PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Associated impairments among children with cerebral palsy: Findings from a hospital-based surveillance in Vietnam
AUTHORS	Khuc, Thi Hong Hanh; Karim, Tasneem; Nguyen, Van Anh; Giang, Nguyen; Dũng, Trịnh; Dossetor, Rachael; Cao Minh, Chau; Van Bang, Nguyen; Badawi, Nadia; Khandaker, Gulam; Elliott, Elizabeth

VERSION 1 - REVIEW

REVIEWER NAME	***HC Chiu***
REVIEWER AFFILIATION	I-Shou University, Kaohsiung, Taiwan (ROC), Physical Therapy
REVIEWER CONFLICT OF INTEREST	No conflict of interests
DATE REVIEW RETURNED	18-Jul-2023

GENERAL COMMENTS	Comments General comments The topic under investigation is not innovative and there are a number of omissions in the reporting of the study that need to be addressed. Information is messy, so it is difficult to read. Main problem is the purpose and design of study is not clear. As there are a number of omissions in the design of this study, the value of this topic under review is questionable. Abstract. The abstract will need to re-write after finalizing the content of paper. Introduction-aim The aims are not specific enough, for example name of impairments. Methods: general -It may be clearer if methods follow this order “Design”, “Participants”, “Intervention”, “Outcome measures”. It may be better to include “Procedure” in the “Design”. -Too many unnecessary subheadings, such as setting, cerebral palsy description…etc..Those information can be part of others. -Subheading, “outcome measures” is missing. Methods: Design -Name of design is missing. For example, it should be “an observational study……”.

	-Information is messy. It should be “an observational study….was carried out. Children with…were recruited…. Outcome measures were carried out… Methods: Participants -Ethics approval should be part of this section. Methods: outcome measures Authors should state the reasons to choose these outcome measures. Results: Table 1 1. Table 1: Information is messy. Should have a table 1 as example. The example of table 1 is as follow: Table 1: Characteristics of participants with cerebral palsy Characteristic of participants n = XX Age (yr), mean (SD) Gender, n males (%) Type of cerebral palsy Hemiplegia, n (%) Quadriplegia, n (%) Diplegia, n (%) Education, n main stream (%) GMFCS, n (%) Level I Level II ---- Cognitive, n (%) Average Mild impairment Moderate impairment *GMFCS: Gross Motor Function Classification Scale Discussion/ Conclusion: context. As there are so many questions in the method and results, the discussion and conclusion are questionable.

REVIEWER NAME	***Jane Wotherspoon***
REVIEWER AFFILIATION	Queensland University of Technology - Kelvin Grove Campus, School of Psychology and Counselling
REVIEWER CONFLICT OF INTEREST	No competing interests to declare.
DATE REVIEW RETURNED	22-Jul-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript, which looks at associated impairments in children with cerebral palsy through hospital-based surveillance in Vietnam. The authors note the importance of understanding comorbidities in CP to better intervene and minimise long-term impacts through intervention. They also note the lack of research investigating associated impairments in children with CP in Vietnam, so the research reported in this manuscript addresses this gap in knowledge. While the topic is important, I have some comments about the paper. 1. Abstract - It would help to report participant information (e.g. age, subtype, GMFCS level) here. This information is important to think

	about when evaluating study design but was not reported until the Results section. 2. Strengths and Limitations - while the Introduction discusses the lack of previous research for this population of children with CP, this is not listed as a strength. Challenges with generalising from hospital-based surveillance (and possible over-representation of associated impairments) not mentioned. 3. Introduction - the rationale and study aim are stated. One reference is about caregiver burden in children with neurodevelopmental disorders, the following paper might be relevant - Vadivelan K, Sekar P, Sruthi SS, Gopichandran V. Burden of caregivers of children with cerebral palsy: an intersectional analysis of gender, poverty, stigma, and public policy. BMC Public Health. 2020 May 8;20(1):645. doi: 10.1186/s12889-020-08808-0. PMID: 32384875; PMCID: PMC7206712. 4. Materials and Methods - the authors discuss assessment of associated impairments. I am unclear as to how intellectual impairment was assessed, especially given the median age and challenges with assessment in children with CP (e.g., see Yin Foo, Guppy & Johnston, 2013). Could more information be provided on how intellectual impairment was determined. E.g., when assessment was undertaken, what measures were used? What percentage of participants completed formal assessment v. informal? Did distribution patterns across the categories vary by age? 5. Results - participant characteristics are reported in a table, but I would also be interested to see the age range reported along with median and IQR. In Table 2, different categories are used (severe, not severe, no impairment) than discussed in the methods section (mild, moderate, severe, no impairment) - can you clarify how these align? In Table 3, there are significant associations between epilepsy, speech, hearing, visual and intellectual impairments. The authors do mention in the discussion that such co-occurring impairments are unsurprising, given CP results from widespread injury to the developing brain, but it also raises questions again about how intellectual impairment was assessed. Were speech, vision and/or hearing impairments taken into account when assessing intelligence? 6. Discussion - the authors provide an overview of the results of statistical analysis, and discuss similarities and contrasts within the broader literature. I wonder whether further discussion of some of the challenges with assessment, as well as some of the associations reported, might further strengthen this section and highlight the novel features of this study. For example, challenges around confirmation of diagnosis of CP and intellectual impairment in the children assessed are mentioned in a sentence in the study limitations, but I would be interested to hear how the authors managed such challenges, and any suggestions for future, as accurate diagnosis and assessment of impairments are key to ensuring best outcomes. Furthermore, some associations could be discussed further - for example, with the univariate logistic model, associations were reported between severe underweight and stunting, and intellectual impairment. It was also reported that one-third of children assessed were malnourished. How could additional factors that can influence intellectual development be considered?

