

## **Autism with Intellectual Disability Related to Dynamics of Head Circumference Growth during Early Infancy**

### ***Supplemental Information***

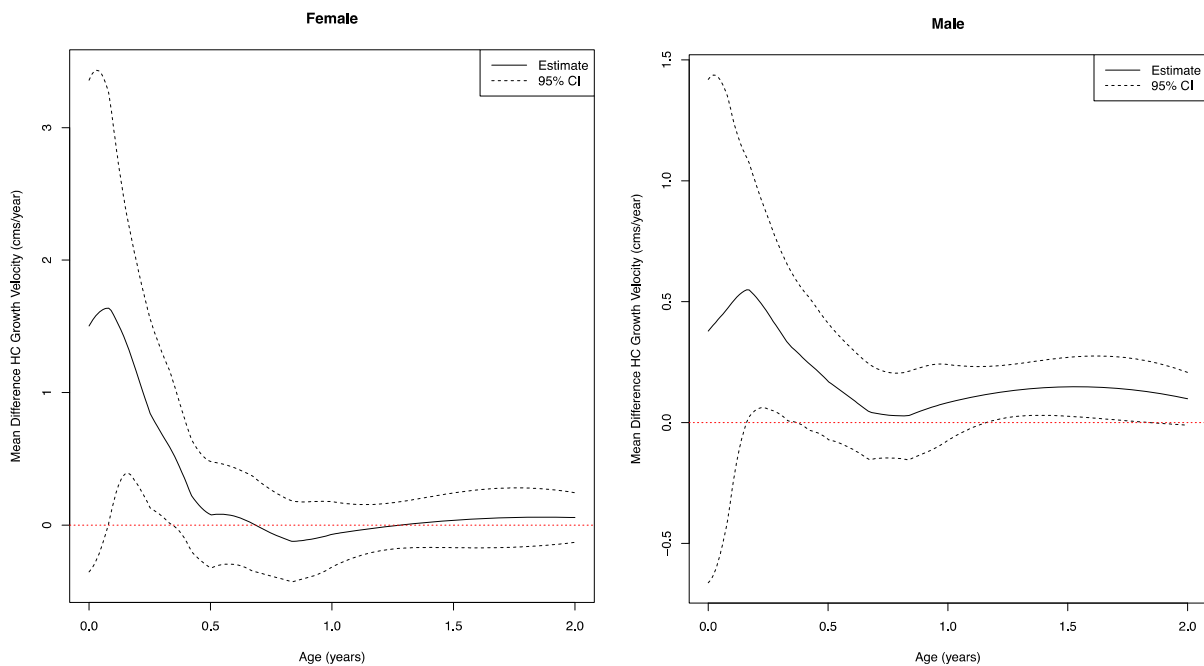
In this supplement, we first briefly describe the nonparametric Bayes inversion method for reconstructing the growth velocity curves. For a full account of the method the reader should consult the referenced articles (1, 2, 3). Worked examples implementing the method can be found in the R package `growthrate` (3). The key idea is that each individual growth velocity curve is treated as a separate (unknown) functional parameter, and endowed with a flexible prior distribution. This prior is specified hierarchically by a general multivariate normal distribution at a small set of fixed (“nominal”) observation times, and a (conditional) tied-down Brownian motion between the nominal observation times. This nonparametric prior distribution depends on various hyperparameters: the mean and covariance matrix of the multivariate normal, and the infinitesimal variance ( $\sigma^2$ ) of the tied-down Brownian motion; these hyperparameters are estimated from the data (i.e., by empirical Bayes).

Once the hyperparameters are specified, Bayes formula leads to the posterior distribution of the growth velocity curves for each subject. This posterior is determined by a mean growth velocity curve, as plotted for 50 subjects in the left panel of Figure 1, and a posterior standard deviation used to calculate the 95% credible intervals shown in the right panel of Figure 1. The important hyperparameter  $\sigma$  was selected by cross-validation ( $\sigma = 2, 1.4$  and  $1$  for the head circumference (HC), height and weight growth velocity reconstructions, respectively).

