

## Zika Microcephaly Cutoffs Revisited: Nonparametric Methods in Fetal Growth

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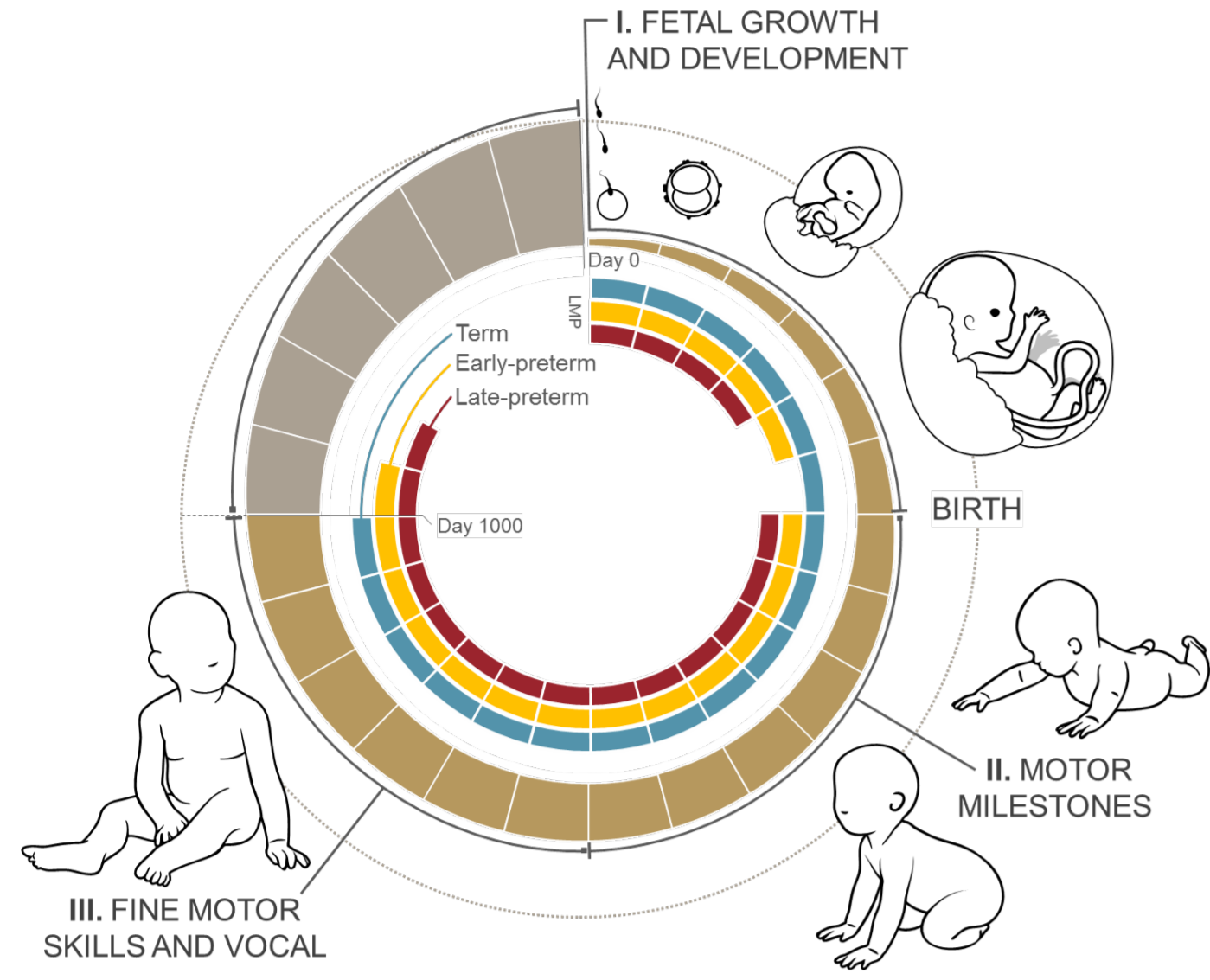


Fig. 1 Healthy Birth Growth and Development Lifecycle diagram.

### Objectives

- An increase in the number of microcephaly cases in Brazil has been associated with exposure to Zika virus.
- Screening thresholds for microcephaly have been published in terms of newborn head circumference.<sup>1</sup>
- We evaluated these criteria based on modeling of data about:
  - Longitudinal fetal growth trajectories.
  - Newborn size.

