PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health-related quality of life in children and adolescents born very preterm and its correlates: a cross-sectional study
AUTHORS	Haile, Sarah; Peralta, Gabriela; Adams, Mark; Bharadwaj, Ajay N; Bassler, Dirk; Moeller, Alexander; Natalucci, Giancarlo; Radtke, Thomas; Kriemler, Susi

VERSION 1 - REVIEW

REVIEWER NAME	***Corneliu Bolbocean***
REVIEWER AFFILIATION	None disclosed
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	31-Jul-2024

GENERAL COMMENTS	This is an interesting paper, which utilizes novel data. The study aims to assess differences in KIDLE scores by preterm birth status using linear mixed models. I have several comments which might be helpful for the authors. Abstract: • “Patients Children born <32 weeks gestation”, should we also include full-term controls. Include N. • In this statement may be detail the main chronic health conditions “Chronic health conditions, age, and respiratory symptoms …” • In this statements “by current respiratory symptoms that may be modifiable.” Do you mean by current respiratory symptoms that may be modifiable respiratory symptoms? Introduction: “Yet, the many systematic reviews4,5,7,8 on HRQOL in the premature born often cannot account for important potentially modifiable factors… “ please be specific about modifiable factors and why are these important. Methods: • Please try to justify the use of KINDLE in populations born preterm given the literature in the field around HRQoL measures in individuals born preterm. • Please justify the use of linear mixed models using random effect for family. I think the use of fixed effects to capture the time-invariant unobserved heterogeneity will also be helpful to show as a sensitivity analysis. • This statement requires more details: “Comparisons of FLiP preterm and Ciao Corona control participants were made using

	linear regression, after 2:1 matching on age in years, sex"; what type of matching? Are you constructing a doubly robust estimation? More details are needed. Discussion I think it is important to address the use of KINDLE as an appropriate HRQoL measure to assess HRQoL in preterms. It will be helpful to clearly state the contribution of this study to the literature.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Corneliu Bolbocean

Comments to the Author

This is an interesting paper, which utilizes novel data. The study aims to assess differences in KIDLE scores by preterm birth status using linear mixed models. I have several comments which might be helpful for the authors.

Abstract:

- "Patients Children born <32 weeks gestation", should we also include full-term controls. Include N.

Thank you for this comment. We have added this information as follows: "Children born <32 weeks gestation (N = 442) as well as their fullterm born siblings (N = 145)".

- In this statement may be detail the main chronic health conditions "Chronic health conditions, age, and respiratory symptoms …"

Chronic health conditions here refers primarily to attention deficit hyperactivity disorder (ADHD) asthma, and heart problems, but does not include cerebral palsy in that sentence. We have added this information to the abstract: "Chronic non-respiratory health conditions (such as atten- tion deficit hyperactivity disorder (ADHD) or heart conditions, but not including cerebral palsy),..."

- In this statements "by current respiratory symptoms that may be modifiable." Do you mean by current respiratory symptoms that may be modifiable respiratory symptoms?

This sentence has been rephrased to read "However, lower HRQOL was explained by other factors, such as older age, the presence of chronic health conditions, but also by possibly modifiable current respiratory symptoms."

Introduction:

“Yet, the many systematic reviews4,5,7,8 on HRQOL in the premature born often cannot account for important potentially modifiable factors… “ please be specific about modifiable factors and why are these important.

Thank you for this important point, which is described further in the 2nd paragraph of the introduction. To clarify this point, an additional sentence has been added to the beginning of the 2nd paragraph: “Identifying modifiable correlates of HRQOL is essential in order to develop

targeted interventions for HRQOL in the very preterm born.”, and potential correlates are listed below that.

Methods:

- Please try to justify the use of KINDLE in populations born preterm given the literature in the field around HRQoL measures in individuals born preterm.

As is perhaps to be expected, there are many instruments to measure HRQOL [1, 2], among them, the KINDL. KINDL is a validated multidimensional instrument for assessing HRQOL in children that has been used in a variety of studies, including those studying preterm born children [3, 4, 5], especially in the German-speaking region [3, 6, 7]. It is available in many languages [8] and norm data is available. Thus, it was perfect for the use in our study due to its original validated version in German, and our opportunity to be comparable to other studies in premature children. Using the KINDL allowed us to compare HRQOL to the control population, fullterm siblings, and to the general school-aged population. This comparison would not have been possible with an instrument specific to preterm born children.

[1] Vieira, M.E.B., Linhares, M.B.M. Quality of life of individuals born preterm: a systematic review of assessment approaches. Qual Life Res 25, 2123–2139 (2016). https://doi.org/10.1007/s11136-016-1259-9

[2] Colver A, Jessen C. Measurement of health status and quality of life in

neonatal follow-up studies. Semin Neonatol 2000; 5: 149–157. doi:10.1053/siny.1999.0002

[3] Landsem IP, Handegård BH, Ulvund SE, Kaaresen PI, Rønning JA. Early intervention influences positively quality of life as reported by prematurely born children at age nine and their

parents; a randomized clinical trial. Health Qual Life Outcomes. 2015 Feb 22;13:25. doi: 10.1186/s12955-015-0221-9. PMID: 25888838; PMCID: PMC4343051.

