1	ONLINE SUPPLEMENTARY MATERIAL
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3	Gestational weight gain charts: Results from the Brazilian Maternal and Child
4	Nutrition Consortium
5	
6	First authors: Gilberto Kac, Thais R. B. Carrilho
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8	SUPPLEMENTARY METHODS
9	
10	Supplementary methods 1. Steps to construct the gestational weight gain charts
11	All the following steps were performed stratifying according pre-pregnancy BMI
12	category.
13	
14	Step 0. Constructing histograms for GWG in each gestational age (10-40 weeks) to
15	understand the distribution of GWG during pregnancy according to each pre-pregnancy
16	body mass index (BMI) category (R code 1).
17	
18	Step 1. Adjusting linear mixed models and extracting percentiles and z-scores. This
19	is a very naïve approach. The aim was to keep the models as simple as possible.
20	However, the diagnostic of the models (graph of residuals vs. fitted values) and the
21	plotting of the percentiles revealed the presence of heteroscedasticity. Based on those
22	results, linear mixed models were found to be inappropriate, as they only model the
23	mean according to gestational age. In cases where heteroscedasticity is observed,
24	modeling the standard deviation (SD) is necessary (Stata code 1).
25	

Step 2. Adjusting fractional polynomials (FP) and extracting percentiles and z-26 27 scores. This model was performed in two ways: using clusters of individuals and without clusters. The first approach attempted to incorporate the intra-individual 28 29 variance, which exists because of the repetition of weight measurements for some women in our sample. With FP, it is possible to model both the mean and the SD 30 31 according to gestational age, providing a solution for the heteroscedasticity problem (1). 32 The incorporation of clusters did not affect percentiles estimation, as they interfere only with the standard error, which is not used in the calculation of the percentiles. Thus, 33 considering the clusters did not change the estimation of the percentiles, which are the 34 35 values of interest, in our case. The problem of the FP models was the 'internal validation'. When we compared the percentages of observations above or below some 36 selected percentiles (3/97, 10/90, 25/75, 50) or z-scores (-2/2, -3/3), the values were 37 38 different from what one should expect, especially in the extreme percentiles (Stata code 2). For instance, in the 3/97 percentiles, one would expect that 3% of the sample would 39 be above the 97<sup>th</sup> and below the 3<sup>rd</sup> percentile. In our case, for normal weight women, 40 when FP models were adjusted, 4.8% of the sample were above the 97<sup>th</sup> centile. 41 According to Cole (2), this is an indication of bias of the models. 42 43

### 44 Step 3. Adjusting random effects models modeling gestational age using restricted

45 **cubic splines.** This approach allowed us to model weight gain as a function of

46 gestational age using a flexible non-linear model (in each specified knot) (3). A random

47 effects model with unstructured covariance matrix was adjusted, with several knots (3,

48 4, 5). In those models, the k knots are introduced on the x-axis (in this case, x =

49 gestational age) located at  $t_1, t_2, ..., t_k$ . A model of the expected value of weight gain (y)

50 given the gestational age (x) is selected, that is linear before  $t_1$  and after  $t_k$ , consists of

piecewise cubic polynomials between adjacent knots and is continuous and smooth in 51 52 each knot (3). This way, it is possible to account for non-linear relations between weight gain and intervals of gestational age. This approach is the same applied by Hutcheon et 53 54 al. (4) and Huang et al. (5) when constructing GWG charts for the USA and China, respectively (Stata code 3). The same challenges mentioned on step 2 were present here, 55 i.e., the performance of the model regarding the internal validation was poor even with 56 57 5 knots. Increasing the number of knots could lead to overfitting (6), so we decided not to use those models. 58

