HEALTHY BIRTH, GROWTH & DEVELOPMENT

Primary Microcephaly: Do All Roads Lead to Rome?

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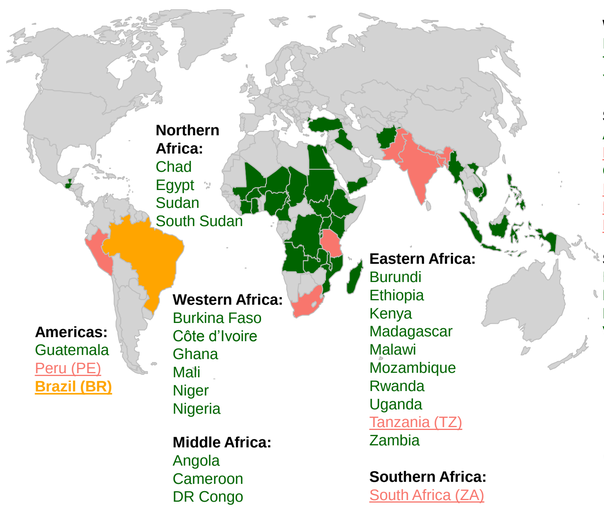
Objectives

- Symmetric intrauterine growth restriction has a growth pattern where all biometric measurements are affected to the same degree.
- Similarly growth after birth is expected to be symmetrical.
- The objectives of this study were:

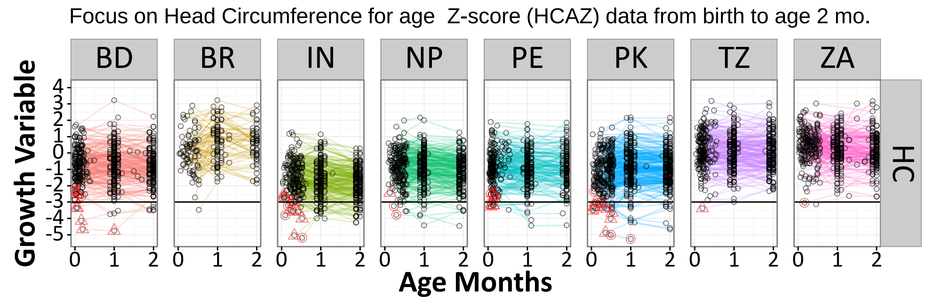
(1) To determine the joint probability distributions of growth parameters describing Weight/Length and Head Circumference (WT/LEN/HC) from age 0 to 24 mo, and

(2) To study symmetry across the 3 growth measures to provide useful guidance to Zika clinicians and researchers on measurements of individuals with a normal/mild-to-moderate/small head relative to other anthropometric measures.



Countries:
- High burden of stunting: **dark green**
- Contributing to this analysis: **red**
- **Recent outbreak of microcephaly: orange**

HCAZ: Head Circumference for Age Z-score
HAZ: Length/Height for Age Z-score



Bivariate density 3D and contour of HAZ and HCAZ (India)

Proposed microcephaly detection criteria

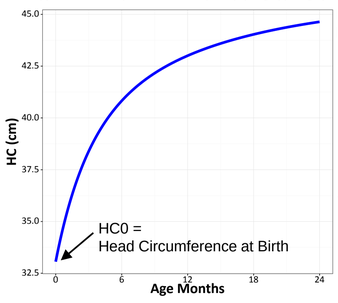
- PAHO preliminary guidelines[1]: HCAZ < -2, which corresponds to term birth HC < 31.9 cm for boys and < 31.5 cm for girls (red circles boys, red triangles girls).
- Fenton curves, where microcephaly equals HCAZ < -3 for age and gender[2] (Horizontal line ———).
- Proportionality criteria, where microcephaly equals a HC less than ((height/2)+ 10) ± 2.[2,3]

Hypothesis:

Difference between HCAZ and HAZ determines disproportionate sub-population ?

Model Equations for Head Circumference, Length and Weight (HC illustrated)

HC(t) = HCinf - (HCinf - HC0)*exp(-Kgr(t)*Age)

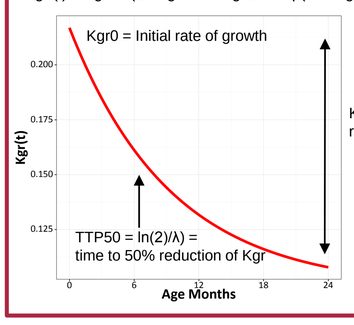


Hcinf =
Head Circumference Asymptote

Kgr(t) is the growth rate that varies over time as per the equation below.

