HEALTHY BIRTH, GROWTH & DEVELOPMENT

Primary Microcephaly: Do All Roads Lead to Rome?

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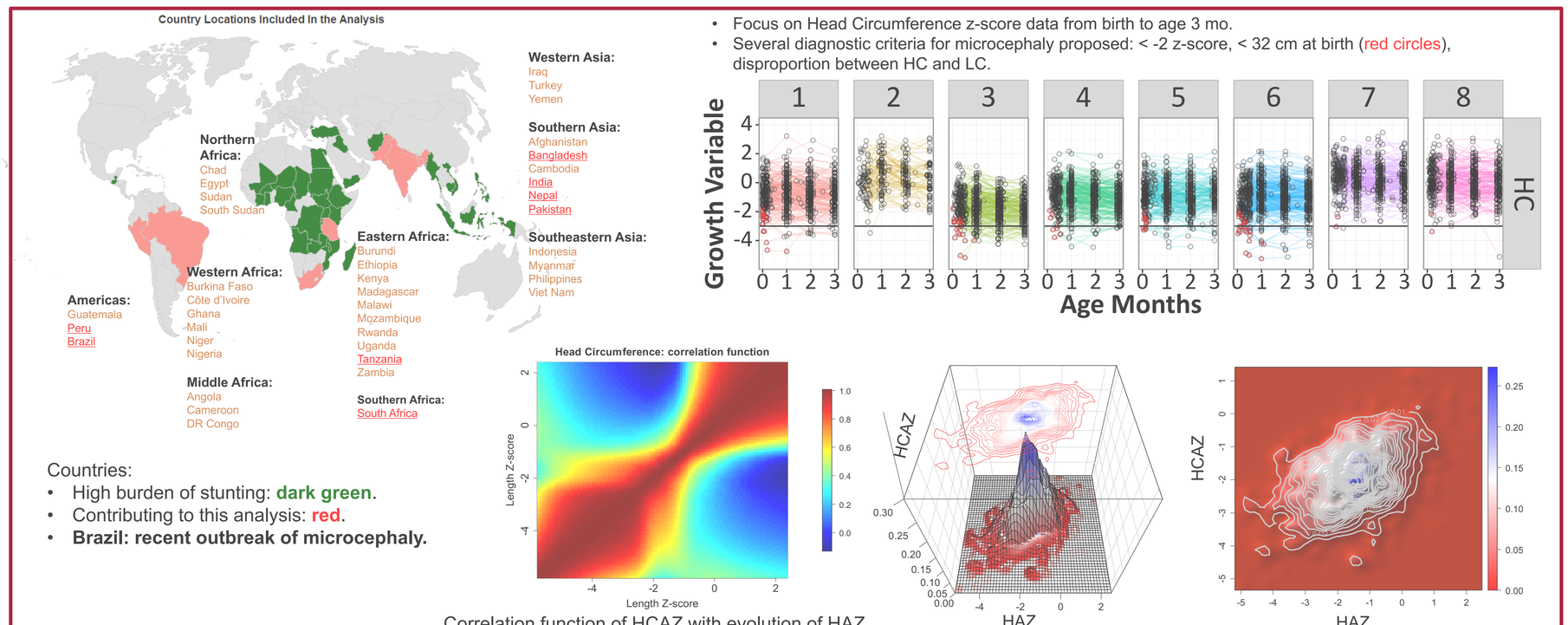
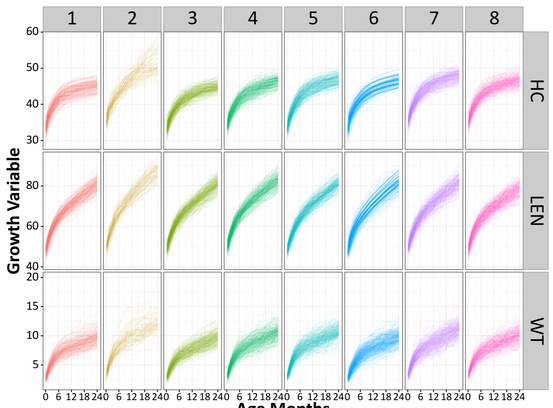
Objectives

- Symmetric intrauterine growth restriction (IUGR) has a growth pattern where all biometric measurements are affected to the same degree.
- Asymmetric IUGR has growth with small abdominal circumference (AC) compared with other growth parameters:
  - Abnormal head circumference/AC (HC/AC) ratio
  - Abnormal femur length/AC (FL/AC) ratio.
- The objectives of this study were:

