

Dear Christa

Sorry for the delay and longwinded answer, but this is a complex issue. We should remember that while we are debating this as Paediatric Endocrinologists, these charts are actually far more commonly used in community / primary care settings, particularly for growth monitoring to assess 'adequate growth and nutrition' of infants and young children.

Hence, in my view, the first step is to adopt/retain the concept of a growth standard that defines optimal growth of young children. Fortunately, Eiholzer et al. does not challenge this, at least for 0-2 years as their paper does not focus on this age range. 2-5 years is a grey zone, as the WHO study was less robust at this age, but the same concept applies and the WHO 2-5 growth data were aligned to their 0-2 year data.

Beyond age 5 years, I have sympathy with arguments in favour of using representative national data. This is because 1) the WHO concept of optimal growth standard has not been extended beyond age 5 years, and 2) the WHO reference for this age is a 'smoothed construct' that even WHO admits does not represent any population. Hence in the UK, we opted for a 'transition' at this age to UK1990 data. My views on this are further described in my commentary cited by Eiholzer et al.

So, whether or not (similarly to UK charts) Swiss charts should transition at age 5 (or 2) years depends on the availability of robust representative national data. The study design and appearance of the Eiholzer et al. reference seems far better than Prader et al. 1989, but that is not the question here. The major limitation of Eiholzer et al. is its lack of national representation:

- 70% were from the Canton of Zurich and 30% from the rest of Switzerland. By comparison, Zurich represents 17.6% of the national population (Ref: Switzerland's population 2016 www.statistics.admin.ch).
- Eiholzer et al. reported reasonable/moderate alignment with North/Central Italy data (Fig. 1) but they did not have access to recent French data, which have very recently been published (Heude et al. attached). I could not find the values, so have visually taken values from Supplementary Figure 5, and it seems that height at age 18 years is lower in Heude et al. vs. Eiholzer et al.: Girls 164 vs. 166.1, Boys 176 vs. 178.6. Hence, it remains a very real question whether or not Eiholzer et al. is representative of Switzerland.

Two further considerations are I think of value:

Firstly, I do not believe that the argument made by Eiholzer et al. relating to better detection of children with growth disorders is convincing, e.g. "*use of the 3rd percentile of the WHO standard and reference curves could lead to missed or delayed diagnoses in European populations (Christesen et al. 2016).*" It is a truism of screening that setting a more inclusive threshold will include more true cases (children with organic short stature) - but such papers rarely test the other key aspect of screening i.e. how many normal children are included and undergo unnecessary referral and investigation, which is inevitably higher. In face of such uncertainty, in public health / clinical epidemiology we find it useful to consider the maxim 'first do no harm'. In clinical practice, this issue is minimised by following the basic rule that the child's height velocity and relationship to parental heights is far more informative than a single percentile value. Following this rule, it should not be any more difficult to identify children with organic disorders among the (possibly genetically) taller children of Zurich.

Note, this does not apply to some thresholds described for eligibility for GH treatment in non-GHD conditions (SGA, idiopathic short stature) where the reference used does have a big impact - but those are societal/economics level arguments.

Secondly, from my experience of being part of the UK assessment of the WHO charts and Chair of the UK scientific committee on maternal and child nutrition, I would caution that frequent changes in national guidance often lead to confusion. Hence, in summary I would vote against a current change to using Eiholzer et al. but this question could be revisited if and when the above significant uncertainties are addressed.

Kind regards, Ken

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