Random effects added as:
HCinf = exp(tvlnHCinf + nHCinf))
Where nHCinf is the random effect associated with HCinf.
nHCinf is assumed to have a mean of 0 and a variance Ω HCinf.

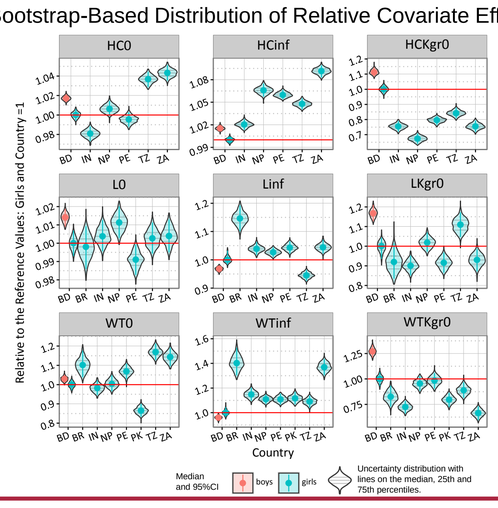
Kgr (t) = Kgr0 * (1 - Kgrdec + Kgrdec*exp(- λ * Age))



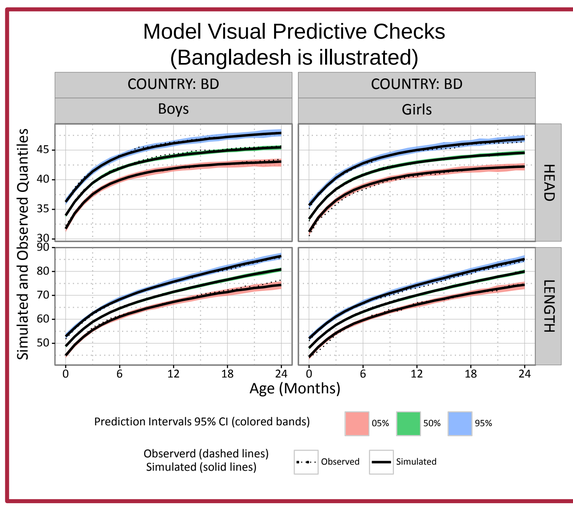
Kgrdec = Asymptotic fractional reduction of Kgr0

Similar parameters names in the model were differentiated by adding HC ,WT or L as a prefix.

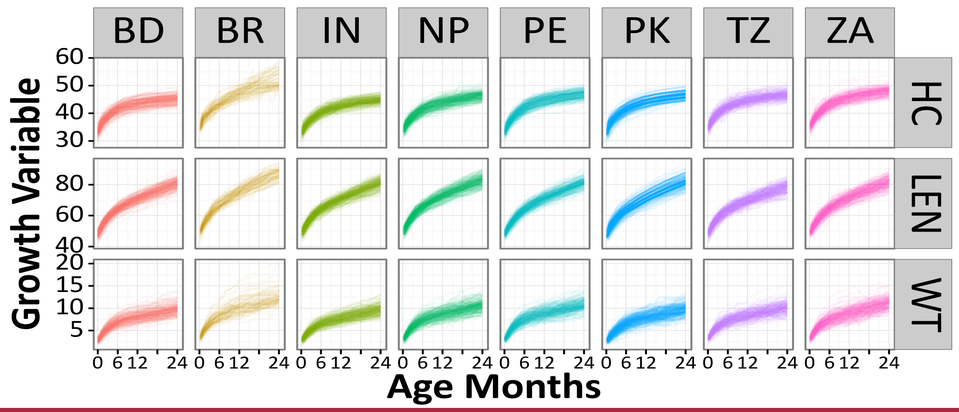
Bootstrap-Based Distribution of Relative Covariate Effects



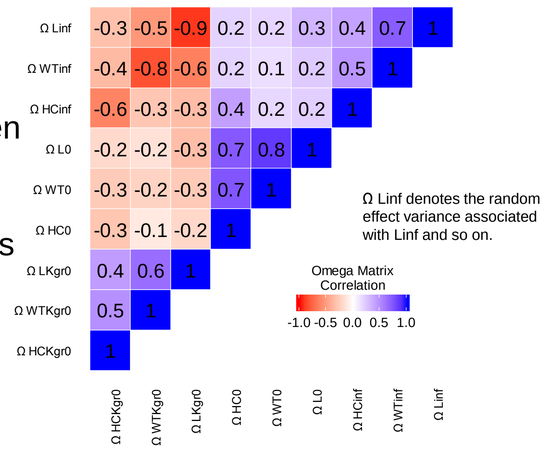
Model Visual Predictive Checks
(Bangladesh is illustrated)



