pädiatrie schweiz

Die Fachorganisation der Kinder- und Jugendmedizin

Recommendation of pädiatrie schweiz regarding the request to adapt the current Swiss growth charts[1] based on the findings of the study of Eiholzer et al. 2019[2] by an expert group, convened by pädiatrie schweiz, in which the areas of developmental pediatrics, pediatric gastroenterology, pediatric endocrinology, obesity, public health and school physicians are represented, who weigh the observations resulting from the new Swiss growth data and the advantages and disadvantages of new growth curves in Switzerland

1) Background: Role of Growth Charts

There is a wide debate about the accuracy of using the WHO curves at national level [3] [4]. One argument for the use of national curves is the fact that there are variations in adult height across regions, that are mainly linked to genetic variations [5] [6]. However, one important conclusion of the systematic review on growth monitoring is: "*From studies that only compared population growth data with WHO or other growth charts, which chart will be better for growth monitoring is not obvious, because performance depends on the goal, measurement, and age group of children studied. Therefore, whether national growth charts should be replaced greatly depends on the main objective of the user.*"[5].

a. **Use of growth charts as reference to describe the growth of a population (descriptive/reference growth charts)**[7] [8]
Basis is the statistical summary of anthropometric data of a population or a representative sample of it. Thus, the reference chart represents the health status in terms of anthropometric development by age and sex of a population at time of data collection. Environmental (e.g. exposure to endocrine disrupting agents), nutritional (e.g., starving), socio-economic, behavioral (e.g., lack of physical activity) and macrosystemic factors (e.g., a health system that enables survival of a large number of children with genetic or chronic conditions) might affect health and growth. Thus, reference curves can be used to compare the health status within populations and - provided using the same reference chart - also internationally and across time. However, they are inappropriate to define growth targets.

b. **Use of growth charts for growth monitoring of individual children, as a "screening tool"**[9] [5] **for early identification of variations indicating underlying serious conditions amenable to prevention/treatment.** For this purpose prescriptive/ standard growth charts are needed reflecting how healthy children should grow. WHO has developed such standard growth charts [10] [11] that are derived from individuals with optimal health. The role of prescriptive growth charts gets more complicated when they are used as an indicator of health care coverage, e.g. that certain therapies might only be covered by health insurances

when exact cut-offs of deviations from growth curves are reached. However, in clinical practice in Switzerland diagnoses, decisions for referral as well as interventions are always based on several parameters and clinical findings, assessment of the growth curve being just one out of those. Thus, growth monitoring is not a screening instrument according to classical definitions[12]. However if used so – even partially -, it should be in line with the principles of screening[13].

2) Detailed Evaluation of the Study of Eiholzer U, et al.[2]

Summary of the study

Funding: Foundation Growth Puberty Adolescence, Zürich (no further details are given). *Die Stiftung Wachstum, Pubertät und Adoleszenz ist eine am 29.12.1992 gegründete Schweizer Stiftung mit Domizil in 8002 Zürich. Sie untersteht folgender Aufsichtsbehörde: BVG- und Stiftungsaufsicht des Kantons Zürich (BVS) (CHE-239.560.630)*
The authors reported no possible conflict of interest

Ethics: local ethics committee was not within its jurisdiction to evaluate the project, but stated that the conduct of this study was ethically harmless and involved no risk and/or a low burden for the participants

a. Subjects
   1. Prospective:
      - _Cross-sectional data from 34 paediatric practices and 25 educational institutions
      - _Central and eastern parts of Switzerland between the lakes of Lucerne and Constance : around 70% from the Canton of Zurich, 30% from the Canton of Lucerne
      - _Children with growth problems were excluded
   2. Retrospective
      - _Birth data registered 2012-2016
      - _Zurich school medical service 2017
      - _Swiss military recruits 2013-2017

   Total: 16,540 boys and 13,601 girls. Age groups per year included 303–1726 cases.
   Proportion: prospective – retrospective values was in boys 1.3:1
   Proportion: prospective – retrospective values was in girls 1.8:1
   Variations in proportions prospective – retrospective in between ages
   Parent nationality and residential postcode were recorded

b. Growth measurements
   In the prospective cohort, paediatricians and 2 medical staff members who made the school visits trained in their own practice by one person (the first author)
   - _Each stadiometer used in paediatric practice was checked, calibrated and adjusted at the beginning of the study
   - _Body weight was measured on a professional medical scale
   - _Only one measurement was done
   - _No details for methods of the retrospective values are given

c. Calculation of percentile curves:
   - LMS method
   - Height values lying outside the interval [P25 – 4.5(P50 – P25); P75þ4.5(P75 – P50)] and weight values lying outside the interval [P25 – 5(P50 – P25);