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1: Dr. HC Chiu, I-Shou University, Kaohsiung, Taiwan (ROC)

Comment 4. General comments: The topic under investigation is not innovative and there are a number of omissions in the reporting of the study that need to be addressed. Information is messy, so it is difficult to read. Main problem is the purpose and design of study is not clear. As there are a number of omissions in the design of this study, the value of this topic under review is questionable.

Response: Thank you for identifying critical omissions in our manuscript. We have addressed each of your concerns, and believe they have improved the manuscript significantly. Please see a point by point response to each of your comments below.

Comment 5. Abstract: The abstract will need to re-write after finalizing the content of paper.

Response: Thank you, we have revised the abstract as suggested.

Comment 6. Introduction-aim: The aims are not specific enough, for example name of impairments.

Response: We clarified the aim as follows in page 3, line 112-114,

"The aim of the study was to describe associated impairments (i.e., epilepsy, intellectual, visual, hearing, and speech impairments) among children with CP and their various correlates (e.g. Sex, type and topography of CP, GMFCS level, MACS level, etc.) ."

Comment 7. Methods: general

- It may be clearer if methods follow this order "Design", "Participants", "Intervention", "Outcome measures". It may be better to include "Procedure" in the "Design".
- Too many unnecessary subheadings, such as setting, cerebral palsy description…etc..Those information can be part of others.
- Subheading, "outcome measures" is missing.

Response: Thank you for these helpful suggestions. We revised the Headings of the Methods as follows: *Study design, Study setting, Participants, Outcome measures, Statistical analysis, and Patient and public involvement.*

Comment 8. Methods: Design

- Name of design is missing. For example, it should be “an observational study……”.

- Information is messy. It should be “an observational study….was carried out. Children with…were recruited…. Outcome measures were carried out…

Response: Thank you for pointing this out. We mentioned the study design in the abstract and described in the method earlier. We have clarified in the method as below:

- *“Study design: This is a descriptive cross-sectional study using hospital-based surveillance*.” (line 118)
- *“Participants: Participants were children aged less than 18 years, who attended the rehabilitation department at NCH and were newly diagnosed with CP, according to the definition used by the Surveillance of Cerebral Palsy in Europe and the Australian Cerebral Palsy Register (ACPR) [5,7,15].”* (line 141-143)

Comment 9. Methods: Participants - Ethics approval should be part of this section.

Response: We have included the ethics statement under the Participants sub-section. (line 147-150)

Comment 10. Methods: outcome measures

Authors should state the reasons to choose these outcome measures.

Response: We have provided the reasons for the selection of these outcome measures as follows,

“These are the common associated impairments among children with CP often resulting from the causal injury to the developing brain. We assessed and collected data on each associated impairment using evidence-based tools and definitions (ILEA [25], DSM-5 [20] and WHO [24,25]) which are used extensively by clinicians. Chosen assessment and classification of the measures were also widely used by CP registers internationally including the Australian CP Register, Surveillance of CP in Europe and Bangladesh CP Register which has ensured generation of robust comparable data.” (line 203-209).

