Journal of Epidemiology 27 (2017) 265–273

Contents lists available at ScienceDirect

Journal of Epidemiology

journal homepage: http://www.journals.elsevier.com/journal-of-epidemiology/

Original Article

Growth charts for Brazilian children with Down syndrome: Birth to 20 years of age

Fabio Bertapelli [a, b, *], Stamatis Agiovlasitis [c], Maira Rossmann Machado [b], Raísa do Val Roso [b], Gil Guerra-Junior [b, d]

[a] CAPES Foundation, Ministry of Education of Brazil, Brazil
[b] Growth and Development Lab, Center for Investigation in Pediatrics, Faculty of Medical Sciences, University of Campinas, Brazil
[c] Department of Kinesiology, Mississippi State University, USA
[d] Department of Pediatrics, Faculty of Medical Sciences, University of Campinas, Brazil

ARTICLE INFO

Article history:
Received 31 January 2016
Accepted 29 June 2016
Available online 18 March 2017

Keywords:
Trisomy 21
Weight
Height
Development

ABSTRACT

Background: The growth of youth with Down syndrome (DS) differs from that of youth without DS, and growth charts specific to DS have been developed. However, little is known about the growth of Brazilian youth with DS. The objective of this study was to construct growth charts for Brazilian youth with DS and compare the growth data with the Child Growth Standards of the World Health Organization (WHO) and charts for children with DS from other studies.

Methods: Mixed longitudinal and cross-sectional data were collected at University of Campinas, 48 specialized centers for people with intellectual disabilities, and two foundations for people with DS between 2012 and 2015. A total of 10,516 growth measurements from birth to 20 years of age were available from 938 youth with DS (53.7% boys) born between 1980 and 2013. The Lambda Mu Sigma method was applied to construct the curves using generalized additive models for location, scale, and shape.

Results: Length/height-for-age, weight-for-age, and head circumference-for-age percentile curves were generated for Brazilian boys and girls from birth to 20 years of age. Differences in growth of Brazilian youth ranged from −0.8 to −3.2 z-scores compared to WHO standards, and −1.9 to +1.3 compared to children with DS in other studies.

Conclusions: These specific growth charts may guide clinicians and families in monitoring the growth of Brazilian children and adolescents with DS.

Introduction

Down syndrome (DS) is a chromosomal disorder with prevalence estimates ranging from 6.1 to 13.1 per 10,000 people.[1,2] Children with DS have different growth patterns compared to children without DS.[3,4] Abnormal bone development is the most common feature and is hypothesized to be regulated by genetic factors.[5] A review showed that stature of children with DS was 0.4–4.0 standard deviations below that of children without DS.[6] This growth restriction has led to the development of specific growth charts for children with DS around the world.[6–9] Specific growth charts are essential for guiding clinicians and families in monitoring the growth of infants, children, and adolescents with DS from different racial and ethnic backgrounds.

The Brazilian Ministry of Health recommends using the growth charts by Mustacchi[10] for Brazilian children with DS aged 0–24 months.[11] These growth charts were developed in a sample of children with DS born before 2000. Studies around the world show a secular trend in growth, especially for weight status,[12,13] so updated growth charts may be needed. Furthermore, the previous charts for Brazilian children were developed with a relatively small sample using exclusively retrospective data from a single community. For Brazilian youth with DS older than 2 years and up to 18 years of age, the Brazilian Ministry of Health[11] recommends using

* Corresponding author. Growth and Development Lab, Center for Investigation in Pediatrics, Faculty of Medical Sciences, University of Campinas, SP 13083-887, Brazil.
E-mail address: fbertapelli@gmail.com (F. Bertapelli).
Peer review under responsibility of the Japan Epidemiological Association.

http://dx.doi.org/10.1016/j.je.2016.06.009

the growth charts by Cronk et al,[14] which were developed for American youth with DS; however, these charts may not represent the growth of Brazilian youth with DS. In addition, they date back to the 1980s, and their overall applicability has been questioned.[15] Importantly, there is a need to construct updated growth charts for Brazilian youth with DS employing newer and more accurate statistical methods for constructing growth curves. Taken together, these data suggest that new growth charts are necessary because previously developed references may not be representative of the present growth of infants, children, and adolescents with DS in Brazil.

Existing charts for children in the general population developed by the World Health Organization (WHO) and charts for children with DS in other countries may not be representative of the growth of Brazilian youth with DS. Past research has shown that the WHO growth standards may underestimate the growth of youth with DS,[9] but the extent to which this applies to Brazilian youth with DS is not known. Furthermore, Brazil is a large and developing multi-cultural country with a population differing from that of other countries in racial, ethnic, and economic backgrounds. Children from low- and middle-income countries are more likely to show higher prevalence of growth restriction and stunting.[16] Therefore, the growth of Brazilian youth with DS may differ from those of youth with DS in other countries; however, this has not been empirically examined. More research is needed to examine whether previously developed standards reflect the current growth of Brazilian youth with DS.

The objective of this study was to construct length/height-for-age, weight-for-age, and head circumference-for-age growth charts specifically for Brazilian youth with DS from birth to 20 years. We also compared the growth data with the WHO Child Growth Standards, and specific growth charts for youth with DS of other studies.

Materials and methods

Participants

We derived data from youth with DS using two approaches: (a) by actively recruiting participants; and (b) by retrospectively examining medical records. Active recruitment of youth with DS and examination of retrospective medical records occurred at several sites across the State of São Paulo, Brazil. Participating sites were the University of Campinas, 48 specialized centers for people with intellectual disabilities, and two foundations for people with DS. The State of São Paulo has an estimated population of 44,035,304 people, or 21.7% of the total population of Brazil. The sites were selected to represent distinct geographic regions of State of São Paulo, with population composition similar to that of the total Brazilian population in terms of racial and ethnic backgrounds. We included in the sample individuals who had complete data for weight, height, birthdate, and trisomy 21 karyotype. We excluded children who were born very prematurely (before 32 weeks of gestation).