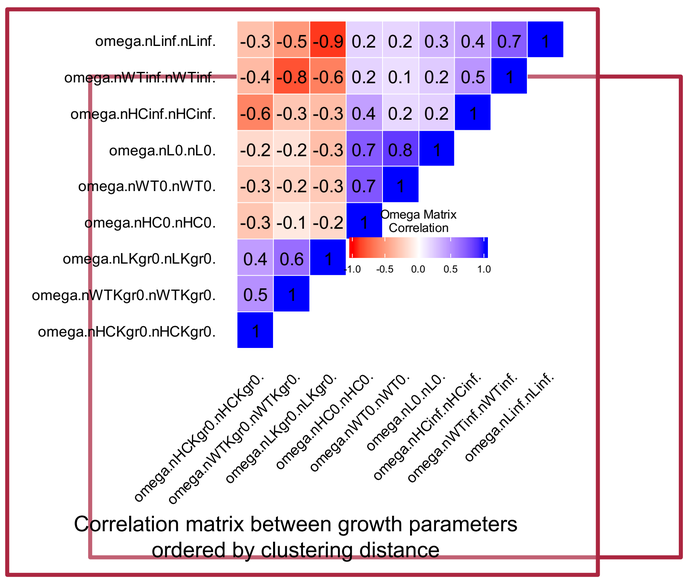
(1) To determine the joint probability distributions of growth parameters describing Weight/Length and Head Circumference (WT/LEN/HC) from age 0 to 24 mo, and

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

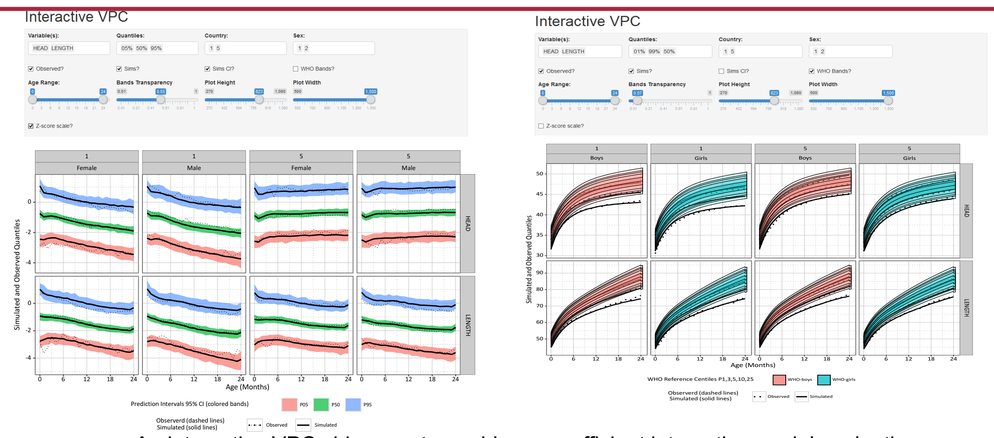




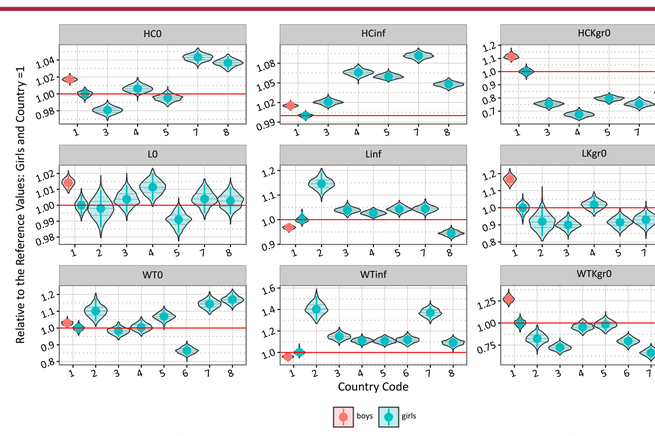
115 060 observations; 71 missing



Correlation matrix between growth parameters ordered by clustering distance



An interactive VPC shiny app to enable more efficient interactive model evaluation