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60 Step 4. Adjusting a combination of FP and multilevel models (ML). These types of models are similar to those adjusted by Ohuma & Altman (7) for head circumference 61 data, and by Cheikh-Ismail et al. (8) for GWG. The use of these models requires the 62 63 determination of the best-fitting powers for gestational age by modelling GWG as a function of GA using FP. In our case, the best powers were provided by a 2<sup>nd</sup> order FP 64 65 for all BMI categories. The functional form of GA was then incorporated to a two-level (individuals and visit) random intercept and slope model. In this model, both mean and 66 SD vary according to GA. However, although it is possible to obtain an equation of the 67 68 mean, it is not possible to retrieve the equation for the SD, and both are necessary in the calculation of the percentiles. So, after the adjustment of the ML model, it is necessary 69 to model the SD according to GA by using another FP model, to emulate the SD from 70 the ML and to obtain an equation for it. We decided to model the log(SD) to stabilize 71 72 variance, in the same way as performed by Ohuma & Altman (7) (Stata code 4). Those models should be the best approach for our data, since there are women with repeated 73 74 GWG measurements, and they provide more accurate equations for the mean and SD. Unfortunately, when we performed the internal validation, by comparing the 75

percentages of observations above or below some selected percentiles (3/97, 10/90,
25/75, 50) or z-scores (-2/2;-3/3), the values were, again, different from the expected,
especially in the most extreme percentiles. Besides bias, as mentioned by Cole (2), we
considered that the modelling of those percentiles could be affected by kurtosis (9), and
none of the models performed could account for that.

81

82 Step 5. Adjusting the GAMLSS models. These models are the same used by the World Health Organization when constructing the growth charts for children (9). By the 83 time of the construction of the charts, a team of experts was consulted and reviewed 84 85 several models available to construct those types of charts and they concluded in favor of using GAMLSS even with repeated measures, which are not accounted for in those 86 models (10). However, the incorporation of the intra-individual variance in the models 87 would affect the estimation of standard errors of the point estimates of the model, which 88 are not used in the determination of percentiles and z-scores (9). 89

In our dataset, several attempts were made to find the best distribution, smoother 90 and degrees of freedom for each parameter (mean, deviation, skewness and kurtosis, 91 mu, sigma, nu and tau, respectively) being modeled (all the options are listed in (11)). 92 93 To avoid the infinite possibilities of tests of specifications of the models, the 'LMS' function was used. This function tests and selects the best model from LMS (lambda, 94 mu, sigma, the method proposed by Cole & Green (12)), and besides mean and SD, 95 96 includes skewness in the modelling and models the parameters using a Box-Cox Cole Green distribution. This function also tests LMST (a modification of LMS that also 97 98 models kurtosis and used Box-Cox-t as distribution) and LMSP (a modification of the LMS that also models kurtosis and used Box-Cox power exponential as distribution). 99 By using this function, the adjustment of the percentiles improved substantially, and the 100

101	diagnostic revealed very well-adjusted models. Details regarding the implementation of
102	the GAMLSS models are described in the 'methods' section (R code 2).
103	
104	REFERENCES
105	
106	1. Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous
107	Covariates: Parsimonious Parametric Modelling. Journal of the Royal Statistical
108	Society Series C (Applied Statistics) 1994;43(3):429-67. doi: 10.2307/2986270.
109	
110	2. Cole TJ. Commentary: Methods for calculating growth trajectories and constructing
111	growth centiles. Statistics in medicine 2019;38(19):3571-9. doi:
112	10.1002/sim.8129.
113	
114	3. Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining
115	relationships between predictors and response Journal of the National Cancer
116	Institute 1988;80(15):1198-202. doi: 10.1093/jnci/80.15.1198.
117	
118	4. Hutcheon JA, Platt RW, Abrams B, Himes KP, Simhan HN, Bodnar LM. Pregnancy
119	weight gain charts for obese and overweight women. Obesity 2015;23(3):532-5.
120	doi: 10.1002/oby.21011.
121	
122	5. Huang A, Xiao Y, Hu H, Zhao W, Yang Q, Ma W, Wang L. Gestational weight gain
123	charts by gestational age and body mass index for Chinese women: A population-
124	based follow-up study. Journal of Epidemiology 2019. doi:
125	10.2188/jea.JE20180238.