“All of these outcome measures have been widely used and investigated in similar research contexts [32-35]. The chosen outcome measures allow us to assess and analyze the specific variables and parameters that are essential to answering the research questions.”(line 258-260)

Comment 11. Results: Table 1

1. Table 1: Information is messy. Should have a table 1 as example. The example of table 1 is as follow:

Table 1: Characteristics of participants with cerebral palsy

Characteristic of participants	n = XX Age (yr), mean (SD)
Gender, n	
males (%)	
Type of cerebral palsy	
Hemiplegia, n (%)	
Quadriplegia, n (%)	
Diplegia, n (%)	
Education, n	
mainstream (%)	
GMFCS, n (%)	
Level I	
Level II	
Cognitive, n (%)	
Average	
Mild impairment	
Moderate impairment	

*GMFCS: Gross Motor Function Classification Scale

Response: We have represented Table 1 as per your advice. Thank you.

Comment 12. Discussion/ Conclusion: context.

As there are so many questions in the method and results, the discussion and conclusion are questionable.

Response: We have addressed your concerns outlined above and appreciate your detailed comments. Thank you for your time and consideration.

REVIEWER 2 Ms. Jane Wotherspoon, Queensland University of Technology - Kelvin Grove Campus

Comment 13. Comments to the Author: Thank you for the opportunity to review this manuscript, which looks at associated impairments in children with cerebral palsy through hospital-based surveillance in Vietnam. The authors note the importance of understanding comorbidities in CP to better intervene and minimise long-term impacts through intervention. They also note the lack of research investigating associated impairments in children with CP in Vietnam, so the research reported in this manuscript addresses this gap in knowledge. While the topic is important, I have some comments about the paper.

Response: Thank you for reviewing our manuscript. Your valuable comments have helped us to improve our article (see below).

Comment 14. Abstract - It would help to report participant information (e.g. age, subtype, GMFCS level) here. This information is important to think about when evaluating study design but was not reported until the Results section.

Response: Thank you both reviewers identified this. We have provided the participant information in a new Table 1 (e.g., age, subtype, GMFCS level) as per your suggestions (line 43-45).

Comment 15. Strengths and Limitations - while the Introduction discusses the lack of previous research for this population of children with CP, this is not listed as a strength. Challenges with generalising from hospital-based surveillance (and possible over-representation of associated impairments) not mentioned.

Response: Thank you for your suggestions. We have provided that *"This is the first study reported about significant related factors to associated impairments."* (line 354)

"Firstly, this is a hospital-based study which imposed a potential risk for biased representation of children with CP in Vietnam. Thus, the findings must be interpreted with caution and may not be generalizable" (line 477-479)

Comment 16. Introduction - the rationale and study aim are stated. One reference is about caregiver burden in children with neurodevelopmental disorders, the following paper might be relevant - Vadivelan K, Sekar P, Sruthi SS, Gopichandran V. Burden of caregivers of children with cerebral palsy: an intersectional analysis of gender, poverty, stigma, and public policy. BMC Public Health. 2020 May 8;20(1):645. doi: 10.1186/s12889-020-08808-0. PMID: 32384875; PMCID: PMC7206712.

Response: Thank you, we have cited this article in our manuscript and added the following text:

“Caregivers play a vital role in the rehabilitation of children with CP, [10] and often face a wide range of challenges due to the heavy physical burden of caregiving, guilt about their child's condition and financial burden.[11]” (line 101-103)

Comment 17. Materials and Methods - the authors discuss assessment of associated impairments. I am unclear as to how intellectual impairment was assessed, especially given the median age and challenges with assessment in children with CP (e.g., see Yin Foo, Guppy & Johnston, 2013). Could more information be provided on how intellectual impairment was determined. E.g., when assessment was undertaken, what measures were used? What percentage of participants completed formal assessment v. informal? Did distribution patterns across the categories vary by age?

Response: Thank you for your comment. Intellectual assessment in very young children with CP is challenging us. We combined use of different tools (DSM-5, American Association on Intellectual and Developmental Disabilities (AAIDD) and Australian Cerebral Palsy Register guidelines) to assess intellectual impairment of each child with CP as described in the Method (line 174-177).

However, we understand that a young age (median = 1.7 years), cognitive assessment has limitations, and that testing may need to be repeated when children are older. We acknowledge this as a limitation (line 64-65).

Comment 18. Results

- participant characteristics are reported in a table, but I would also be interested to see the age range reported along with median and IQR.

- In Table 2, different categories are used (severe, not severe, no impairment) than discussed in the methods section (mild, moderate, severe, no impairment) - can you clarify how these align?

- In Table 3, there are significant associations between epilepsy, speech, hearing, visual and intellectual impairments. The authors do mention in the discussion that such co-occurring impairments are unsurprising, given CP results from widespread injury to the developing brain, but it also raises questions again about how intellectual impairment was assessed. Were speech, vision and/or hearing impairments taken into account when assessing intelligence?

Response:

- We included reported the age range, please see Table 1.