Bootstrap-Based Distribution of Relative Covariate Effects

Methods

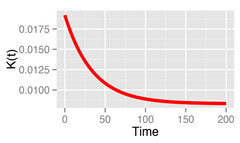
- Joint parametric nonlinear mixed effects (NLME) model built for WT/LEN/HC.
- Several parametric models tested such as exponential growth with and without decelerating growth rate.
- Key element: to determine the potential correlations between various growth outcomes WT/LEN/HC.
- Limited covariate testing done including covariates such as country site, sex, and socioeconomic factors.
- Model fitted using QRPEM fitting engine in Phoenix NLME parallelized on 20 cores.
- Model goodness-of-fit assessed using graphical tools and simulation based diagnostics (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

$$f(t \mid \boldsymbol{\theta}_i) = A_i - (A_i - B_i)\exp\{-k(t)\cdot t\}$$
$$k(t) = Kg_{r0,i}\{1 - C_i + C_i\exp(-\lambda_i t)\}$$
$$\boldsymbol{\theta}_i = (A_i, B_i, Kgr_{0,i}, C_i, \lambda_i) = \begin{pmatrix} \psi_i + \eta_{i1} \\ \psi_2 + \eta_{i2} \\ \exp(\psi_3 + \eta_{i3}) \\ \text{logit}^{-1}(\psi_4 + \eta_{i4}) \\ \exp(\psi_5 + \eta_{i5}) \end{pmatrix}$$

Parameter	Description
A	Growth asymptote
B	Growth at time=0
Kgr0	Growth rate constant at t=0
C	Asymptotic fractional reduction of Kgr0
TTP50 ($ln(2)/\lambda$)	Time to 50% reduction in growth rate constant

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KgrdecL = 1/(1+exp(-logitLKgrdec))
lambdaL = log(2) /LTTP50
KgrL = LKgr0 * (1 - LKgrdec + LKgrdec*exp(-lambdaL * AGEMONTHS))
LENCM = Linf - (Linf - L0)*exp(-Kgr L* AGEMONTHS)

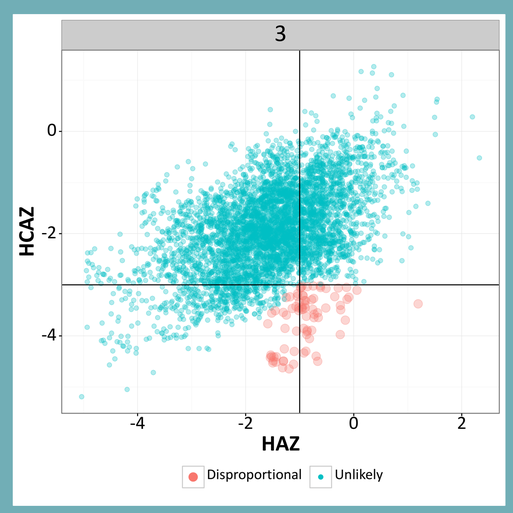
KgrdecHC = 1/(1+exp(-logitHCKgrdec))
lambdaHC = log(2) /HCTTP50
KgrHC = HCKgr0 * (1 - KgrdecHC + KgrdecHC*exp(-lambdaHC * AGEMONTHS))
HCCM = HCinf - (HCinf - HC0)*exp(-KgrHC * AGEMONTHS)

stparm(HCinf = exp(tvlnHCinf + nHCinf))

ranef(block(nWTinf, nWT0,nWTKgr0,nLinf, nL0,nLKgr0,nHCinf, nHC0,nHCKgr0) ,…)
```

Results

- Joint nonlinear deceleration model for WT/LEN/HC best fit the data (115 060 observations from 1568 subjects) with full random effects variance-covariance matrix.
- Between-subject variability: range, 50% (weight rate of growth) to 10% (length at 0 mo).
- Overall good agreement between observed and simulated data (1 to 97 percentiles).
- Country and sex kept in the model.
- Parameter uncertainty < 30%.
- Model accurately simulated correlated longitudinal data of WT/LEN/HC from 0-24 months.
- Model accurately predicted probability of stunting and trajectories of HC growth including microcephaly conditional on WT and LEN.
- WT/HC, LEN/HC, and WT/LEN standards were generated by simulating from the model.

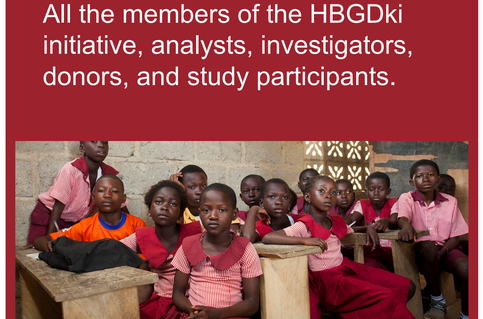


Conclusions

- 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.
- Microcephaly-disproportionate subpopulation may be identified for further study and intervention.

Acknowledgment

All the members of the HBGDki initiative, analysts, investigators, donors, and study participants.



References

1. Peleg et al. Intrauterine growth restriction: identification and management. *Am Fam Physician.* 1998;58(2):453-460
2. Geraedts et al. Association between head circumference and body size. *Horm Res Paediatr.* 2011;75:213–219

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