126 127 6. Perperoglou A, Sauerbrei W, Abrahamowicz M, Schmid M. A review of spline function procedures in R. BMC Medical Research Methodology 2019;19(1):46. 128 129 doi: 10.1186/s12874-019-0666-3. 130 131 7. Ohuma EO, Altman DG, International F, Newborn Growth Consortium for the 21st C. Statistical methodology for constructing gestational age-related charts using 132 cross-sectional and longitudinal data: The INTERGROWTH-21(st) project as a 133 case study. Statistics in medicine 2019;38(19):3507-26. doi: 10.1002/sim.8018. 134 135 8. Cheikh Ismail L, Bishop DC, Pang R, Ohuma EO, Kac G, Abrams B, Rasmussen K, 136 Barros FC, Hirst JE, Lambert A, et al. Gestational weight gain standards based on 137 138 women enrolled in the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: a prospective longitudinal cohort study. BMJ 2016;352:i555. doi: 139 140 10.1136/bmj.i555. 141 9. Borghi E, de Onis M, Garza C, Van den Broeck J, Frongillo EA, Grummer-Strawn L, 142 Van Buuren S, Pan H, Molinari L, Martorell R, et al. Construction of the World 143 Health Organization child growth standards: selection of methods for attained 144 growth curves. Statistics in Medicine 2006;25(2):247-65. doi: 10.1002/sim.2227. 145 146 147 10. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. Journal of the Royal Statistical Society: Series C (Applied Statistics) 148 2005;54(3):507-54. doi: 10.1111/j.1467-9876.2005.00510.x. 149

150

151	11. Stasinopoulos DM, Rigby RA. Generalized Additive Models for Location Scale and
152	Shape (GAMLSS) in R. Journal of Statistical Software 2007;23(7):46. doi:
153	10.18637/jss.v023.i07.
154	
155	12. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and
156	penalized likelihood. Statistics in Medicine 1992;11(10):1305-19.
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#### R and STATA codes used for the analysis

For all codes, an example with normal weight women is provided. In all cases, the models were restricted to 10-40 weeks, due to availability of data.

#### Step 0. R code 1

```
# Read The dataset - only normal weight women
library(ggplots2)
nwdata$GA=round(nwdata$gawk_)
nwdata$GA=as.factor(nwdata$GA)
ggplot(nwdata, aes(x=gain_, fill=GA)) +
geom_histogram(binwidth=5) +
facet_wrap(GA~.) +
theme_bw()
```

#### Step 1. Stata code 1 (Based on codes gently provided by Dr. Eric Ohuma)

\* Read the dataset (Normal weight women only) \* Fit the model for each pre-pregnancy BMI, using xtmixed xtmixed gain gawk || id: gawk \* Evaluating residuals – looking for heteroscedasticity: predict fit1, fitted predict residuals, rstandard twoway (scatter residuals fit1) \*Extracting z-scores and percentiles \*Calculating the estimated mean: predict p\_mean, xb \*Calculating the estimated variance: estat recov matrix mymatrix=r(cov) matrix list mymatrix local var\_slope=mymatrix[1,1] display `var\_slope' local var\_cons=mymatrix[2,2] display `var\_cons' local cov=mymatrix[2,1] display `cov' \*local var\_resfgls\_no= (exp(2 \* [lnsig\_e]\_cons)) local var\_resfgls\_no= 2 \* [lnsig\_e]\_cons display `var\_resfgls\_no' gen p\_var = `var\_cons' + (`var\_slope')\*gawk\_^2 + 2\*gawk\_\*`cov'+`var\_resfgls\_no' label var p var "Variance" gen p\_sd=sqrt(p\_var) \* Generating the percentiles \*P3/97 gen p97=p\_mean+1.88\*p\_sd

```
gen p3=p_mean-1.88*p_sd
*P5/95
gen p5=p_mean-1.645*p_sd
gen p95=p_mean+1.645*p_sd
*P10/90
gen p10=p_mean-1.28*p_sd
gen p90=p_mean+1.28*p_sd
tabstat p97 p3, s(min max mean)
tabstat p95 p5, s(min max mean)
tabstat p90 p10, s(min max mean)
* Graphing the percentiles
twoway (scatter gain_ gawk_, ms(Oh) mc(gs10)) ///
(line p_mean p3 p10 p90 p97 gawk_, lcolor(red green blue blue green) ///
lwidth(thin thin thin thin) sort lpattern(dash dash dash dash dash)), ///
ylabel(-10(10)30) xlabel(10(2)40) ///
 scheme(s1mono) plotregion(style(none)) yscale(r(-10 40)) ///
   xscale(r(0 40)) xtitle(Gestational age in weeks) ytitle("GWG (Kg)") legend(off)
```

# Step 2. Stata code 2 (Based on codes gently provided by Dr. Eric Ohuma and Dr. Michael Reichenheim)

\* Read the dataset (Normal weight women only)
\* Fit the model for each pre-pregnancy BMI
\* A) FP without clusters