### Methods

Functional Principal Component Analysis (fPCA)<sup>2</sup> was used to model head circumference growth trajectories using nonparametric functions to characterize:

- Mean trajectory
- Subject-level random effects

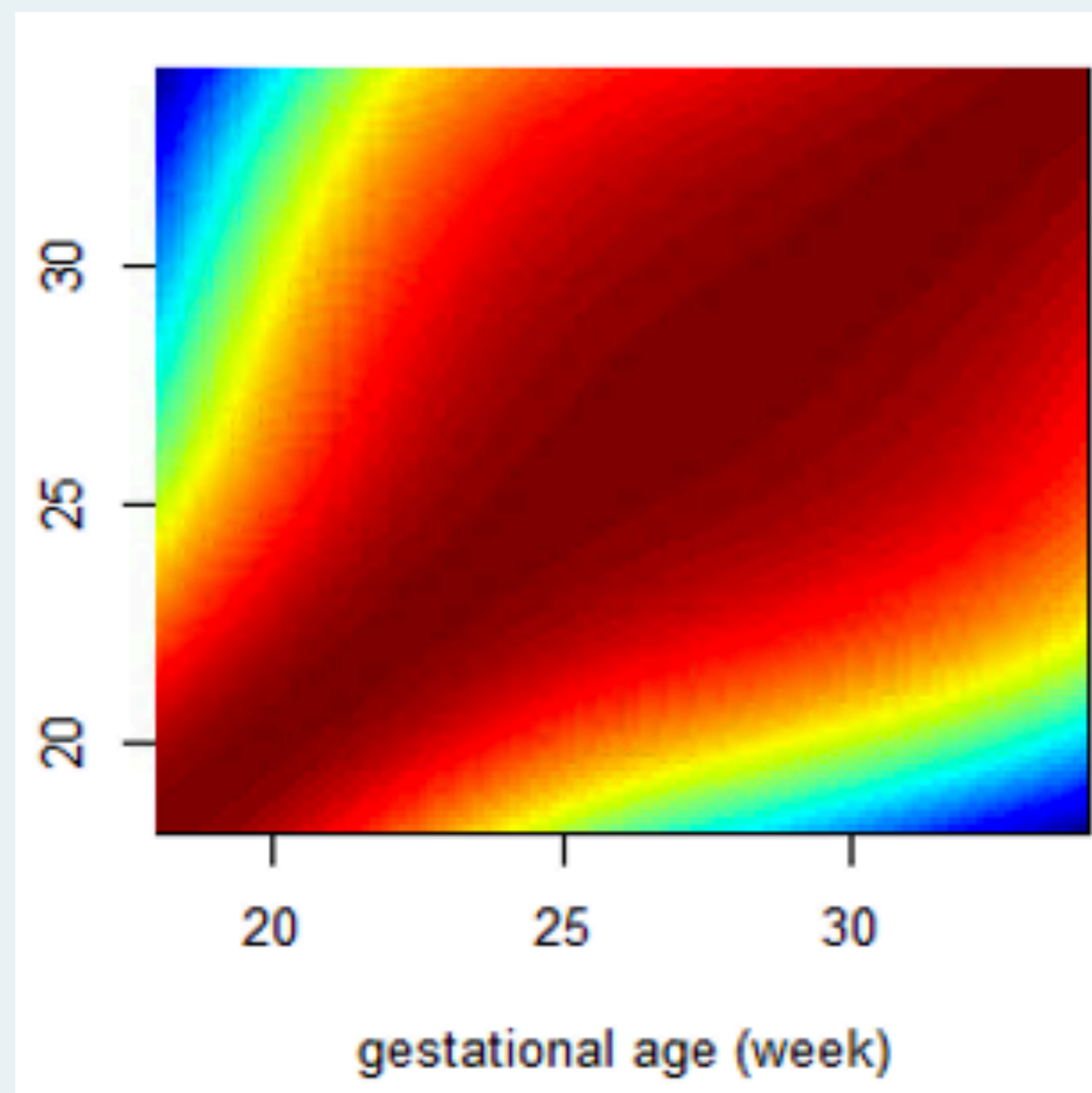
$$Y_i(t) = \mu(t) + X_i(t) + \varepsilon_i(t)$$

$$Y_i(t_{ij}) = \mu(t_{ij}) + \sum_{k=1}^r \xi_{ik} \varphi_k(t_{ij}) + \varepsilon_{ij}$$