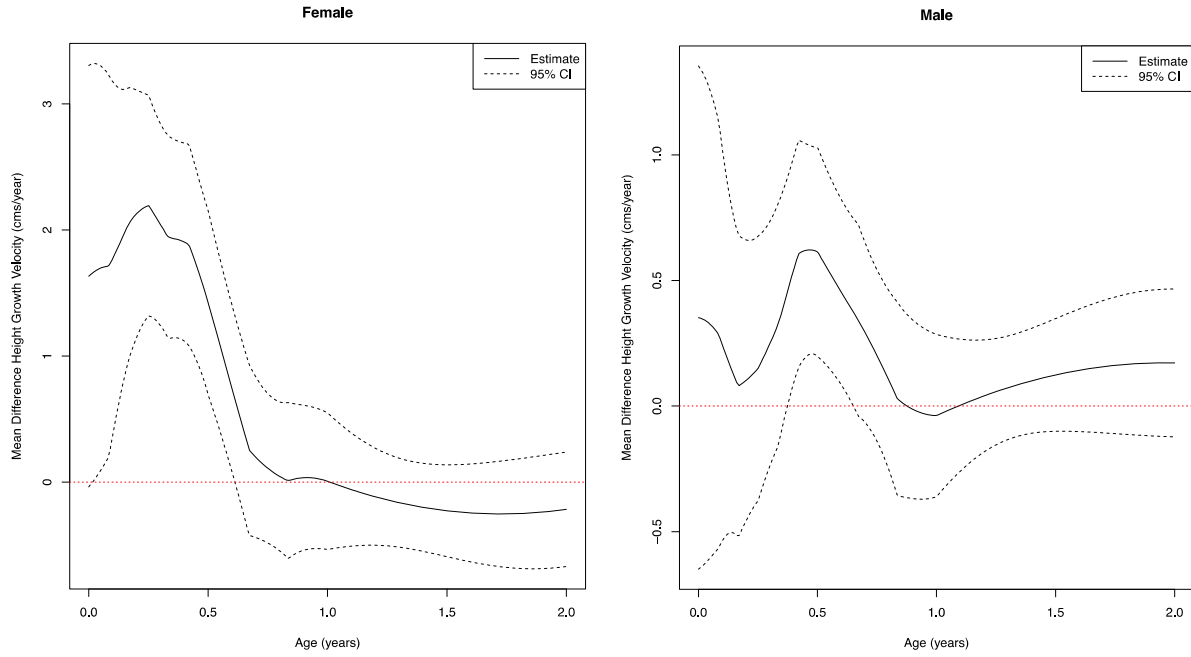
Some pre-processing of the data was needed to implement the reconstruction method in this setting because the actual observation times vary between subjects. To obtain data at the nominal observation times, taken to be the same for all subjects, spline smoothing was used to

interpolate/extrapolate from the actual growth data when no data were available at a nominal observation time. The spline smoothing was implemented in R using the function `spline.smooth` with the smoothing parameter `spar = 0.5`. The nominal observation times were chosen to roughly correspond to expected ages for clinic visits (ages 0, 31, 61, 92, 122, 153, 183, 245, 305, 365, and 730 days), around which the actual observation times cluster.