\*Identifying the best FP: xrigls gain\_ gawk\_, detail nogr

\*Best FP Model: m:df 0 0,s:df 2 xrigls gain\_ gawk\_, fp(m: 0 0,s: 2) centile(3 10 50 90 97) detail nogr

\* B) FP with clusters:
\* TOGGLE
global clus "ropts(m:vce(cluster id), s:vce(cluster id))"

\*Identifying the best FP: xrigls gain\_ gawk\_, detail nogr \${clus}

\*Best FP Model: m:df 0 0,s:df 2 xrigls gain\_ gawk\_, fp(m: 0 0,s: 2) centile(3 10 50 90 97) detail nogr \${clus}

\*\*\*\* Procedures to be adopted for both approaches:
\*Generating z-scores and centiles:
foreach var of varlist C3\_gls C50\_gls C97\_gls C10\_gls C90\_gls C25\_gls C75\_gls
Z\_gls {
 gen `var'\_no=`var'

}

```
*Plotting centiles
set more on
#delimit;
twoway (scatter gain_ gawk_, ms(Oh) mc(gs10) )
    (line C3_gls_no C50_gls_no C97_gls_no gawk_, lcolor(blue blue blue)
    sort lpattern(dash dash)), ylabel(-10(5)40) xlabel(10(2)40)
    scheme(s1mono) plotregion(style(none)) ysca(titlegap(*6))
    xsca(titlegap(*6)) xtitle(Gestational age in weeks) ytitle("GWG (Kg)")
legend(off)
#delimit cr
*Internal validation
gen complete_weeks=int(gawk_)
** Number of obs below 3<sup>rd</sup> or above 97<sup>th</sup> centiles
gen below_c3 = cond(gain_<C3_gls,1,0)
tab below_c3
bysort complete_weeks: tab below_c3
gen above_c97 = cond(gain_> C97_gls, 1, 0)
tab above c97
bysort complete_weeks: tab above_c97
** Number of obs below 10<sup>th</sup> or above 90<sup>th</sup> centiles
gen below_c10 = cond(gain_< C10_gls ,1,0)
tab below_c10
bysort complete_weeks: tab below_c10
gen above_c90 = cond(gain_> C90_gls, 1, 0)
tab above_c90
bysort complete weeks: tab above c90
** Number of obs below 25<sup>th</sup> or above 75<sup>th</sup> centiles
gen below_c25 = cond(gain < C25_gls, 1, 0)
tab below c25
bysort complete_weeks: tab below_c25
gen above_c75 = cond(gain_> C75_gls, 1, 0)
tab above_c75
bysort complete_weeks: tab above_c75
```

### Step 3. Stata code 3 (Based on codes gently provided by Dr. Eric Ohuma and Dr. Jennifer Hutcheon)

\* Read the dataset (Normal weight women only)\* Fit the model for each pre-pregnancy BMI

