PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	High body mass index in children with sickle cell disease- a retrospective single-centre audit
AUTHORS	Hall, Rachael; Gardner, Kate; Rees, David; Chakravorty, Subarna

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Eirini Koutoumanou Institution and Country: UCL, UK Competing interests: None
REVIEW RETURNED	30-May-2018

GENERAL COMMENTS	- Could the authors please clarify why they did not use BMI at its original raw numeric format and instead broke it up to 3 levels (low, medium, high)? If BMI was analysed as a numerical variable, there would not be a loss of cases where the group size was small (e.g. low BMI group with 20 subjects or less was excluded from some analysis). Nevertheless, even if the authors persist with the categorical version of BMI, non-parametric techniques can be used to account for small group sizes so there is no waste of collected data. - There is however inconsistency in the report as it stands regarding BMI as the authors swap to BMI centile values for some analysis and report the mean BMI in Table 3. All these choices should be reviewed and the way BMI is analysed should be consistent throughout the paper and/or at least fully justified as to why its format is changing. - How does this specific clinic differ from other clinics in London, UK? Could the authors add a brief comment about this as it would assist in the generalisability of the results, especially as there seems to be a bias towards African and Caribbean ethnicities? I believe this is worth noting in the discussion section too as I am sure there are BMI differences to be accounted for amongst White, African and other children. - The 1990 BMI growth charts were used as opposed to more recent editions of them. Did the authors look into using more up-to-date ones? - Table 5 needs better labelling of the comparisons made and the corrections performed via regression modelling. Are the p-values of the HbSC section corrected or not? Was the low bmi group left out of all comparisons in this table? - Additionally, a p-value of 0.0048 is neither significant nor non-signficant.

	It's an indecisive result that can only lead to an affirmation that further research is needed in the field with possibly larger sample size to be able to get a more definitive answer to this question. All subsequent statements regarding this p-value should be edited to *not* say that it's a significant result. - I do not think the following statement is supported by the results on table 3 or any other results shown in this report "This supports the data suggesting HC can decrease the resting energy expenditure by 8%, by decreasing the severity of anaemia and increasing red cell survival, making more energy available for normal growth (13) (21) (22)." Please amend accordingly. Minor: Please explain all acronyms in the abstract and in the Data Collection section, HsDβ, etc. In the Statistical Analysis section, please add 'linear' next to multiple regression; there is no better place to be specific about the type of regression than this section. At the beginning of the "BMI, clinical and laboratory data" section, please refer to table 4 first followed by table 5 in the 2nd paragraph.

REVIEWER	Reviewer name: Helen Sammons Institution and Country: North Devon District Hospital and University of Nottingham Competing interests: Nil
REVIEW RETURNED	06-Jul-2018

GENERAL COMMENTS	This is an interesting local retrospective case series from an individual centre, from a local audit. It has reasonable number >300 children. It is well written and flows. The methodology is sound. It finds that children with a higher BMI in SS disease have a higher Hb on average. Also the link between BMI and HC use. BMI is not however related to disease severity. I think these are important findings from this single centre and will help generate future hypothesises for exploration. The tables are clear and support the findings.

VERSION 1 – AUTHOR RESPONSE

We outline our changes to the manuscript as per your suggestions below:

As recommended by Dr Koutoumanou:

1. Could the authors please clarify why they did not use BMI at its original raw numeric format and instead broke it up to 3 levels (low, medium, high)?

Answer: Due to age dependency of weight and height in children, BMI has not been conventionally used for estimation of fatness in children, and age-dependent BMI centiles are used instead. The BMI centiles are classified into normal (BMI between 5th and 85th Centile), high (>85th Centile) and low (<5th Centile), based on well-established clinical criteria (Cole TJ Growth monitoring with the British 1990 growth reference. Arch Dis Child 1997;76:47–9). This has been clarified in the 'Methods' section of the manuscript under the sub-heading 'Clinical and laboratory data'.

2. If BMI was analysed as a numerical variable, there would not be a loss of cases where the group size was small (e.g. low BMI group with 20 subjects or less was excluded from some analysis).

Nevertheless, even if the authors persist with the categorical version of BMI, non-parametric techniques can be used to account for small group sizes so there is no waste of collected data.

Answer: We agree with this comment on principle and agree that continuous data may have been more helpful for borderline cases, for example BMI on the 84th centile. However, data were collected and analysed with the primary aim of investigating the role of obesity in disease severity and as such well defined criterion of obesity was used.

3. There is however inconsistency in the report as it stands regarding BMI as the authors swap to BMI centile values for some analysis and report the mean BMI in Table 3. All these choices should be reviewed and the way BMI is analysed should be consistent throughout the paper and/or at least fully justified as to why its format is changing.

Answer : All BMI data apart from the mean BMI of patients on hydroxycarbamide is based on BMI centiles and not raw BMI value. We acknowledge the importance of using BMI centiles for paediatric populations and have removed the raw BMI calculations from the paper.

4 How does this specific clinic differ from other clinics in London, UK? Could the authors add a brief comment about this as it would assist in the generalisability of the results, especially as there seems to be a bias towards African and Caribbean ethnicities? I believe this is worth noting in the discussion section too as I am sure there are BMI differences to be accounted for amongst White, African and other children.

Answer: In our discussion chapter we have highlighted that our data reflects an urban London population only and may not extend to rural populations in the UK. However, sickle cell disease in the UK is predominantly prevalent in people of Afro-Caribbean ethnicity and therefore data pertaining to these ethnicities are applicable to a UK sickle cell population. We have further highlighted that in the 'Discussion' section of the manuscript.

5. The 1990 BMI growth charts were used as opposed to more recent editions of them. Did the authors look into using more up-to-date ones?

Answer: BMI centiles in this study were based on the 1990 growth reference charts, as this is the recommended reference source currently. We have clarified that in the 'Methods' section under 'Clinical and laboratory data' .

6. Table 5 needs better labelling of the comparisons made and the corrections performed via regression modelling. Are the p-values of the HbSC section corrected or not? Was the low bmi group left out of all comparisons in this table

Answer: We documented at the bottom of Table 5 that the comparisons were made using a t test and not by corrections using regression modelling. Regression modelling was not done for the HbSC section. Comparison was made between normal and high BMI only- low BMI was not used in the analysis. This is documented at the end of Table 5.

6. Additionally, a p-value of 0.048 is neither significant nor non-signficant. It's an indecisive result that can only lead to an affirmation that further research is needed in the field with possibly larger sample size to be able to get a more definitive answer to this question. All subsequent statements regarding this p-value should be edited to *not* say that it's a significant result.

Answer: We completely agree and have modified the manuscript to reflect that in the 'Results' section under the paragraph 'BMI, clinical and laboratory data' and in the 'Discussion' section .

7. I do not think the following statement is supported by the results on table 3 or any other results shown in this report “This supports the data suggesting HC can decrease the resting energy expenditure by 8%, by decreasing the severity of anaemia and increasing red cell survival, making more energy available for normal growth (13) (21) (22).” Please amend accordingly.

Answer: We agree with this comment and have amended the statement.

8. Minor:

Please explain all acronyms in the abstract and in the Data Collection section, HsDβ, etc.

In the Statistical Analysis section, please add ‘linear’ next to multiple regression; there is no better place to be specific about the type of regression than this section.

At the beginning of the “BMI, clinical and laboratory data” section, please refer to table 4 first followed by table 5 in the 2nd paragraph.

These suggestions have all been actioned.