WHO, 2013) (See page 4).*
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- We have added details on the type of audiometry machine and the methodology employed: *The participants were screened for hearing and visual acuity using a pure-tone audiometry machine-Kamplex model R17A AUD Type 3 (Harlor & Bower, 2009) and the Snellen and E-Chart, respectively. For audiometric testing, first, we talked to the participants while walking towards the sound-proof assessment room to assess how well they are hearing. We then inspected their ear canals using an otoscope. We then instructed the participants to push the button when they hear a sound through the headphones and tested to see if the instructions were clear. We started at 1000 Hz and decreased the level by 10dB until no response was obtained. We then increased the level by 5 Db steps until a reply was captured again. We did these steps until the lowest level at which the participant responded was received. We continued with this procedure at 2000 Hz, 4000 Hz, 500 Hz, 250 Hz, and 125 HZ for both ears. Almost all the participants had normal hearing and vision functioning except one who had mild vision problems (page 4-5).*

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Competing Interests: No competing interests

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Bolajoko O. Olusanya

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This cross-sectional study set out to determine long-term neurodevelopmental disorders associated with survivors of neonatal jaundice (NNJ) and hypoxic-ischemic encephalopathy (HIE) at school age. The Gross Motor Function Classification System (GMFCS), Adapted Communication Profile, Raven's Coloured Progressive Matrices (RCPM) and an epilepsy screening tool were used to assess gross motor function, communication function, intellectual functioning, and epilepsy,

respectively. The participants were also screened for hearing and visual acuity using an undisclosed auditory brainstem response instrument and the Snellen and E-Chart, respectively. The principal findings reported by the authors were that children who survived NNJ and HIE have normal vision, hearing, motor functioning, and communication functioning, but have poorer intellectual functioning compared to the normative sample.

Conceptually, this study was intended to fill a critical gap in available research evidence on the long-term sequelae of NNJ and HIE in sub-Saharan Africa. However, the validity of the study and the reported findings are compromised by the following major methodological drawbacks:

1. The clinical profile of the participants as neonates is quite deficient and does not provide an objective basis for evaluating the risks of neurodevelopmental disorders. For example, the operational definitions of NNJ used in the study are rarely associated with neurodevelopmental disorders. NNJ is generally benign except in children with or at risk of acute bilirubin encephalopathy (ABE). Since the authors acknowledged inconsistencies in clinical documentation of bilirubin levels at admission (and presumably on discharge also), it would have been useful to identify those who received phototherapy and/or exchange transfusion as proxies for identifying participants with severe NNJ. This is even more crucial in a developing country like Kenya where delays in receiving appropriate care are not uncommon (see Olusanya *et al.* (2014)¹).
2. The study suggests that the clinical diagnosis of HIE was based on Apgar scores. Please clarify and report the criteria for HIE.
3. It is unclear why the authors opted for auditory brainstem response (ABR) in these school-aged children rather than pure-tone audiometry which is a more accurate and common measure of auditory threshold especially in resource-limited settings. The authors need to provide details of the type of ABR and the methodology employed for hearing screening in their population.
4. These limitations essentially foreclose any objective comparison of the reported findings in this study and those from the studies cited in the discussion section.

Given the extensive and robust evidence on the long-term neurodevelopmental disorders frequently associated with survivors of NNJ and HIE in the literature, the authors may wish to represent their findings, more plausibly as evidence of a lack of significant neurodevelopmental disorders in children without any verifiable record of severe NNJ with or without ABE requiring phototherapy and/or exchange transfusion. Same for HIE.

References

1. Olusanya BO, Ogunlesi TA, Slusher TM: Why is kernicterus still a major cause of death and disability in low-income and middle-income countries?. *Arch Dis Child*. 2014; **99** (12): 1117-21 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

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

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neonatal jaundice, Newborn hearing screening, School hearing screening, Developmental disabilities, Childhood hearing loss, Clinical epidemiology.

I confirm that I have read this submission and 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 27 Feb 2020

Dorcias Magai

Response to Reviewer Comments

Reviewer 1: Tina Slusher

1. Notably, a serum bilirubin of 85 micromoles/litre would not be expected to cause any problems except perhaps for the extremely low-birth weight infants. Even 250 micromoles/litre would rarely be expected to cause motor or developmental problems. Furthermore, the complete absence of any children with deafness along with the lack of other markers of severe neonatal jaundice such as the need for exchange transfusion or even phototherapy make it unlikely that the population included in this study were at risk for neurodevelopmental delay from neonatal jaundice.