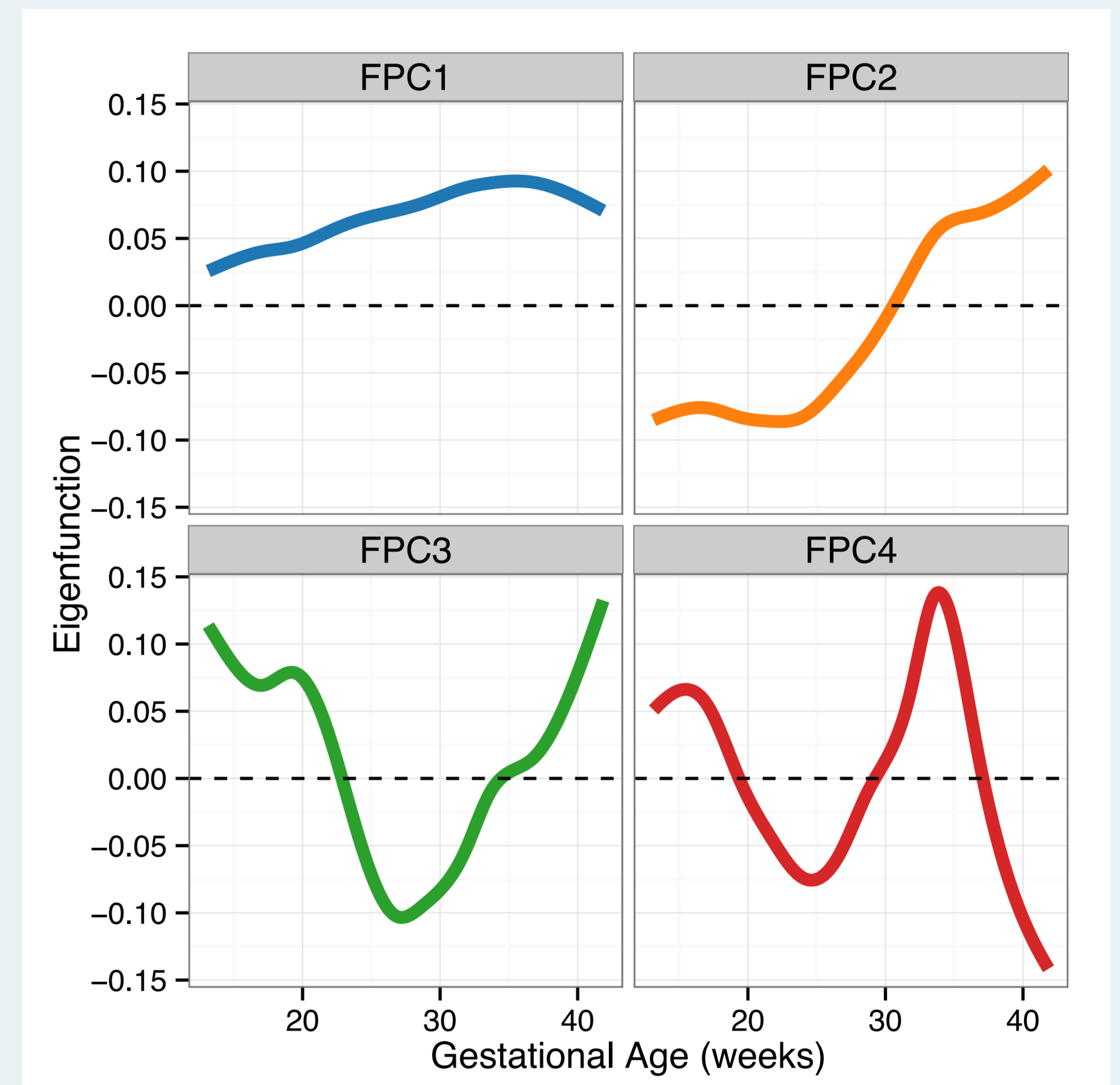
$$\text{Cov}(X_i(s), X_i(t)) = \sum_{k=1}^r \lambda_k \varphi_k(s) \varphi_k(t)$$