P75þ9(P75 – P50)] were defined as outliers and the respective cases were excluded.
- BMI: the mean height-for-age and BMI-for-age SDS of children whose parents were: (1) either Swiss or belonging to the most important immigrant groups originating from (2) Germany, Austria, France and countries within the Scandinavian or Benelux regions as well as (3) Italy, Portugal or Spain or (4) the Balkan region were compared

d. Main results:
The study provides sex specific curves
- Height as compared with WHO standards[14] and references [11]
  - A. 50% percentile
    Age 0-2 years: Median length in boys and girls similar to WHO
    Age 2-5 years: small differences (max +0.3 SDS in boys, SDS not reported for girls, seems equally small (1 cm difference) on figure 1 in the article
    Age 5-12: larger differences, max in boys + 3.4 cm (0.6 SDS) max in girls <3 cm (2.9?) (0.5 SDS)
    Age 12-16: moderate to large differences (+ 3 cm in boys, + 2 cm in girls)
    Age 16-18 and final height: moderate differences (+ 2 cm in boys, 2.9 cm in girls)
    Final height: + 2 cm in boys, +3.7 cm in girls
  - B. 3rd percentile:
    Age 0-5 years: small differences (0-1.8 cm) in boys and girls
    Age 6-12 years. + 4 cm in boys, + 3 cm in girls
    Final height: + 2.9 cm in boys, + 3.7 cm in girls
- BMI as compared with WHO standards and references
  - A. The WHO median BMI for age curves for boys and girls are similar to the respective median curves.
  - B. More pronounced differences are found concerning the 97th percentile:
    - in boys 12-14 years +3 kg/m2 (+8kg in boys at length P.50)
    - In girls > 9 years +1 - +1.3 kg/m2 (+3 kg in 12 year old girl at length P.50)
  - C. If obesity and overweight are defined as proposed by the IOTF (Cole 2000)[26], namely applying the percentiles starting at BMI 30 and 25 kg/m2, respectively, throughout childhood, this approach results in a similar prevalence of obesity and overweight as actually found by WHO /Swiss charts. Hence, 17-20% of children would be overweight (approximately above P.80 of Eiholzer charts) and 4-6 % obese (approximately above P.97 of Eiholzer charts).D) Differences according to parental origin are observed.

3) Comments

a. General considerations
We consider the study to be very good scientifically and methodologically, in particular statistically adequate.
The study aim of establishing updated contemporary height, weight- and BMI-for-age reference curves for monitoring the growth of children in Switzerland is acknowledged.
The study by Urs Eiholzer is a first step in this direction.

Some general limitations exist:

- 62 pediatricians and a number of school staff did the prospective measurements which could lead to heterogeneous data acquisition
- No plan for regular calibration of the stadiometers is mentioned
- Height/length was not measured in triplicate (with arithmetic mean)
- 70% were from the Canton of Zurich and 30% from the rest of Switzerland. By comparison, Zurich represents only 17.6% of the national population (Ref: Switzerland's population 2016 www.statistics.admin.ch).
- The relevant data of children between 5-16 years (see specific comments on height) were collected in the Zurich and Lucerne region only
- Hence, it is questioned whether or not the study of Eiholzer et al. is representative for Switzerland.
- The funding of this study is not completely provided (who founds the foundation?) and potential conflict of interest might exist.
- As this is not a longitudinal study, no growth velocity assessments could be done.

b. Specific considerations:

Length/Height :
We will differentiate the discussion between 3 age groups:

A. 0-2 years: we retain the concept of a growth standard that defines optimal growth of young children as provided by the WHO (longitudinal data available). The data of Eiholzer et al. do not seem to challenge the WHO data in this age group.
B. 2-5 years: as the WHO study was less robust at this age, it is interesting to see that the WHO 2-5 growth data were closely aligned to the data of Eiholzer et al.
    - For height between 0 and 5 years of age, it is interesting and relevant to observe only small differences in height and weight between the data provided by Eiholzer and the WHO data. This supports the current use of the standard WHO curves in these age groups, as it is done in several other countries.
C. Beyond age 5 years, we agree with Eiholzer et al. that their data differ significantly from the historical study by Prader et al. (1988) and the WHO reference data.

Comment regarding the use of WHO-Growth standards and references: While accepting limitations of any growth chart including the WHO charts, it is important to remember that Eiholzer et al produced a descriptive (reference) and not a prescriptive (standard) chart as the one established by the WHO. Descriptive studies aim to accurately represent the population of a country or region From a public health point of view, the approach of the WHO with "standard curves" instead of "reference curves" is probably the best, as standard curves allow monitoring of time trends and across country comparisons. We also know that the WHO reference curves have considerable weaknesses and that there are no optimal "standard curves" that cover all public health and clinical needs. Given the increasing heterogeneity in population globally, only equally heterogeneous growth data could alleviate this weakness.