\*Log-transforming the weight gain variable \*Adding a constant to the weight gain variable so that there are no negative values (which can't be log-transformed) sum gain hist gain\_ gen gwg\_=gain+25 gen logweight gain cumulative=log(gwg) sum logweight\_gain\_cumulative \*Creating a spline for gestational age (in weeks) \* Compare models with different knots to identify the best one rc spline gawk , nknots(3) \*Random intercept and random slope model, unstructured covariance xtmixed logweight gain cumulative  $S^* \parallel id$ : Sgawk 1, cov(unstr) mle variance estat ic drop S\* rc\_spline gawk\_, nknots(4) xtmixed logweight\_gain\_cumulative \_S\*|| id: \_Sgawk\_1, cov(unstr) mle variance estat ic drop \_S\* rc\_spline gawk\_, nknots(5) xtmixed logweight\_gain\_cumulative \_S\*|| id: \_Sgawk\_1, cov(unstr) mle variance estat ic drop S\* \*Consider the model with lowest BIC and AIC and run it again \* Final model rc\_spline gawk\_, nknots(5) \*Random intercept and random slope model, unstructured covariance xtmixed logweight\_gain\_cumulative \_S\*|| id: \_Sgawk\_1, cov(unstr) mle variance estat ic \* Calculating the estimated mean: predict p\_mean, xb \*Calculating the estimated variance: estat recov matrix mymatrix=r(cov) matrix list mymatrix local var\_slope=mymatrix[1,1] display `var\_slope' local var\_cons=mymatrix[2,2] display `var cons' local cov=mymatrix[2,1] display `cov' local var\_resfgls\_no= (exp(2 \* [lnsig\_e]\_cons))

```
gen p_var = var_cons' + (var_slope')*_Sgawk_1^2 +
2*_Sgawk_1*`cov'+`var_resfgls_no'
label var p_var "Variance"
gen p_sd=sqrt(p_var)
* Back-converting to unstransformed scale
gen exp_p_mean = exp(p_mean) - 25
gen C50_rcs = exp(p_mean) - 25
* Obtaining SDs TO PLOT
*i.e., to obtain 1 SD
gen exp lower sd=(exp(p mean-1*sqrt(p var))) - 25
gen exp_upper_sd=(exp(p_mean+1*sqrt(p_var))) - 25
* Graphing mean and SD
twoway (scatter gain_ gawk_, msymbol(oh) mcolor(gs10)) ///
(connected exp_p_mean gawk_, msymbol(none) lcolor(blue) lwidth(medthick)
lpattern(solfgls no)) ///
(connected exp lower sd gawk, msymbol(none) lcolor(red) lwidth(medthick)
lpattern(dash)) ///
(connected exp_upper_sd gawk_, msymbol(none) lcolor(red) lwidth(medthick)
lpattern(dash)), legend(off) ///
vtitle("Gestational weight gain (kg)") xtitle("Gestational age (weeks)") scale(1.35)
vlabel(, nogrid) graphregion(color(white)) ///
xlabel(10(2)40) xsca(titlegap(*6)) ysca(titlegap(*6))
```

\* Perform internal validation as before

### Step 4. Stata code 4 (Based on codes gently provided by Dr. Eric Ohuma)

\* Read the dataset (Normal weight women only)
\* Fit the model for each pre-pregnancy BMI
\* Identifying the best FP xrigls gain\_ gawk\_, detail nogr

\*\* Best model: Powers for the mean: -1, 0.5; for the SD 1.0 xrigls gain\_ gawk\_, fp(m: -1 0.5,s: 1) centile(3 10 50 90 97) detail

\*\* Multi-level models
\*\* 1) using the best FP powers (-1,0.5)
global MLwiN\_path C:\Program Files (x86)\MLwiN trial\i386\mlwin.exe
bysort origin id (gawk\_): gen occasion = \_n
tab occasion
format gain\_ %9.3f
gen cons=1

\* Creating variables according to the FP model

```
gen gw1 = (gawk)^{-1}
gen gw2 = (gawk_)^0.5
cap drop u0 u1 u2 u0se u1se u2se
sort id occasion
runmlwin gain_ cons gw1 gw2, level2(id: cons gw1 gw2,residuals(u)) level1(occasion:
cons) maxiterations(1000) nopause rigls
est store rs_2levels
estimates table rs_2levels, stats(N deviance ll) b(%4.3f) stfmt(%4.0f) varwidth(18)
* Predict the average gwg for the average subject
predict rsmean 2levels, xb
* Add the subject residuals onto the predictions for the average gwg line
generate rsmean_2levelsxbu = rsmean_2levels + u0 + u1*gw1 + u2*gw2
* Sort the data by id and then by gawk_ within each subject
sort id gawk
* Plot the predicted subject lines for GWG
twoway (line rsmean_2levelsxbu gawk_, connect(ascending)), ///
       ytitle("Predicted GWG") xtitle("Gestational age (weeks)") ///
        title(RS model (2-levels)) ///
        scheme(s1color) plotregion(style(none)) xsize(20) ysize(18) ///
         ylabel(-20(5)35) xlabel(10 (4) 40) ysca(titlegap(*10)) ///
         xsca(titlegap(*6))
* Predict the level 2 variance function
generate rslev2var = ///
       [RP2]var(cons) ///
       + 2*[RP2]cov(cons\gw1)*gw1 + [RP2]var(gw1)*gw1^2 ///
           2*[RP2]cov(cons\gw2)*gw2 + 2*[RP2]cov(gw1\gw2)*gw1*gw2
       +
[RP2]var(gw2)*gw2^2
generate rslev2sd = sqrt(rslev2var)
* Plot the subject-level variance function
* Observe the variance/sd increase with GA
line rslev2var gawk_, sort xlabel(10 (2) 40) xtitle(Gestational age (weeks)) ///
vtitle("Between-subject variance") title("RS (2-levels) variance by GA")
scheme(s1color) ///
 plotregion(style(none)) legend(off) ysca(titlegap(*10)) xsca(titlegap(*6)) xsize(20)
ysize(18)
line rslev2sd gawk_, sort xlabel(10 (2) 40) xtitle(Gestational age (weeks)) ///
vtitle("Between-subject variability (SD)") title("RS (2-levels) in SD") ///
 scheme(s1color)
                    plotregion(style(none))
                                               legend(off)
                                                                 ysca(titlegap(*10))
xsca(titlegap(*6)) xsize(20) ysize(18)
* Generate the predicted 97 and 3 centiles
generate rslev2high97 = rsmean_2levels + 1.88*rslev2sd
```