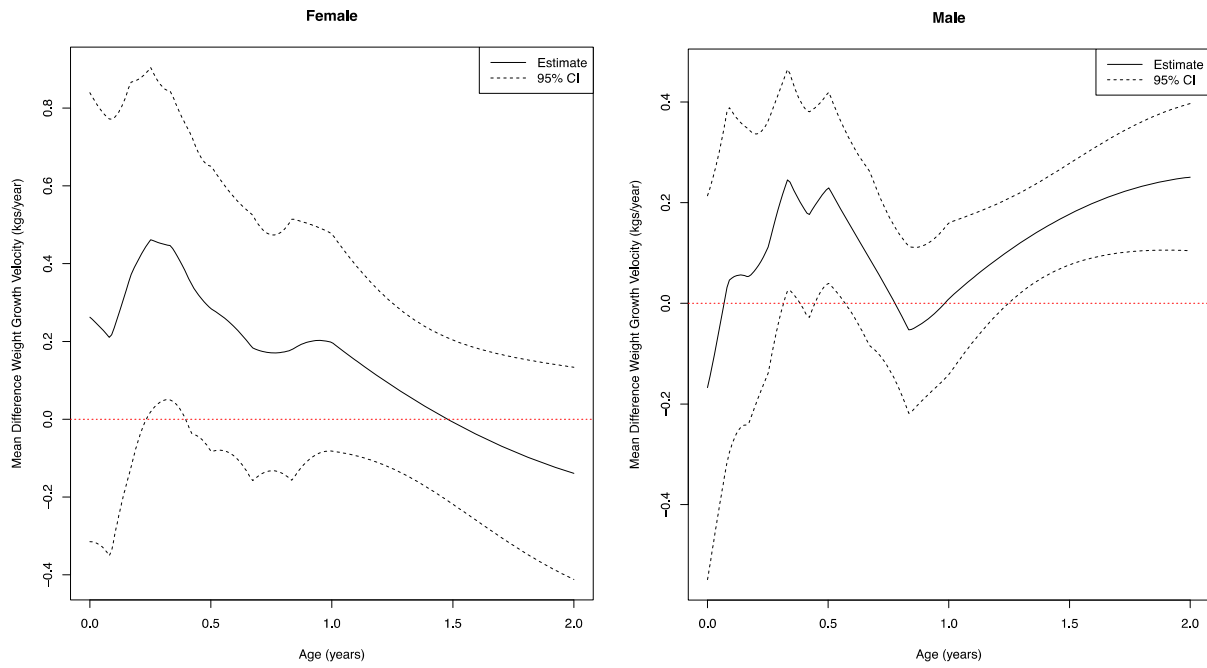
A referee asked whether gender has any effect on the reported differences in the mean growth velocity between cases and controls (as plotted for HC in Figure 2). Figure S1 shows Figure 2 broken down by gender, and we see that the significant effect at 3 months of age is still present in each gender. The corresponding plots for height and weight (broken down by gender) are provided in Figures S2 and S3.



**Figure S1.** Mean HC growth velocity difference (solid line) between cases and their matched controls, 95% confidence limits (dashed lines), separately for females (left panel) and males (right panel).