Detection of target conditions: While the choice to use descriptive charts to describe actual population growth is acceptable, we must remember that these charts are not targeted to identify any specific condition like growth hormone deficiency, Turner syndrome, coeliac disease, cystic fibrosis, renal tubular acidosis or small for gestational age. Screening for growth disorders like celiac disease or Turner syndrome does not rely on a single measurement. For the example of celiac disease, the study by Saari et al.[15] demonstrated that the mean height SDS at diagnosis of celiac disease was in the normal range. Furthermore, the study showed that the best growth screening accuracy

was longitudinally monitored growth rather than via one-off measurements. Population-based screening for coeliac disease only performed well when several parameters including height standard deviation score, BMI SDS, target height SDS, change in height SDS across time, and change in BMI SDS across time) were used simultaneously. For Turner syndrome, the same group showed that height distance from target height needs to be included in the screening for patients [16].

As such, the statement of Eiholzer et al. that the use of a more recent descriptive chart is "of clinical significant relevance" would be limited to the situation of a clinician considering only one measurement for clinical reasoning which is not good clinical practice. In fact, which chart will eventually be better for growth monitoring is not obvious, because performance depends on the goal, measurement, and age group of children studied[5], as well as sensitivity, specificity and positive and negative predictive value for any given health condition.

It is of course true that by using the ideal population growth chart for a child of the same origin, a given threshold will include more true cases (children with organic short stature). In this case, children with "taller" origins might theoretically be diagnosed later, but children from "shorter" origin would unnecessarily fall under the standards and could undergo unnecessary and costly exams. We feel that by generalizing the data of Eiholzer et al. to all children living in Switzerland, too many children would fall into this last category.

Puberty
A tendency of earlier puberty, which affects growth at given ages, has been observed and has been explained by the increasing prevalence of obesity[17].Thus, pubertal staging needs to be included in any growth evaluation.

Swiss population specificities:
Height and weight are genetically determined and subject to environmental factors. Hundreds of common genetic variants have been described. Height variation across geographic regions is well known, and expected in the 3 regions of Switzerland:
The Swiss population historically derives from an amalgamation of Gallic or Gallo-Roman, Alemannic and Rhaetic background. Modern Switzerland is characterized by the integration of a multiethnic and multilingual population. A recent study showed a **divergence and predicted genetic divergence in height and body mass index (BMI) and height across 14 European nations including Swiss Data from the Colaus study (Lausanne population)**[6]**.** In this study, the observed "Swiss" height was closer to the Southern /Italian height then "Nordic" height, probably due to the lack of data from German speaking Cantons.

Eiholzer et al. reported reasonable/moderate alignment with North/Central Italy data but they did not have access to recent French data[18]: Heude et al. included 1'458'468 height and 1'690'340 weight measurements from 238'102 children living in France. The newly generated French modelled curves were much closer to the WHO curves than the existing French growth charts. The new growth charts were closer to the WHO growth charts but differed at some ages, as illustrated by a Z score evolution towards zero of the WHO median values based on the new growth charts[18].

These findings differ from the data of Eiholzer et al. (50th height-for-age percentile) where children where more significantly "taller" than the WHO reference. Eiholzer et al. correctly refer to German and Austrian populations when comparing the Zurich/Lucerne population studied to find close correlations.

When comparing the final height at age 18 years with the data of Eiholzer et al., we find (Heude et al. vs. Eiholzer et al.): Girls 164 vs. 166.1cm, Boys 176 vs. 178.6.cm.

We further have to consider the fact that the distribution of foreign residents in Switzerland differs from one region to the other (https://www.atlas.bfs.admin.ch/maps/13/de/14477_11705_89_70/23071.html). This will affect growth deviation from standard/percentiles for these populations.

In summary, height variation across geographic regions is well known, and, thus, is expected in the 3 language regions of Switzerland. Therefore, we feel that the data provided by Eiholzer et al. are not quite representative for all Swiss regions. Thus, complementary data collected in different regions (notably the Ticino and the Romandie) should be obtained before labeling the data as "Swiss reference".

Parameters of growth assessment:
It is well known that growth assessments are never made solely on one single parameter like a growthchart, as all have their limitations. Internationally validated clinical decision rules to define abnormal growth never rely on one single parameter like the standardized length, but include the age of the patient, birthweight or length, the presence of dysmorphic features, the distance to target height, and height velocity or height deflection per time interval[5]. As long as the findings from the growth chart are placed within the context of the greater clinical picture for each child, no children should be harmed irrespective of the growth chart used. Ultimately, clinical decision rules can only help to make decisions and should not replace expertise or clinical perceptions.

