Author’s response to reviews

Title: Growth from birth to two years in a cohort of children diagnosed with CF by newborn screening

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Author’s response to reviews:

Dear Editor

Many thanks for the reviewer’s comments. We have addressed each of the points in turn.

Reviewer 1
• Could the authors provide a few more sentences on how the validation and modelling was carried out?
  We have added an additional four sentences at the end of the methods section to explain this further.

• Is the age of diagnosis equal to the age at which treatment was initiated, or is there an additional gap between diagnosis and therapy?
  The age of diagnosis was taken as the date of the first clinic visit or the date of diagnosis of meconium ileus. This is now clarified in the methods section. This was the date that treatment was started in all children. This clarified in the first part of the results section.

• Is there a way to more clearly state that the later the day of life that therapy is initiated, the poorer the growth outcomes? This might then prompt more discussion of justification for earlier reporting of NBS results for earlier initiation of therapy. Is there any evidence from the data that very early diagnosis (even from a positive family history or prenatal testing) with immediate initiation of treatment impacts outcome?

  These are really interesting and important points but unfortunately our data do not give us these answers. The median (range) age of diagnosis was 22 (3-55) days. Most of those who were diagnosed at the later end of this were pancreatic sufficient and so any meaningful comparison is difficult.
Reviewer 2

1. using the annualized value to represent growth status at certain ages could lead to not only the loss of the critical information, but also the false/misleading information.

We agree that all retrospective data of a serial nature is problematic from an analysis perspective e.g. some children will not have been measured at each time point (missing values) and an individual measurement may be subject to some variation. Our solution to this potential problem was to the mean z scores over each year. Whilst it can be argued that this approach lacks granularity, it seeks to minimise the error that would be introduced by calculating rates over shorter periods. Whilst we accept the limitation of using these outcomes we do not think that there was a better alternative. We have acknowledged the limitations more clearly in the discussion section.

2. Figure 1: Please explain what growth outcomes z-score=-1, z-score=0, z-score=1, and z-score=2 stand for. Does z-score=-1 indicate that z-score is exactly equal to -1? What is the clinical relevance of these cutoff values?

We are particularly grateful for your careful proof reading of Figure 1 which we agree is unclear. We have changed the labelling in Figure 1 to show the range the z score outcomes refer to a range.

3. Given the important clinical utility of both weight-for-length and BMI, these two growth indexes need to be evaluated in addition to weight and length.

The reviewer is quite correct in the clinical importance of BMI and weight for height. However, the WHO does not recommend using BMI for age in children under the age of two years and so it was not appropriate for our data. We chose not to use weight for height as it is not an independent variable (calculated using weight and height values). If it was included in the model the interdependence of the variables would have made interpretation problematic. We therefore deliberately chose a priori to only use height and weight to avoid misleading the reader and reduce the risk of introducing error. We have now explained this more clearly in the discussion.

We hope that by addressing all the reviewer’s comments the article can now be accepted for publication.

Kind regards

Yours truly

Dr Francis Gilchrist