generate rslev2low3 = rsmean 2levels - 1.88\*rslev2sd \* Generate the predicted 90 and 10 centiles generate rslev2high90 = rsmean 2levels + 1.28\*rslev2sdgenerate rslev2low10 = rsmean\_2levels - 1.28\*rslev2sd \* Generate the predicted 1SD generate rslev2high1SD = rsmean\_2levels + 1\*rslev2sd generate rslev2low1SD = rsmean\_2levels - 1\*rslev2sd \* Generate the predicted 2SD generate rslev2high2SD = rsmean 2levels + 2\*rslev2sd generate rslev2low2SD = rsmean\_2levels - 2\*rslev2sd \* Plotting percentiles format gain\_ %9.0f \* Plot the predicted mean relationship together with the predicted centiles twoway (scatter gain\_gawk\_if ppns==0,msymbol(smcircle\_hollow) mcolor(gs12)) /// (line rslev2low3 rsmean\_2levels rslev2high97 gawk\_ if ppns==0, sort lcolor(red red red) lpattern(dash dash dash)), /// ylabel(-10(5)30) xlabel(10 (2) 40) xtitle(Gestational age (weeks)) ytitle("GWG (kg)") /// title("Random Slope model (2-levels)") scheme(s1color) plotregion(style(none)) legend(col(4) /// order(1 4) lab(1 "Raw data") lab(4 "RS (2-levels)")) ysca(titlegap(\*10)) /// xsca(titlegap(\*6)) xsize(20) ysize(18) \* Plot the predicted mean relationship together with the predicted centiles twoway (scatter gain\_gawk\_if ppns==0,msymbol(smcircle\_hollow) mcolor(gs12)) /// (line rslev2low3 rslev2high97 gawk\_ if ppns==0, sort lcolor(blue blue) lpattern(dash dash dash)) /// (line rslev2low10 rsmean\_2levels rslev2high90 gawk\_ if ppns==0, sort lcolor(red green red) lpattern(dash dash dash)), /// ylabel(-10(5)30) xlabel(10 (2) 40) xtitle(Gestational age (weeks)) ytitle("GWG (kg)") /// title("Random Slope model (2-levels)") scheme(s1color) plotregion(style(none)) legend(col(4) /// order(1 4) lab(1 "Raw data") lab(4 "RS (2-levels)")) ysca(titlegap(\*10)) /// xsca(titlegap(\*6)) xsize(20) ysize(18) \* Plot the predicted mean relationship together with the predicted z-scores twoway (scatter gain\_gawk\_if ppns==0,msymbol(smcircle\_hollow) mcolor(gs12)) /// (line rslev2low2SD rslev2high2SD gawk\_ if ppns==0, sort lcolor(blue blue) lpattern(dash dash dash)) /// (line rslev2low1SD rsmean 2levels rslev2high1SD gawk if ppns==0, sort lcolor(red green red) lpattern(dash dash dash)), /// ylabel(-10(5)30) xlabel(10 (2) 40) xtitle(Gestational age (weeks)) ytitle("GWG (kg)") ///

```
title("Random Slope model (2-levels)") scheme(s1color) plotregion(style(none))
legend(col(4) ///
        order(1 4 ) lab(1 "Raw data") lab(4 "RS (2-levels)")) ysca(titlegap(*10)) ///
         xsca(titlegap(*6)) xsize(20) ysize(18)
*** Internal validation
gen complete_weeks=int(gawk_)
** Number of obs below 3<sup>rd</sup> or above 97<sup>th</sup> centiles
gen below_c3 = cond(gain_<rslev2low3,1,0)
tab below c3
bysort complete_weeks: tab below_c3
gen above_c97 = cond(gain_>rslev2high97,1,0)
tab above c97
bysort complete_weeks: tab above_c97
** Number of obs below 10<sup>th</sup> or above 90<sup>th</sup> centiles
gen below_c10 = cond(gain_<rslev2low10, 1, 0)
tab below c10
bysort complete_weeks: tab below_c10
gen above_c90 = cond(gain_>rslev2high90,1,0)
tab above_c90
bysort complete weeks: tab above c90
```