We remember that absolute indications for specific growth retardation include[19]
- Current size <-3 standard deviations for age and sex.
- Current size <-1.5 standard deviations below target size
- Growth curve > 2 percentile crossover
- Growth rate <-1.5 standard deviations for age and sex

Weight / BMI
In contrast to height, genetic differentiation in BMI is more masked by environmental differences across Europe. We saw with interest the similarity of the median BMI for age curves for boys and girls shown by the present study by Eiholzer et al. There is a difference in the higher percentiles.

Eiholzer et al. included all children in their reference data (including those with obesity), whereas the WHO sets a priori exclusion criteria. This choice is debatable. The data of Eiholzer et al. suggest that median BMI is increasing as compared to the historical Prader et al. study. This has been observed in many countries and is a matter of public health concern. Adapting reference data with contemporary data could "normalize" overweight/obesity and prevent affected children from treatment options, and therefore worsen the actual overweight/obesity epidemic inducing costly public health consequences.

Knowing that currently about 17.3% of Swiss school-aged children are overweight[20] and that comorbidities increase with increasing BMI [23 24 25], we argue against the use of the 90th percentile of the proposed new growth curves to define overweight, because we would not be able to adequately treat comorbidities in children with relevant elevation of BMI. As an example: The prevalence of overweight and obesity for boys would be 10% with the proposed new proposed growth charts, while being 16.5% with IOTF[26] and WHO charts.

For weight and BMI, in line with current international recommendations, we suggest continuing to use the WHO BMI charts, to protect our children from not being advised to take preventive measures early for a healthy future. The implementation of the IOTF[26] definition for overweight and obesity could represent a valid alternative.

In addition, we do not feel that the comparison of BMI rates between parental origins should have been analyzed as done by Eiholzer et al., as the present study was not aimed nor powered to study the very complex interactions between socioeconomic and environmental factors, and body weight. Although it has been shown in Swiss school-age[20] and obese children[21] that the prevalence of overweight is higher in those with specific migration backgrounds (with hints indicating even a more important impact of SES than migration background on prevalence of overweight)[22], it feels dangerous to establish simplistic associations without proper statistical methods. Without exploring all contributing socioeconomic factors, we therefore reject the assumption that the single factor "no Swiss parental origin" could be a contributing "environmental" factor for overweight or obesity.

4) Summary of Recommendations

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- recommends to not change the current growth charts at the present moment. A change to new growth curves would ideally require the new curves to
  - be nationally representative
  - include all growth parameters from the same study sample so that e.g. the influence of weight on growth and pubertal development could be determined.
  - include (especially beyond the age of 2 years) longitudinal data in order to allow for growth velocity assessments from all regions.
  - be nationally and internationally comparable

- acknowledges the need to evaluate the necessity of an update of national growth charts. The study of Eiholzer et al. is a first contribution towards that aim.

A change to new growth charts would imply a previous analysis of the expected impact on the identification of height, weight/BMI classifications (in terms of sensitivity, specificity, positive predictive and negative predictive values) as well as on the economical and human costs incurring from "false negative" and "false positive" classifications as it is usual with any definitions of cut-offs of screening.

- further recommends to continue the current practice of placing growth chart cut-offs into a greater clinical picture in order to prevent harm from children by either under- or overdiagnosis

- recommends to the Federal Office of Health and Swiss Health Promotion to initiate a national study with the following goals:
  Assessment of the performance of the current growth charts in order to define the need of developing new growth charts and if necessary to develop new growth charts that fulfill the above mentioned criteria, specifically the representativeness, by including children living in the different cultural and geographical regions of Switzerland and answer the following questions:
  - Do we need national descriptive and prescriptive growth charts?
  - What is the impact of overweight and obesity on the growth patterns
  - Could the extrapolated cut-offs of adult BMI that are relevant for health (overweight 25kg/m2) and obesity 30kg/m2) be used for clinical decision-making in childhood at the individual level, as proposed by the IOTF definition of overweight and obesity[26]?

  For the development of descriptive reference charts we recommend to include existing data from the periodic BMI studies in children, adolescents (e.g., by Herter-Aeberli and Zimmermann[27]) and from the BMI Monitoring of school health services by Swiss health Promotion[28] [22]).

In addition, we would recommend to explore the opportunity to use a “big-data approach”[18] with routinely collected data in primary care, e.g., by promoting and evaluating the digital Child Health Booklet.

- And finally, we would recommend the initiation of a national child cohort in order to not only answer the question of growth charts, but also to respond to the many unanswered questions in child and adolescent health and health care.

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