[4] Ulvund, S.E. Early Intervention in Families with Preterm Infants: A Review of Findings from a Randomized Controlled Trial Following Children Up to 9 Years of Age. Children 2022, 9, 474. https://doi.org/10.3390/children9040474

[5] Pérez-Tarazona S, Rueda Esteban S, García-García ML, et al. Respiratory outcomes of "new" bronchopulmonary dysplasia in adolescents: A multicenter study. Pediatric Pulmonology. 2021; 56: 1205–1214. https://doi.org/10.1002/ppul.25226

[6] Stahlmann N, Eisemann N, Thyen U, Herting E, Rapp M. Long-Term Health Outcomes and Health-Related Quality of Life in Adolescents from a Cohort of Extremely Premature Infants Born at Less Than 27 Weeks of Gestation in Northern Germany. Neuropediatrics. 2016 Dec;47(6):388-398. doi: 10.1055/s-0036-1593373. Epub 2016 Oct 4. PMID: 27701681.

[7] Schmitt, J., Arnold, K., Druschke, D. et al. Early comprehensive care of preterm infants—effects on quality of life, childhood development, and healthcare utilization: study protocol for a cohort study linking administrative healthcare data with patient reported primary data. BMC Pediatr 16, 104 (2016). https://doi.org/10.1186/s12887-016-0640-8

[8] https://www.kindl.org/english/questionnaires/language-versions-view-and-download/

• Please justify the use of linear mixed models using random effect for family. I think the use of fixed effects to capture the time-invariant unobserved heterogeneity will also be helpful to show as a sensitivity analysis.

Thank you for this comment. First, we would note that there are differing, sometimes incompatible [9], definitions of fixed and random effects as used in regression model. Here, we use the definitions typical to biostatistics and epidemiology (although a colleague with an economics background disagrees with us on the terminology). In biostatistics and epidemiology, fixed effects are generally used when one wants to make statistical comparisons between levels of the variable (e.g. preterm vs fullterm born). Random effects on the other hand are usually used when making statistical comparisons between levels of the variable is not of interest (e.g. family unit), and when levels of the variable are generally assumed to be a sample

drawn from a larger population of levels. [10] A common use of random effects is for modeling non-independent data (e.g. if participants were sampled on a family level).

In the FLiP study, fullterm born children were selected from siblings of the very preterm born children, and therefore there was no independent selection procedure for these fullterm born children. (Children from the Ciao Corona study do however provide an independent sample of fullterm born children here.) To account for this non-independence, we included family unit as a random effect in the models comparing FLiP very preterm and fullterm born children.

We have added fixed effect only models for all children in FLiP (Supplementary Material Figure S12 and Table S11), and by gestational age (Supplementary Material Figure S13 and Table S12). The results from the fixed effects models are quite similar to those of the random effects models.

[9] Andrew Gelman. "Analysis of variance—why it is more important than ever." The Annals of Statistics, 33(1) 1-53 February 2005. https://doi.org/10.1214/009053604000001048

[10] Gurka, M.J., Kelley, G.A. and Edwards, L.J. (2012), Fixed and random effects models. WIREs Comp Stat, 4: 181-190. https://doi.org/10.1002/wics.201

• This statement requires more details: “Comparisons of FLiP preterm and Ciao Corona control participants were made using linear regression, after 2:1 matching on age in years, sex”; what type of matching? Are you constructing a doubly robust estimation? More details are needed.

Thank you for raising this point. We have rewritten the last sentence of the methods section to read “Nearest neighbor matching using robust rank-based Mahalanobis distance to the Ciao Corona data was performed using the MatchIt package.” No doubly robust estimation was used, but the models did adjust for the matched group using random effects.

Discussion

I think it is important to address the use of KINDLE as an appropriate HRQoL measure to assess HRQoL in preterms.

The sentence “HRQOL was assessed using the validated multidimensional KINDL instrument for children and adolescents.” has been added to the discussion (paragraph on study strengths). See also comments above.

It will be helpful to clearly state the contribution of this study to the literature.

Thank you for this comment. This large study with 2 different control populations and stratified for both gestational age and birthweight give a robust picture of HRQOL in very preterm born children. Beyond the novel classification tree models we have used to identify correlates of HRQOL in this population; our study is one of few that have included respiratory symptoms. To clarify these points, the paragraph on study strengths has been expanded (pg 12).

“Our analysis has several strengths. HRQOL was assessed using the validated multidimensional KINDL instrument for children and adolescents. The analysis used a relatively large registry of very preterm born children in Switzerland and included fullterm born siblings as a control group. Family unit was accounted for in the analysis. The Ciao Corona study provided a school-based random sample of school children in the same geographic region and time period. To account for differing severity in terms of prematurity, we stratified the analysis by gestational age and birthweight. We considered a broad range of possible correlates, including respiratory symptoms, of HRQOL in a classification tree analysis, which has to our knowledge not been performed previously in this population, and allowed us to explore a wide range of possible correlates with HRQOL.”

The 2nd-to-last paragraph of the discussion (pg 13) has also been rewritten in order to put the conclusion in the context of our analysis.

“It is a gift of medicine that children born <32 weeks gestation generally have a HRQOL comparable to fullterm born children . Nevertheless, as observed in this large cohort of very preterm born children, there are children that clearly show compromised HRQOL. Low HRQOL was not restricted to those born prior to 28 weeks of gestational age or less than 1000g birthweight, as seen in our stratified analyses. While an association between HRQOL and older age or chronic health conditions may often be expected and considered plausible, the association with respi ratory symptoms observed in our analysis may be neglected and often not addressed.”

VERSION 2 – REVIEW

REVIEWER NAME	***Corneliu Bolbocean***
REVIEWER AFFILIATION	None disclosed
REVIEWER CONFLICT OF INTEREST	
DATE REVIEW RETURNED	30-Sep-2024

GENERAL COMMENTS	Thank you for addressing my comments.