$$\varepsilon_{ij} \text{ i.i.d. } N(0, \sigma^2)$$

$$\xi_{ik} \text{ i.i.d. } N(0, \lambda_k)$$



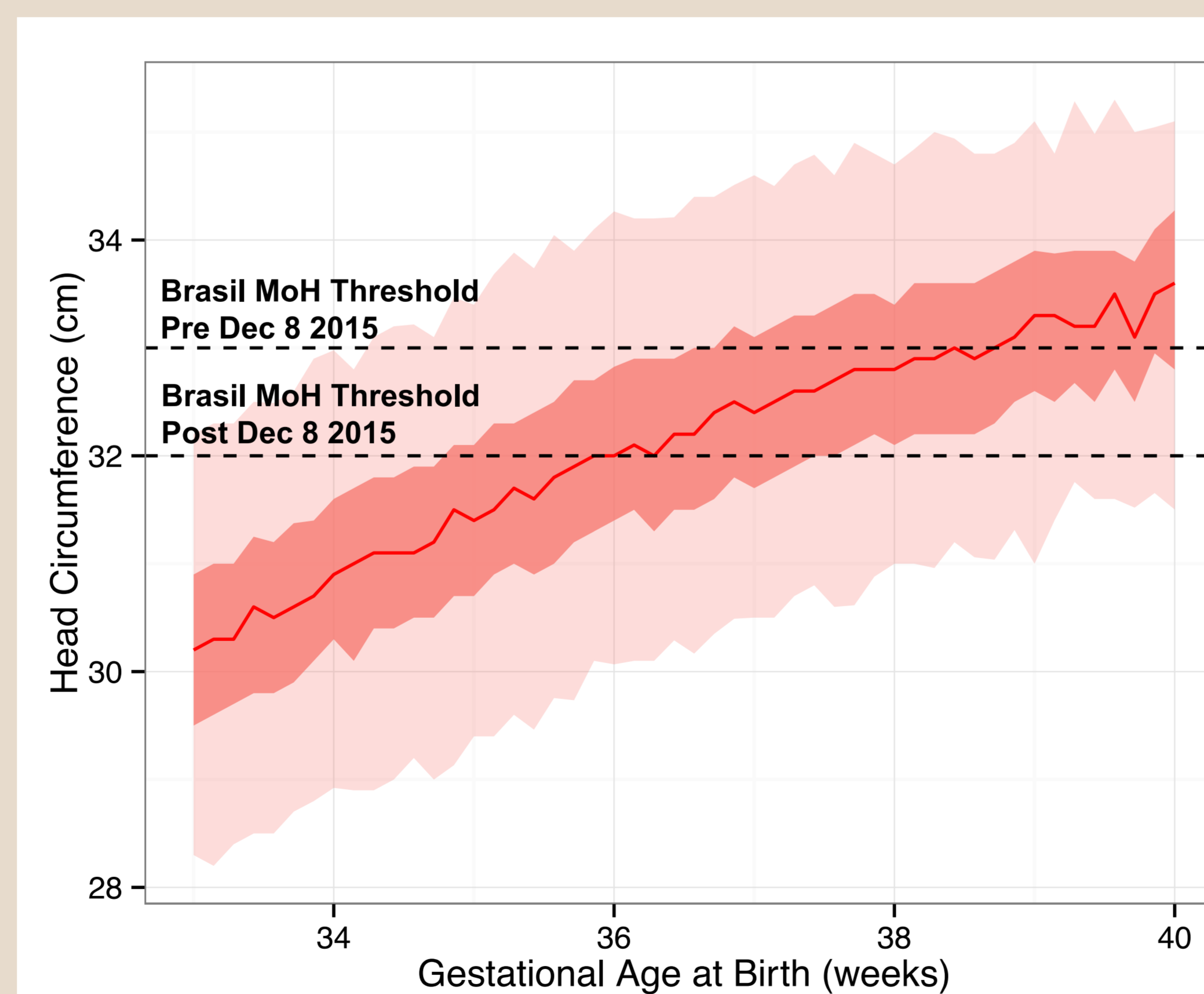
Estimated covariance function based on fetal ultrasound data.