# Step 5. R code 2 (Extraction of GAMLSS centiles used a function created by prof. Stef van Buuren and gently provided by Dr. Iris Eekhout)

```
# Read the dataset (Normal weight women only)
# Fit the model for each pre-pregnancy BMI
library(gamlss)
# Adding 20kg to weight gain, since it cannot have negative or 0 values
summary(nwdata$gain )
nwdata gwg = nwdata gain_+20
summary(nwdata$gwg)
# Rounding the GA for 2 digits
nwdata$ga=round(nwdata$gawk_, digits=2)
# Using LMS function
m1 <- lms(y=gwg, x=ga, data= nwdata, trans.x=F, n.cyc = 20)
# Extracting the DF
df=cbind(m1$mu.df,m1$sigma.df,m1$nu.df,m1$tau.df)
df
# Diagnostic
plot(m1)
```

fittedPlot(m1, x=nwdata\$ga) wp(m1, xvar = nwdata\$ga, n.inter = 20, ylim.worm=1.0) O.stats(m1, xvar = nwdata\$ga, n.inter=20) # Ditribution by GA library(gamlss.util) plotSimpleGamlss(gwg,ga,m1, data=nwdata, x.val=seq(10,40,2),xlim=c(-10,40)) # Selected centiles: 3,10,25,50,75,90,97 centiles(m1, xvar=nwdataga, cent = c(3, 10, 25, 50, 75, 90, 97), legend = F, ylab = "Gestational weight gain (kg)", xlab = "Gestational age (weeks)". main = NULL, main.gsub = NULL, xleg = min(xvar), yleg = max(obj\$y), save = FALSE, plot = TRUE, points = TRUE, pch = 15, cex = 0.5, col = gray(0.75), col.centiles = c("blue", "darkgreen", "orange", "red", "orange", "darkgreen", "blue"), lty.centiles = 1, lwd.centiles = 4) # Codes adapted from Prof. Van Buuren/Dr. Iris Eekhout # Extracting values for the table # Make a new data frame with a column for gestational age and for other covariates if they exist  $nd \le data.frame(ga=c(10:40))$ # Use the predict function from gamlss to predict the mu, sigma, nu and tau for the new data (nd), according the model (m1) refpred.BMI0<- predictAll(m1, terms = c("mu", "sigma", "nu", "tau"), newdata = nd, data = nwdata)ref.fitBMI0 <-data.frame(pop="meta", sex="W", sub="N", x = nd[,1],mu=round(refpred.BMI0\$mu,4), sigma=round(refpred.BMI0\$sigma,4), nu=round(refpred.BMI0\$nu,4), tau=round(refpred.BMI0\$tau,4)) # Transform the weight gain variable (gwg) in the data, to a z-score using the reference table. # In the distribution option, you can specify the model that you used. The reference (ref) should contain a column for each parameter in the model. # Package AGD is necessary library (AGD) nwdata\$Zscores<- y2z(y=nwdata\$gwg, x=nwdata\$ga, sex="W", sub="N", ref=ref.fitBMI0, dist="BCT", dec=4) ## Function to get the centiles based on the z-scores get.centiles <- function( z=z, x = x. ref=ref. sex="W".

```
sub=sub,
 dec=2) {
 zr <- rep(z,times=length(x))
 xr <- rep(x, each = length(z))
 w <- z2y(z=zr,x=xr,sex=sex,sub=sub, ref=ref,dec=dec,dist="BCT")
 w <- matrix(w,ncol=length(z), byrow=TRUE)
 w <- data.frame(sub=sub,sex=sex,x=x,round(w,dec), row.names=NULL)
 dimnames(w)[[2]] <- c("sub", "sex", "x", as.character(z))
 return(w)
}
## Get the centiles to use for the plot
x <- c(10:40)
percentiles <-
c(0.01,0.023,0.03,0.05,0.10,0.16,0.20,0.25,0.50,0.75,0.80,0.84,0.90,0.95,0.977,0.99)
z \leq qnorm(percentiles) \# transform percentiles to z-scores