- The “Not severe” group comprises of individuals with mild and moderate impairments. We clarified this in the foot note of Table 2 (line 298).

- We have described how intellectual impairment was assessed in page 9, line 170-180. We also acknowledged the limitations in page 2, line 66-67 including the bias noted in your previous comment. Assessments were completed by trained pediatricians who used their best clinical judgement in their

assessment of intelligence and they considered other associated impairments (i.e., speech, vision, and/or hearing impairments) as required and possible.

Comment 19. Discussion - the authors provide an overview of the results of statistical analysis, and discuss similarities and contrasts within the broader literature. I wonder whether further discussion of some of the challenges with assessment, as well as some of the associations reported, might further strengthen this section and highlight the novel features of this study. For example, challenges around confirmation of diagnosis of CP and intellectual impairment in the children assessed are mentioned in a sentence in the study limitations, but I would be interested to hear how the authors managed such challenges, and any suggestions for future, as accurate diagnosis and assessment of impairments are key to ensuring best outcomes.

Furthermore, some associations could be discussed further - for example, with the univariate logistic model, associations were reported between severe underweight and stunting, and intellectual impairment. It was also reported that one-third of children assessed were malnourished. How could additional factors that can influence intellectual development be considered?

Response: Thank you for your suggestion. We agree that accurate diagnosis and assessment are key to ensuring best outcomes. We have now elaborated further on the challenges around confirmation of diagnosis of CP and the assessment of intellectual impairment assessment in the children assessed. We have additionally outlined recommendations for addressing these challenges for future studies as below,

“In regions like Vietnam, where the use of best practice tools such as GMA, HINE and brain MRI is limited for early detection of CP, confirmation of diagnosis can be challenging particularly in young children. Within the National Children Hospital, alternative diagnostic methods employed by experienced pediatricians emphasize on the reliability of comprehensive history taking, clinical assessment and review of medical records. These methods, though effective and often the best alternative in several LMICs in absence of professionals trained in GMA and HINE, come with acknowledged limitations. These challenges have guided our team’s continued advocacy for improved access to these tools in LMIC including Vietnam. Our broad research program has since ensured training of the first certified GM scorer in Vietnam (add your initial here), which is a key step towards the implementation of the use of the best practice tools in addition to clinical assessment by experienced clinicians for enhanced diagnostic accuracy for CP in Vietnam.

In our study, experienced pediatricians relied on the DSM-5 criteria and AAIDD guideline for confirmation and classification of severity of intellectual impairment [20] [21]. This had additional acknowledged limitations which can be addressed in future studies through professional training and implementation of use of other tools for the assessment of cognitive function among infants and toddlers.[59] ” (line 486-503)

In this study, we considered nutritional status as a correlate (not a risk factor) of associated impairments. We discussed the association between nutritional status and associated impairments in our previous publication [29] so we did not discuss further it further in this manuscript. We have now mentioned this in the Method as below *"Anthropometric measurements (height and weight) were documented to assess the nutritional status of children using a World Health Organization (WHO) guideline [28]. We reported these data separately in a previous publication [29]"* (line 238-240).

[29] Karim T, Jahan I, Dossetor R, et al. Nutritional Status of Children with Cerebral Palsy-Findings from Prospective Hospital-Based Surveillance in Vietnam Indicate a Need for Action. Nutrients. 2019;11(9).

VERSION 2 – REVIEW

REVIEWER NAME	***Jane Wotherspoon***
REVIEWER AFFILIATION	Queensland University of Technology - Kelvin Grove Campus, School of Psychology and Counselling
REVIEWER CONFLICT OF INTEREST	None.
DATE REVIEW RETURNED	14-Mar-2024

GENERAL COMMENTS	Thank you for additional information in the abstract regarding participants. A key remaining question that I have is around the assessment of intellectual impairment in a sample with a mean age of 1.7 years. It remains unclear to me on what basis the diagnosis and decisions around severity were made in this group in the absence of formal assessment, and as such it would still be difficult to replicate this study. You note that you combined the use of tools, but these were not standardised measures such as intelligence tests or adaptive behaviour measures. Questions around diagnosis impact how the results are received as there is frequent discussion of factors associated with intellectual impairment. Perhaps if you clarify how the paediatricians determined participants met criteria for intellectual impairment as noted in the DSM-V-TR that would help address this and make it more likely the study could be replicated. I think the additional discussion around

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 Comments to the Author: Thank you for additional information in the abstract regarding participants. A key remaining question that I have is around the assessment of intellectual impairment in a sample with a mean age of 1.7 years. It remains unclear to me on what basis the diagnosis and decisions around severity were made in this group in the absence of formal assessment, and as such it would still be difficult to replicate this study. You note that you combined the use of tools, but these were not standardised measures such as intelligence tests or adaptive behaviour measures. Questions around diagnosis impact how the results are received as there is frequent discussion of factors associated with intellectual impairment. Perhaps if you clarify how the paediatricians determined participants met criteria for intellectual impairment as noted in the DSM-V-TR that would help address this and make it more likely the study could be replicated.