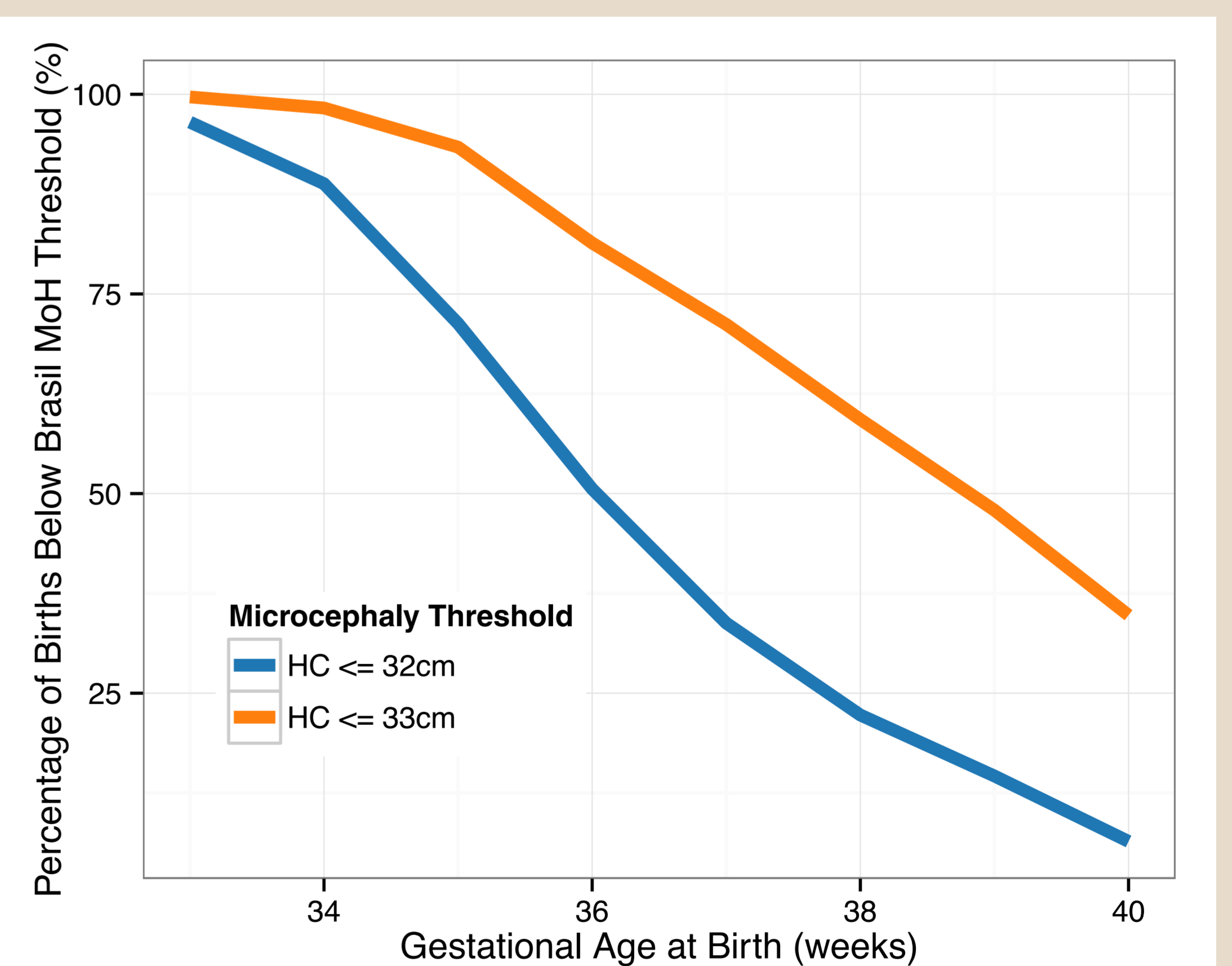
Principal eigenfunctions derived from the covariance function that are orthogonal functions characterizing fetal growth phenotypes. **Abbreviation:** FPC, functional principal component.

### Results

- Microcephaly thresholds that did not account for gestational age ignored an important source of biological variation.
- Factors associated with maternal health also contributed to population and subject-level deviations from international standards, which accounted for gestational age.<sup>3</sup>



Relation between head circumference and gestational age at birth.



Relation between births below Zika threshold and gestational age at birth.

### References

1. Victora CG, et al. Microcephaly in Brazil: how to interpret reported numbers? *Lancet*. 2016;387(10019):621-624.
2. Xiao L, et al. Fast covariance estimation for high-dimensional functional data. *Stat Comput*. 2016;26(1):409-421.
3. Villar J, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet*. 2014;384(9946):857-868.

### Conclusions

- Establishing fixed cutoffs for microcephaly in terms of newborn head circumference size ignores important sources of variation.
- This variation can be accounted for using a model-based approach.

### Acknowledgment

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