centile_refs_BMI0 <- get.centiles(x=x, sub="N",z=z,ref=ref.fitBMI0)
centile_refs_BMI0 <- data.frame(bmigr=1,centile_refs_BMI0)
colnames(centile_refs_BMI0) <- c("bmigr", "sub", "sex", "x",
paste0("p",as.character(percentiles*100)))
# Set the centile refs back to the original scale (0 is no gain)
centile_refs_BMI0[,paste0("p",as.character(percentiles*100))] <-
(centile refs BMI0[,paste0("p",as.character(percentiles*100))])-20
## New graph – scale back to zero
g1 <- ggplot(centile refs BMI0, aes(x,p50))+geom line(size=1.2, colour="red")+
 geom_line(aes(x,p10), colour="darkgreen", size=1.2)+
 geom_line(aes(x,p90), colour="darkgreen", size=1.2)+
 geom_line(aes(x,p25),colour="orange", size=1.2)+
 geom_line(aes(x,p75), colour="orange", size=1.2)+
 scale_x_continuous(breaks=seq(10,40,1), limits=c(10,40))+
 scale_y_continuous(breaks=seq(-10,25,2), limits=c(-10,25))+
 theme bw() +
 theme(panel.border = element_blank(),
     axis.line = element_line(colour = "black"),
    panel.grid.major = element line(),
    panel.grid.major.x = element_blank(),
    panel.grid.major.y = element blank(),
    panel.grid.minor = element_blank(),
    panel.grid.minor.x = element blank(),
    panel.grid.minor.y = element_blank(),
    strip.background = element_rect(colour = "black", size = 0.5),
    legend.key = element_blank(),
     axis.text.y = element_text(size=12, family="serif", color="black"),
     axis.text.x = element text(size=14,family="serif", color="black", hjust = 1,
vjust=0.5),
     axis.title.x = element_text(size=15,family="serif",
color="black",margin=margin(20,0,0,0)),
```

```
axis.title.y = element_text(size=15,family="serif",
color="black",margin=margin(0,20,0,0))
)+
xlab("Gestational age (weeks)")+ ylab("Weight gain (kg), BMI Normal")
g1
# Saving the parameters and centiles
save(ref fitBMI0_file="reffitBMI0_10_40 RData")
```

save(ref.fitBMI0, file="reffitBMI0\_10-40.RData") write.csv2(centile\_refs\_BMI0, file="centiles\_normal10-40.csv")

19

4

Example: Woman with self-reported pre-pregnancy weight of 60.0 kg and height of 160 cm, has a pre-pregnancy BMI of 23.4 kg/m<sup>2</sup>, and is classified as normal weight. At the 32<sup>nd</sup> gestational weeks, she has gained 10 kg. This value is used to classify her z-score according to gestational age, using the equation from figure 2 (copied below) and the model parameters from Supplementary table 3. At 32 gestational weeks, M = 29.9311, S = 0.1305, L (or nu) = 0.3089 (hence L  $\neq$  0), so, using the first equation:

11

$$Z = \begin{cases} \frac{1}{S \times L} \left[ \left( \frac{GWG + 20}{M} \right)^{L} - 1 \right], & \text{if } L \neq 0 \\ \frac{1}{S} \log \left( \frac{GWG + 20}{M} \right), & \text{if } L = 0 \end{cases}$$

12

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$$Z = \frac{1}{0.1305 \times 0.3089} \left[ \left( \frac{10+20}{29.9311} \right)^{0.3089} - 1 \right] = 0.0176$$

15

This woman is in the 0.0176 z-score, consequently, around the 50<sup>th</sup> percentile at
the 32<sup>nd</sup> gestational week.

18

19 20