Response: Thank you for reviewing our manuscript and providing your thoughtful suggestions. Following careful consideration of your comments, we expanded on the methods employed for the

assessment of probable intellectual impairment further as follows (page 5, line 172 - 182 - clean version),

“Intellectual impairment was defined as notable deficits in age-appropriate intellectual functioning, adaptive skills, and developmental delays. Assessment of children to identify those with and/or likely to develop intellectual impairment was based on clinical history, and/or assessment of adaptive function, and/or report by the parents/primary caregivers and/or review of available medical records including IQ by clinicians. In the absence of relevant medical records of formal assessment, which was the case for the majority of our study participants, a clinical assessment was made by experienced paediatricians at the National Children’s Hospital. Assessment of probable severity of intellectual impairment was based on each child’s age-appropriate intellectual and adaptive functioning, and daily skills in accordance with the DSM-5 criteria for diagnosis and classification of severity of intellectual disability [20] and classified as follows: ‘children who were clinically assessed to be slower in all areas of conceptual development and social and daily living skills’ relative to age were classified as mild to moderate; ‘children with major delays in development, poor intellectual and adaptive functioning skills’ for age were classified as severe.”

In contrast to its earlier versions, the DSM-5 encourages a more comprehensive view of the individual in the definition of intellectual disability c based on difficulties in conceptual, social, and practical areas of living. [20] The DSM-5 abandons specific IQ scores as a diagnostic criterion while retaining the grouping with a greater focus on daily skills and it additionally notes that ‘intellectual functioning reflects several different components: verbal comprehension, working memory, perceptual reasoning, quantitative reasoning, abstract thought, and cognitive efficacy.’ Furthermore, it acknowledges that ‘accurate measurement requires an instrument that is psychometrically valid, culturally appropriate, and individually administered. In the absence of appropriate measurement instruments, screening instruments are still able to assist in the identification of individuals who need further testing’.[20]

“Due to the difficulties in accurately assessing the likelihood of intellectual impairment among a young cohort to ensure alignment with DSM-5 criteria, the experienced clinicians used additional assessment tools to support their assessment and decision-making about the probable severity. This included the additional use of the American Association on Intellectual Developmental Disabilities-AAIDD [21] as a screening instrument to evaluate the extent of support required, thus certain adaptive skills of each child relative to their age. This determined the extent of developmental delays to support the DSM-5 criteria of ‘major developmental delays’ reflecting severe intellectual impairment. Collective use of these multiple tools, completion of detailed history taking and clinical assessment by experienced pediatricians, and review of available medical records ensured a rigorous approach to identification and classification of probable intellectual impairment among these children with the available information. This multipronged approach additionally enabled classification consistent with the categories used by the Australian Cerebral Palsy Register and hence allow estimation of the IQ category: normal (IQ >70), Mild impairment (IQ 50-69), Moderate impairment (IQ 35-49), Severe impairment (IQ <35). [22, 23].” (page 5, line 184 - 197).

The mean age of our study participants was 1.7 years, which poses significant challenges for the assessment of intellectual impairment. We ensured that the understandable limitations of the method employed for the overall assessment and classification of intellectual impairment among a young cohort are clearly acknowledged to support cautious interpretation and careful consideration of

assessment tools and methodology for future research. We additionally recommend professional training and implementation of specific tools for assessment of intellectual functioning among infants and toddlers.

See below the updated section of study limitations reflecting these additions (page 15, line 51024-531),

“In our study, experienced pediatricians relied on the DSM-5 criteria and AAIDD guideline for confirmation and classification of severity of intellectual impairment [20, 21]. This had additional acknowledged limitations which can be addressed in future studies through professional training and implementation of use of other tools for the assessment of cognitive function among infants and toddlers.[59] It is imperative to ensure continued follow up and referral of all children identified to have probable intellectual impairment through the methods employed in our study for further assessment using age appropriate validated tests for adaptive function and IQ at the appropriate age.”

The additions made to address your comments have significantly enhanced the comprehensiveness of the methods employed and the acknowledged limitations around the assessment of intellectual impairment among young children. Thank you for your in-depth review. We hope that our responses provide greater clarity and adequately address each of the valid concerns raised by you.