The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e3528–e3529
https://doi.org/10.1210/clinem/dgac243
Advance access publication 18 April 2022
Commentary

The Beauty of Age-dependent Standardization in Pediatric Endocrine Research and Practice

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Childhood consists of developmental periods during which the endocrine system develops and matures. For instance, reproductive endocrine organs are active during minipuberty and puberty and dormant between these 2 key periods (1). Endocrine function during these developmental periods correlates with adult health, as illustrated by a recent study that showed that testosterone levels during the minipuberty correlated with semen quality some 20 years later among healthy male subjects (2). It is likely that these developmental periods shape the adult endocrine function and health. It is also conceivable that interactions between various organ systems of the endocrine system may take place during these developmental windows and participate in the programming of the long-term health.

However, the study of these interactions between endocrine organ systems as well as childhood health is complicated by differences in scale between biomarkers and the substantial age-dependent variability. The latter challenge is also faced in clinical pediatric endocrine practice, in which the reference ranges are often given for partitioned age groups such as for subjects aged 3 to 5.99 years and 6 to 8.99 years because more narrow intervals would not satisfy the Clinical and Laboratory Standards Institute guidelines of sample size (3). Such reference intervals do not catch the subtle changes within each partition and the interpretation of results is less certain at both ends of the partition in which a substantial change is expected to take place overnight when a subject moves from 1 partition to the next.

During recent years, the challenge of age-dependent variability has been addressed by reference curve modeling techniques such as LMS method and GAMLSS (generalized additive models for location size and scale) (4, 5). These approaches model the normal range of a biomarker on age as a continuous variable and produce smooth age-dependent reference curves. Furthermore, values can be converted to age-adjusted *Z*-scores that describe the departure from the modelled population average relative to the age-dependent standard deviation of the population. Very recently, reference values were published for serum IGF-1 and reproductive hormones during the minipuberty of infancy and puberty (1, 6, 7). They should prove to be very helpful for clinicians who face the challenge of evaluating the endocrine system while it is in flux.

In addition, *Z*-scores can be leveraged further in research. Busch et al modeled reproductive hormones during minipuberty and Madsen et al modeled testicular or breast tissue volume and serum concentrations of several steroid hormones and growth factors during childhood and puberty (1, 7). They both standardized these endocrine parameters on age and studied correlations between various markers in a way that is not biased by differences in the scale between the markers. Madsen et al found a correlation between body mass index and testicular or breast tissue volume, which fits with an earlier onset of puberty among the overweight and obese subjects (7). Busch et al found evidence for a negative correlation between FSH and anti-Müllerian hormone, which suggests a negative feedback (1). Unlike in adulthood, testosterone and anti-Müllerian hormone did not correlate, which illustrates that the effects of intratesticular testosterone are not relayed to Sertoli cells because the androgen receptor is still missing in Sertoli cells.

Busch et al also analyzed the shape of a typical longitudinal hormone profiles during minipuberty by fitting random coefficient spline models and noticed that the Leydig cell-derived hormones peaked earlier than their Sertoli cell-derived counterparts (1). GAMLSS modelling would be limited for this objective because the shape of the longitudinal hormone profiles of individuals may differ from the average GAMLSS curve during these developmental periods if there is interindividual variability in their timing. For instance, if a peak in a hormone level occurs in individual subjects with variable timing, the shape of the peak in the average GAMLSS curve is flatter than in each subject.

Finally, Madsen et al completed their interesting study by using their age-dependent *Z*-scores in unsupervised learning analyses to assess whether overweight and underweight subjects cluster and differ based on their reproductive

Received: 12 April 2022. **Editorial Decision:** 13 April 2022. **Corrected and Typeset:** 6 May 2022

phenotype (7). They showed that, unsurprisingly, variability between groups was seen in serum lipids (triglyceride and high-density lipoprotein cholesterol), leptin, SHBG, and adiponectin as well as gonadal volume. Furthermore, their full model could distinguish the groups with an impressive accuracy of almost 95%, suggesting that their endocrine profiles clearly differed.

The somewhat unsurprising findings in the well-described field of overweight and obesity demonstrate that their novel approach itself is valid. However, their approach might produce novel insights for several phenotypes that are not equally well described. For instance, subjects characterized by some other phenotype might fall into smaller clusters, perhaps different endotypes that are driven to the same phenotype by distinct biological mechanisms as exemplified by subjects with type 1 diabetes (8). These phenotypes, or possible endotypes, might be visible only during specific windows of development such as minipuberty.

These 2 recent studies have done the field of pediatric endocrinology a great service by providing a blueprint for future analyses, Madsen et al by even sharing their statistical analysis workflow (7). As we learn more and more how early development determines adult health, such approaches should enable analyses of versatile connections in the endocrine system and between organ systems during critical developmental periods.

Disclosures

The authors have nothing to declare.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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