An overview of the data used in the modeling



Correlation matrix between growth parameters random effects ordered by clustering distance



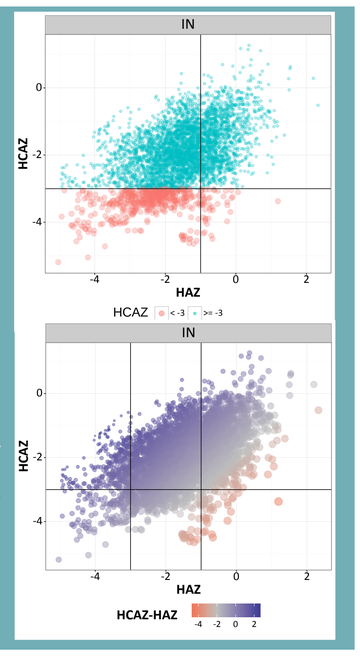
Methods

- Joint parametric nonlinear mixed effects (NLME) model built for WT/LEN/HC.
- Several parametric models tested such as exponential growth with and without decelerating growth rate.
- Key element: to determine the potential correlations between various growth outcomes WT/LEN/HC.
- Limited covariates testing performed including country site, sex, and socioeconomic factors.
- Model fitted using QRPEM fitting engine in Phoenix NLME parallelized on 20 cores.
- Model goodness-of-it assessed using graphical tools and visual predictive checks (VPC) .
- Parameter uncertainty obtained from bootstrap resampling over Linux Torque Grid on Global Health Analytics Platform (ghap.io).

R packages and Shiny Apps used to streamline modeling:
- Graphical quick exploration: https://pharmacometrics.shinyapps.io/ggplotwithyourdata/
- Hbgd https://github.com/hafen/hbgd to quickly compute z-scores, velocity, statistics on growth curves.
- Trelliscope http://tessera.io/docs-trelliscope/
- data.table processing up to 100 M rows of simulation data
- Dplyr/ggplot/tidyr to process medium-sized data sets
- FACE to estimate high-dimensional correlation matrices
- Rworldmap to graph world map with custom projection
- Markdown and knitr to automate outputs and reports

Results

- Joint nonlinear deceleration model for WT/LEN/HC best fit the data (115 060 observations from 1568 subjects, 71 missing) with full random effects variance-covariance matrix.
- Between-subject variability: range, 50% (weight rate of growth) to 10% (length at 0 mo).
- Country and sex kept in the model.
- Parameter uncertainty < 30%.
- Model accurately simulated correlated longitudinal data of WT/LEN/HC from 0-24 months from (1 to 97 percentiles).
- Model accurately predicted growth trajectories of HC conditional on WT and LEN.
- We propose to fit the current model on longitudinal data to determine conditional HCAZ/HAZ and then HCAZ-HAZ can be used as a potential predictor of disproportionate HC/LCM.
- Taking into account HCAZ without any other growth variable is not sensitive.
- Jointly taking into account HCAZ and HAZ helps in flagging disproportionate growth.



Conclusions

- Results address key aspect of characterizing WT/LEN/HC relations and predicting their evolution over time for a specific child, not just the population.
- Potential application of this model includes individualized bivariate or trivariate growth trajectories for early detection of serious conditions such as stunting and microcephaly.
- Identifying disproportionate subpopulation for further study and intervention should be validated against collected microcephaly data.

Acknowledgment

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References

1. Preliminary guidelines for the surveillance of microcephaly in newborns in settings with risk of Zika virus circulation. Pan American Health Organization Web site. http://iris.paho.org/xmlui/handle/123456789/18601. Accessed May 19, 2016.
2. Soares de Araújo JS, et al. Microcephaly in northeast Brazil: a review of 16 208 births between 2012 and 2015. *Bull World Health Organ.* E-pub: 4 Feb 2016. doi:http://dx.doi.org/10.2471/BLT.16.170639
3. Geraedts EJ et al. Association between head circumference and body size. *Horm Res Paediatr.* 2011;75(3):213-219.

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