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Estimating peak height velocity in individuals: a response to Cole (2020)

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Choosing a statistical methodology for modelling human growth is an important decision for researchers and clinicians alike. In Boeyer et al. (2020), we presented three common approaches for modelling childhood and adolescent growth (i.e. Natural Cubic Splines, SuperImposition by Translation and Rotation (SITAR), and Fifth Order Polynomials) with the primary aim to elucidate the advantages and disadvantages of each methodology. In a recent Letter to the Editor, Cole (2020) challenged two specific aspects of this work, including: (1) interpretations related to the derived “population average” and individual-level random effects in the SITAR methodology, and (2) our conclusions regarding the use of the polynomial methodology in paediatric clinical practice.

Cole (2020) objects to our interpretation of the “population average” derived from the SITAR methodology, which we defined in our publication as the single curve derived from the data of all individuals combined. This definition is consistent with the documentation for the `sitar()` function, which states that “sitar is a methodology that summarises a set of growth curves with a mean growth curve as a regression spline.” Given this language, the regression curve applied is approximating the mean or, using our terminology, “population” average trajectory.

Cole (2020) also claims that Table 1 in Boeyer et al. (2020) “confirms that the SITAR mean curve is unbiased,” because the values for PHV and aPHV derived from the “mean” or population average curve are the same as the mean estimate for all individuals included in our analyses. It is true that the average values we report for PHV and aPHV at both the population and individual level are not statistically different, but this specific comparison does not indicate the lack of “bias” within this methodology; instead, it highlights its shape-invariant structure. To properly assess statistical bias, a cross-validation analysis is needed. In Boeyer et al. (2020), we performed a leave-one-out cross-validation analysis for each of

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the three statistical methodologies assessed. We agree that when employed on a large longitudinal sample, the SITAR methodology exhibits the “‘smallest overall’ bias,” which we note in the Discussion Section (Page 443, Line 9) of Boeyer et al. (2020).

We agree with Cole (2020) that the population average curve derived from the polynomial and natural cubic spline methodologies does not account for longitudinal data from a single individual unless one employs a multilevel approach. We note in Boeyer et al. (2020), that using estimates of PHV or aPHV derived from the population average curve often results in an underestimation of estimates, a type of bias. Boeyer et al. (2020) also mention that the systemic underestimation observed in such a methodological approach is well known (see Statistical Methods Section, Page 436, Line 24 and Conclusion Section, Page 443, Line 3) and also cite both Merrell (1931) and Cole et al. (2008).

One particular quote that Cole (2020) uses to question our work was incomplete and therefore out of context. The complete quote from Boeyer et al. (2020) was as follows, “the size, tempo, and velocity parameters derived from SITAR describe each individual’s deviation from the population average (i.e. fixed effects), but do not provide individual estimates of PHV and aPHV that can be assessed without additional data extraction and calculation.” By providing only the beginning of this sentence in his Letter to the Editor, Cole (2020) characterises this statement as “factually incorrect” when our complete statement is in fact true. The `ranef()` function returns only the deviation of each individual estimate from the population average and not individual-specific estimates of PHV or aPHV without additional calculations. Thus, the `getaphv()` function in the `iapvbs` package developed by Cao et al. (2018) was used instead to obtain individual estimates for both PHV and aPHV with only a single additional line of code. In addition, Cole points out that the deviations for each individual from the population average are reported as “random effects (not fixed effects).” We agree. Our reference to fixed effects in the partial quote provided by Cole (2020) was for the population average trajectory, not an individual trajectory. Just a few sentences prior to the quote (SITAR Modelling Section; Page 436, Line 4), we note “estimates for an individual’s growth are returned as deviations from the population average through three random effects, which capture differences in the size, tempo, and velocity of the growth trajectory.”

In Boeyer et al. (2020), we provide an objective comparison of three statistical methodologies, including a discussion of the advantages and disadvantages of each based on a variety of clinical and research scenarios (see Table 2 in Boeyer et al. 2020). We note that each methodology has a place in the field of human growth. Regarding the SITAR methodology specifically, we agree with Cole (2020) in that this approach is less biased than the other two methodologies tested. However, there is no *a priori* reason to assume that individual growth trajectory shape would be identical across an entire population, as mentioned by Cole et al. (2016), necessitating the use of a shape invariant methodology approach. This observation is particularly true in paediatric clinical practice where children are being treated for skeletal growth and developmental disorders such that growth may not follow the population average trajectory derived from a reference sample. Given limited, irregular, shape variant growth that would be observed in paediatric clinical practice, we felt

that, in these situations, the advantages of the polynomial methodology outweighed those provided by either other methodology assessed.

The prediction of future growth is complex and has been recognised as important to our discipline for over a century. This was not a goal of Boeyer et al. (2020). Growth models based on dense longitudinal data including both boys and girls are most appropriate for developing reference models for future growth prediction. If incomplete data are used, inaccurate predictions may follow. The use of any of the methodological approaches outlined in Boeyer et al. (2020) will not be applicable in the prediction of future growth in paediatric clinical practice until the advantages, disadvantages, and biases are well characterised using a dense longitudinal sample where the complete growth trajectory is known. We leveraged data from hundreds of children to compare different growth modelling methodologies and identify how each could influence interpretations of participant-specific growth trajectories. As included in Boeyer et al. (2020), we note that the analyses represent “an important first step” (Discussion Section, Page 443, Line 39) towards the development of patient-specific estimates that may prove useful in paediatric clinical practice. We also provide a description of the way in which the data derived in Boeyer et al. (2020) could be used and purposefully excluded the prediction of future milestones, which was described as a future direction.

In conclusion, Boeyer et al. (2020) provided a comparison of three statistical methodologies commonly employed for longitudinal assessments of growth. The data utilised in our article were not simulated, but rather actual height measurements taken on a biannual basis in hundreds of children. Complete data sets were used for analyses from each modelling methodology so that resulting parameter estimates could be effectively compared. The analytical methods applied to growth trajectories will continue to be an important part of human growth assessments, regardless of whether they are applied to longitudinal data aimed at population-based comparisons or for a single patient; thus, interpretations should be based on objective knowledge of the advantages and disadvantages of available modelling methodologies.

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