- The purpose of this study was to assess more subtle impairments, such as cognitive impairment and communication since this has not been studied in children surviving these insults in sub-Saharan Africa. Our inclusion of children with TSB>85 μ /mols/l is based on two facts: First, this is the level at which jaundice is reliably detected in the neonate. It is the definition used by the American Academy of Pediatrics for hyperbilirubinaemia, and other authors (Avery, 2005; Ho, 1992; Kramer, 1969; Porter & Dennis, 2002). Second, there are considerable difficulties in establishing gestational age (Rijken et al., 2011; Taylor, Denison, Beyai, & Owens, 2010) and time of birth and the severity of hypoxic-ischemic encephalopathy of neonates admitted to hospitals serving rural areas in sub-Saharan Africa, where most births occur at home. Moreover, there is considerable debate about the criteria for a safe level of bilirubin in sick neonates (Bhutani & Johnson, 2009; Smitherman, Stark, & Bhutan, 2006;

Varughese, 2019). This is one of the few studies to provide data that suggests that few problems develop in neonates who have bilirubin levels between 85 and 250 $\mu\text{mol/l}$.

- We have amended the document to include the above information. *Phototherapy was considered if they had any visible jaundice anywhere on the body on day one or TSB > 260 $\mu\text{mol/l}$ on day two (WHO, 2013) (page 4).*
- We have also included the median and interquartile range (IQR) of TSB values in this study as follows: *The median TSB values of the NNJ survivors was 245 (IQR = 144- 322) $\mu\text{mol/l}$ (page 7).*

2. The only possible marker of acute bilirubin encephalopathy they recorded is death. While death certainly is a marker of severe neonatal jaundice, it can be the result of multiple other pathological processes. Unfortunately, the authors do not clarify whether the death was related to jaundice or not, leaving this uncertainty open to interpretation. It follows that the lack of markers for acute bilirubin encephalopathy confounds any possible relationship between the observed (or lack thereof) neurodevelopmental problems and hyperbilirubinemia. In fact, low levels of bilirubin (as reported in this study) have been postulated to be neuroprotective not harmful. The study would have been much more meaningful had the authors looked at children who had suffered from truly severe neonatal hyperbilirubinemia and/or acute bilirubin encephalopathy.

- We have addressed this issue in the discussion as follows: *Moreover, the information on attribution of neonatal insults to cause of death of children admitted to hospital in this setting is difficult due to lack of investigations. The children in this retrospective study were treated in a busy rural district hospital, and the signs for acute bilirubin toxicity were poorly recorded. The study provides evidence on the neurobehavioral patterns of children who have inadequate information at birth but are admitted to hospital and diagnosed with NNJ or HIE. Given that the challenges in medical records are very common in many settings in Low- and Middle-Income countries this question is important to answer as it addresses the day to day reality of the children in this context (page 9-10).*

3. Diagnosis of hypoxic ischemic encephalopathy by "clinical diagnosis" at discharge is also too non-specific to have any idea of the group of neonates being discussed.

- We have amended this part and included the clinical signs of HIE that were used according to the guidelines used by the clinicians for the final diagnosis. *HIE diagnosis was given if the child had the following problems after birth; convulsions, inability to suck, apnoea, or poor motor tone (WHO, 2013) (See page 5)*

4. The authors give no indication of the degree of hypoxic ischemic encephalopathy and thus, as with neonatal jaundice, the interpretation of a possible causal relationship with neurodevelopmental delay in school age children remains uninterpretable.

- We have addressed this issue in the discussion as follows: *During the period when the participants of this study were born (2005 to 2012), most of the births occurred at home and local dispensaries. Therefore, most of the children were either referred to the hospital from the dispensaries or were brought to the hospital when the caregivers noted signs of sickness in their child. Thus, it was impossible to obtain Apgar scores (generally captured at the first 1, 5, and 10 minutes of life) or cord gases for most of the children. For this reason, we are unable to indicate the degree of HIE in this sample. Moreover, there are difficulties in obtaining the gestational age of the neonates (page 10).*

5. In addition, the authors do not clarify the training of the clinicians making the diagnosis

of HIE or how this diagnosis was validated, further complicating any possible meaningful interpretation of the observed results.

