Patterns of neurobehavioral functioning in school-aged survivors of neonatal jaundice and hypoxic-ischemic encephalopathy in Kilifi, Kenya: A cross-sectional study [version 1; peer review: 1 approved with reservations]

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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 detected in 1.6% of survivors of NNJ and 2.3% of survivors of HIE. 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 function compared to the general population.
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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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 functioning\(^1\)\(^-\)\(^4\). The global incidence of severe NNJ is estimated at 9.9 per 10,000 live births among children\(^5\). Africa has the highest burden of severe NNJ with incidence rates of 667.8 per 10,000 live births (95% CI 603-738)\(^6\). 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\(^9\)\(^,\)\(^11\). 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\(^6\)\(^,\)\(^13\)\(^-\)\(^17\).

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%, respectively\(^18\). They were the second and third most common neonatal conditions after sepsis (13%)\(^19\). In 2015, 32% of neonatal mortality was caused by HIE and birth trauma in Kenya\(^20\).

Studies in high-income countries have reported that school-aged children who survive NNJ and HIE develop adverse long-term neurocognitive outcomes\(^21\)\(^-\)\(^23\), 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.

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/mols/l recorded to the clinical notes. Severe hyperbilirubinemia was defined as TSB of >250 µ/mols/l. HIE diagnosis was based on the clinical diagnosis recorded by the clinicians at discharge. Severe disability was defined as the impairment in body structure which results in significant loss and difficulty for a participant to perform a task\(^24\).

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) standards\(^25\). Screening assessments were done for gross motor functioning, communication functioning, intellectual disability, and epilepsy. The participants were screened for hearing and visual acuity using an auditory brainstem response machine\(^26\) and the Snellen and E-Chart, respectively. 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 function\(^27\). 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 intrarater agreement [Kappa 0.76 to 0.88; intraclass correlation coefficient (ICC) ranging from 0.89 to 0.95]\(^28\).

Communication functioning was assessed using the Adapted Communication Profile\(^29\). 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 Kilifi; however, its psychometric properties in Kenya are yet to be established.

The Raven’s coloured progressive matrices (RCPM) 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, Kenya and has good internal consistency (Cronbach alpha = 0.81) and test-retest reliability (ICC = 0.77). The test has good construct validity in the Kenyan population.

The epilepsy screening tool 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, Kenya. Active epilepsy was defined as two or more unprovoked seizures occurring within the last 12 months, 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 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). The anthropometric variables Weight-for-Age (WAZ) and Height-for-Age (HAZ) were standardized using WHO Anthro plus. 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). 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 impairments.

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. A sub-analysis was conducted with participants with severe hyperbilirubinemia on all outcomes and comparable results were obtained. Therefore, we report data with all participants with TSB of >85 µ/mols/l.

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 of the participants was 10 [interquartile range (IQR) = 5–12] years. 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) and -1.0 (SD = 1.6), while the mean HAZ was -1.1 (SD = 1.1) and -0.8

Figure 1. Participants visited, recruited, and assessed.
(SD = 1.5) for NNJ and HIE, respectively. Table 1 presents a summary of these results (see underlying data).

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 1. Demographic characteristics of participants.

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

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.

<table>
<thead>
<tr>
<th>Type of functioning</th>
<th>NNJ n (%)</th>
<th>HIE n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMFCS Levels of functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I</td>
<td>59 (95.2)</td>
<td>41 (95.3)</td>
</tr>
<tr>
<td>Level II</td>
<td>3 (4.8)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Level III</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Level IV</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Level V</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Communication Functioning n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communicative modes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not a problem</td>
<td>58 (90.6)</td>
<td>40 (93.0)</td>
</tr>
<tr>
<td>A bit of a problem</td>
<td>1 (1.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>A big problem</td>
<td>3 (4.7)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Expressive communication functions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not a problem</td>
<td>60 (93.8)</td>
<td>41 (95.3)</td>
</tr>
<tr>
<td>A bit of a problem</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>A big problem</td>
<td>3 (4.7)</td>
<td>2 (4.7)</td>
</tr>
</tbody>
</table>
functions, social communication functions, receptive communication and communicative effectiveness, respectively (Table 2).

### 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) per 100] and HIE [11.6% (95% CI = 3.9 – 25.1) per 100] was twenty times higher than in the normative group [0.5% (95% CI = 0.3 – 0.6) per 100], 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) per 100] and HIE [2.3% (CI = 0.0 – 12.3) per 100] versus the normative group [0.5% (CI = 0.4 – 0.6) per 100], p >0.050 (Table 3).

### 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.

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.

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. who evaluated the frequency of sensorineural hearing loss (SNHL) in children aged 2 to 10 years with a history of exchange transfusion. 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 μmol/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., 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., 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. The results that survivors of NNJ have poor cognitive outcomes corroborate findings by Hokkanen et al., who reported that at 30 years, 40% of survivors of severe NNJ had poor cognitive functions that continued from childhood to adulthood.

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. The finding that survivors of HIE have normal vision and hearing functioning corroborates the results of Mietzsch et al., who investigated auditory function in neonates treated with hypothermia. These authors report that although peripheral auditory 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 colleagues, 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 died in the community.

These findings are similar to those reported by Hayes et al., 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. and Roberson et al. did not find significant impairment in survivors of mild HIE motor and school performance respectively compared to the control groups. However, unlike the findings of Hayes et al., 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 developed 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.

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. 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).

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNJ cases (N=64)</th>
<th>Normative data (N=11,232)</th>
<th>Statistical tests</th>
<th>HIE cases (N=43)</th>
<th>Normative data (N=11,232)</th>
<th>Statistical tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment</td>
<td>7</td>
<td>51</td>
<td>(χ²(1) = 136.8 P &lt; 0.001)</td>
<td>5</td>
<td>51</td>
<td>(χ²(1) = 108.1 P &lt; 0.001)</td>
</tr>
<tr>
<td>Active epilepsy</td>
<td>1</td>
<td>54</td>
<td>(χ²(1) = 1.5 P = 0.215)</td>
<td>1</td>
<td>54</td>
<td>(χ²(1) = 3.0 P = 0.083)</td>
</tr>
</tbody>
</table>

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

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. It is likely that the children who were followed up had mild impairment while those with severe outcomes did not survive.

Ethical statement
Ethical approval for this study was granted by the Kenya Medical Research Institute Scientific and Ethics Review Unit (SERU); protocol number 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

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 do.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).

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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

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.