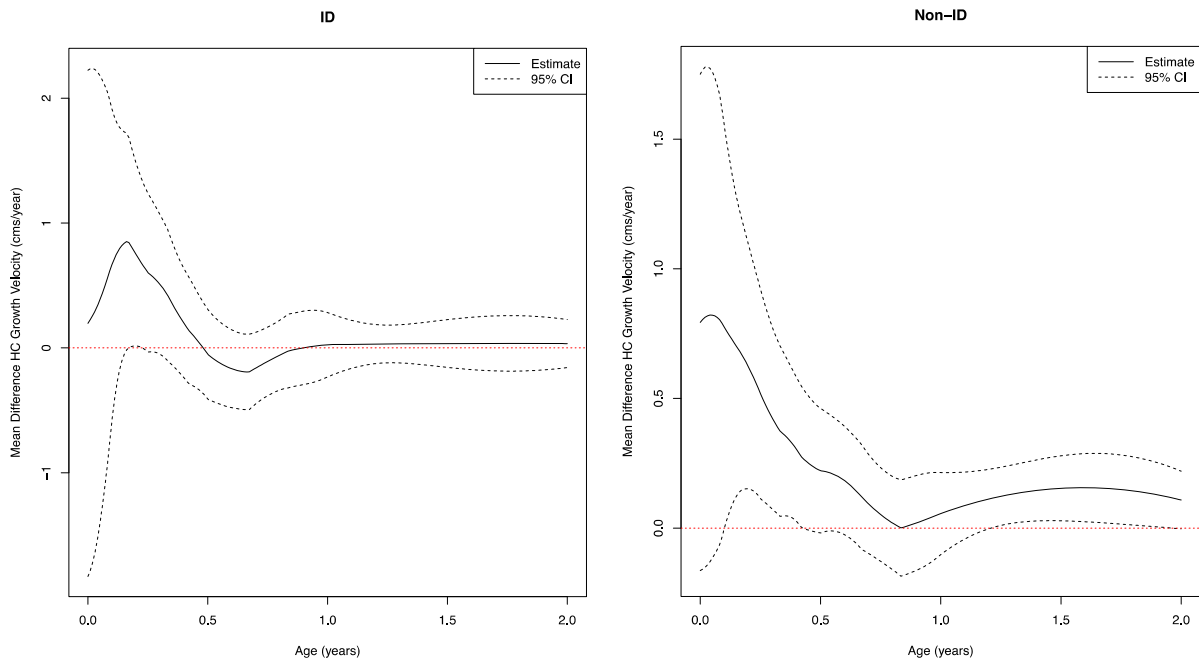


**Figure S2.** As in Figure S1 except for height instead of HC.



**Figure S3.** As in Figure S1 except for weight instead of HC.

A version of Figure 2 on HC growth velocity broken down by intellectual disability (ID) status is presented in Figure S4. The estimated effect at 3 months of age in the ID group is about twice that of the non-ID group; the effect is significant in the non-ID group, but only borderline significant in the ID group. Recall, however, that the *adjusted* analyses of the non-ID group (Table 4) at 3 months were significant, but not with the ID group (Table 4), providing consistent evidence of a more pronounced effect of accelerated HC growth in the ID group.



**Figure S4.** Mean HC growth velocity difference (solid line) between cases and their matched controls, 95% confidence limits (dashed lines), separately for ID (left panel) and non-ID (right panel).

Tables S1 and S2 below provide  $p$  values to go along with Figures 3 and 4 for height and weight (cf. Table 1 for HC).

**Table S1.** Mean height growth velocity (cms/year) in cases and controls.

Age in months	Cases	Controls	Difference	$p$ value based on GEE
0	44.7	44.0	0.7	0.154
1	43.0	42.4	0.6	0.112
2	39.3	38.8	0.5	0.058
3	35.2	34.6	0.6	0.011 <sup>a</sup>
4	30.3	29.6	0.7	0.001 <sup>a</sup>
5	26.3	25.4	0.9	0.001 <sup>a</sup>
6	22.6	21.9	0.7	0.002 <sup>a</sup>

GEE, generalized estimating equations.

<sup>a</sup> significant  $p$  value.

**Table S2.** Mean weight growth velocity (kgs/year) in cases and controls.

Age in months	Cases	Controls	Difference	$p$ value based on GEE
0	11.27	11.35	-0.05	0.665
1	11.61	11.52	0.09	0.587
2	10.84	10.72	0.12	0.349
3	9.41	9.22	0.19	0.094
4	8.05	7.77	0.28	0.003 <sup>a</sup>
5	6.77	6.56	0.21	0.020 <sup>a</sup>
6	5.85	5.61	0.24	0.005 <sup>a</sup>

GEE, generalized estimating equations.

<sup>a</sup> significant  $p$  value.

## Supplemental References

1. Lopez-Pintado S, McKeague IW (2013): Recovering gradients from sparsely observed functional data. *Biometrics* 69: 396–404.
2. McKeague IW, Lopez-Pintado S, Hallin M, Siman M. (2011): Analyzing growth trajectories. *J Dev Orig Health Dis* 2011; 2:322-329.
3. Lopez-Pintado S, McKeague IW (2011): Growthrate: Bayesian reconstruction of growth velocity. R package version 1.2. <http://cran.r-project.org/web/packages/growthrate>.