- We have amended and provided the required information about the training of the clinicians. *A Medical officer with a bachelor's degree in medicine and surgery made the diagnosis of NNJ and HIE and this was often discussed with consultant pediatricians who had been trained in Kenya or the United Kingdom* (page 4).

6. There is no comment regarding neonates who had both neonatal jaundice and hypoxic ischemic encephalopathy. Asphyxiated neonates would be expected to higher risk for acute bilirubin encephalopathy and long-term problems, but this group is not addressed by the authors.

Because of the flaws mentioned above, the study as currently presented does not add sustainably to our understanding of the true magnitude of neurodevelopmental problems from either neonatal jaundice or hypoxic-ischemic encephalopathy.

- We did not have these cases in this cohort. *None of the participants in this study had a diagnosis of both NNJ and HIE as those with a combined diagnosis were excluded from this cohort study* (page 4).

Reviewer 2: Deirdre Murray

1. The definition of hyperbilirubinaemia is very vague. They seem to have included all infants with a bilirubin level > 85. The authors do not give a time for this, beyond stating that the measurement took place in the first 28 days. The majority of infants have some level of jaundice, and will reach this level

- The bilirubin was measured on admission, since many of the neonates were born at home, it was difficult to determine the exact age in hours. Moreover, the inclusion criteria included neonates up to 30 days of age as per the definition of neonatal period as used in other studies (Newman, Xiong, Gonzales, & Escobar, 2000). However, despite the inclusion criteria of 0- 30 days, the median age of the participants at admission was 3 [interquartile range (IQR) = 0-8] days (page 6-7).

2. They state that they have done a sub analysis in the severe group, but do not tell us the numbers or the results in this group, who are actually the more interesting.

- We have provided the actual numbers of children with hyperbilirubinemia. *A sub-analysis was conducted with 25 participants with severe hyperbilirubinemia on all outcomes, and similar results were obtained* (page 6).

3. Surprisingly with this low level of hyperbilirubinaemia the outcomes are poor which makes me wonder whether these infants had other underlying diagnoses, such as sepsis, prematurity, IUGR?

- We have addressed this issue in the methods section as follows: *Some of the participants had sepsis and preterm birth as a secondary diagnosis. For NNJ 23 had neonatal sepsis, and 6 were preterm. In the HIE group, 5 had sepsis, and 2 were preterm. However, based on another study that we conducted, sepsis did not appear to aggravate the developmental outcomes of children with neonatal jaundice and sepsis* (Magai et al., 2020) (page 5).

4. The follow up rate was low. they state that 347 survivors were identified and 121 were followed up. Please explain why the other 227 were not followed?

- This explanation is given under limitations in the discussion section as follows: *Given that this study was designed to screen out children with severe disability (they could not be*

able to carry out tasks during assessment) and only two out of the 107 participants were severely disabled, the prevalence of severe disability in the sample was 1.9% (0.46 -7.32). Data collection on children with severe disability was discontinued (page 10) as we had reached the needed sample size to determine the severity of disability in these children.

5. They have stated in their discussion the other major limitation: the fact that it is likely that a high proportion of children; those with moderate or severe HIE are likely to have died. If the authors could focus on this as a study of outcome following HIE, reporting mortality and survival, with outcome to 10 years then this would be a very valuable article and would add significantly to the literature.

- Plans to study the mortality and survival of NNJ and HIE are underway in future studies. However, in this study, our main research question in the current study was to understand the neurobehavioral patterns of survivors of NNJ and HIE.

6. Minor points:

How did the WAZ and HAZ scores compare to the general population? Do they have this data?

- We have addressed this issue as follows: *The WAZ and HAZ scores of these children were compared to the WAZ and HAZ scores for children in the general population obtained in a study conducted in 2003 with 184 children aged 8 to 11 years (page 6). The mean WAZ was -1.3 (SD = 0.9), -1.0 (SD = 1.6), and -1.2 (SD = 1.1) while the mean HAZ was -1.1 (SD = 1.1), -0.8 (SD = 1.5), and -1.3 (SD = 1.1) for NNJ, HIE, and for the general population respectively. There were no significant differences in the WAZ [F (2, 196) = 0.5, P = 0.623] and HAZ [F (2, 285) = 2.6, P = 0.077] scores between the cases and the general population (Page 7).*

7. The first paragraph of the discussion is repeated twice in the second paragraph.

- We have revised this part and deleted the repetition as needed.

Reviewer 3: Bolajoko O Olusanya

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Competing Interests: No competing interests