Standard protocol approvals

The study protocol was approved by the research ethics committee of the University of Campinas. All parents or guardians of participants with DS provided written informed consent.

Data collection

A mixed longitudinal and cross-sectional study was carried out between 2012 and 2015. Retrospective data were collected at all sites mentioned above. We used existing medical records, which were supplemented in part with an interview with parents or guardians to confirm the following variables: birthdate, age, sex, skin color, gestational age, comorbidities, weight, length/height, and head circumference. All parents/guardians we interviewed maintained and confirmed the growth records of their children. In addition, we used medical records from the sites, which had permission to use the data for research; in those cases, we could not confirm the medical records from the parents/guardians. Prospective growth data were collected from the sites a total of three times in years 2012, 2013, and 2014. Anthropometric measurements were conducted by trained testers using standardized procedures.[17] Youth were measured without shoes and wearing light clothes. Measurements were taken at four sites used standard equipment. Height was measured with a stadiometer (E210; Wiso®, Santa Catarina, Brazil). Weight was measured with a digital scale (W801; Wiso®, Santa Catarina, Brazil). Head circumference was measured with a non-stretch tape.

Data screening and analyses

We used data points at monthly intervals for youth aged 0–36 months, and at annual intervals for youth aged 3–20 years. We performed data screening in several phases. First, we excluded duplicated data based on identification code, birthdate, and measurement date. Second, we removed data points when values were five standard deviations above or below the mean. Third, we excluded data points demonstrating loss of height over time. Fourth, we identified and corrected transcription errors by reexamination of personal source data or medical records. A total of 137 measurements (1.3%) were excluded from the data cleaning.

Growth charts were developed using the generalized additive models for location, scale, and shape package in R software (R Foundation for Statistical Computing, Vienna, Austria).[18] In constructing the growth charts for weight-for-age, length/height-for-age, and head circumference-for-age, we generated percentiles ranging from the 97th to the 3rd. Goodness of fit was checked using worm plots. The Lambda Mu Sigma (LMS) method was selected as the most appropriate to smooth the growth curves.[19] LMS is a transformation of skewness (L), median (M), and coefficient of variation (S).

We calculated z-scores to compare our growth data to the WHO standards[20,21] and to those previously developed for youth with DS of other countries, including the Netherlands, Portugal, United States, and United Arab Emirates,[7,9,22,23] for which data were available. We also compared our growth data with those of Brazilian youth with DS previously published by Mustacchi (2002).[10] When the L, M, and S values were available, we calculated z-scores as:

$$Z = \left[(X/M)^L - 1\right] \Big/ L{*}S,$$

where X is the observed measurement (weight, length/height or head circumference). When the L, M, and S values were not available, the following equation was used:

$$Z = (X - M)/SD,$$

where X is the observed measurement, M is the mean, and SD is the standard deviation; M and SD were obtained from age-specific growth standards. Multilevel regression models were performed to examine the effects of comorbidities, year of birth, gestational age, and data source (prospective vs. retrospective data) on the growth of individuals with DS.

Results

Sample description

The sample consisted of youth with DS aged 0–20 years born between 1980 and 2013. All children lived with their families. A total of 4 infants who were born very prematurely (before 32 weeks of gestation) were excluded. The percentage of prospectively collected data and data extracted from medical records was 10% and 90%, respectively. A total of 10,516 growth measurements (weight = 4723; length/height = 4440; head circumference = 1353 data points) from birth to 20 years of age were available from 938 youth with DS (53.7% boys) born between 1980 and 2013. The characteristics of Brazilian children with DS from birth to 20 years of age are presented in Table 1.

Growth curves

Percentiles curves for Brazilian boys and girls with DS aged 0–20 years were generated for weight-for-age, length/height-for-age, and head circumference-for-age (Figs. 1–10). The subset of data from medical chart reviews had significantly greater Z-scores for weight compared with the prospectively collected data ($p = 0.01$);

Table 1
Characteristics of Brazilian boys and girls with DS from birth to 20 years (n = 938).

	Number of subjects (number of measurements)	
	Boys	Girls
Age, months		
Birth	192 (490)	173 (445)
1–6	124 (979)	110 (990)
7–12	104 (667)	99 (770)
13–18	94 (441)	81 (411)
19–24	90 (355)	74 (309)
25–30	85 (263)	68 (193)
31–36	72 (205)	56 (171)
Age, years		
3–4	118 (367)	103 (337)
5–6	99 (282)	80 (234)
7–8	103 (302)	78 (227)
9–10	104 (301)	79 (219)
11–12	102 (296)	66 (184)
13–14	100 (268)	75 (194)
15–16	77 (181)	56 (154)
17–18	66 (144)	41 (95)
19–20	39 (83)	26 (62)
Number of measurements	Subjects, %[e]	
	Boys	Girls
1	42.2	37.7
2–5	29.9	34
6–10	12.3	8.4
11–20	11.6	15.5
21–32	4	4.4
Infant skin color[a]		
White	70.5	69.8
Black	4.3	7.7
Gestational age[b]		
33–36 weeks	16.2	13
≥37 weeks	39.6	50
Comorbidities		
Heart disease[c]	26	28.8
Heart surgery	7.8	13.9
Hypothyroidism[d]	19.2	29.2

[a] A total of 224 subjects (23.9%) were missing data.
[b] A total of 383 subjects (40.9%) were missing data.
[c] A total of 217 subjects (23.2%) were missing data.
[d] A total of 175 subjects (18.7%) were missing data.
[e] Percentage of subjects who were measured on one or more occasion.

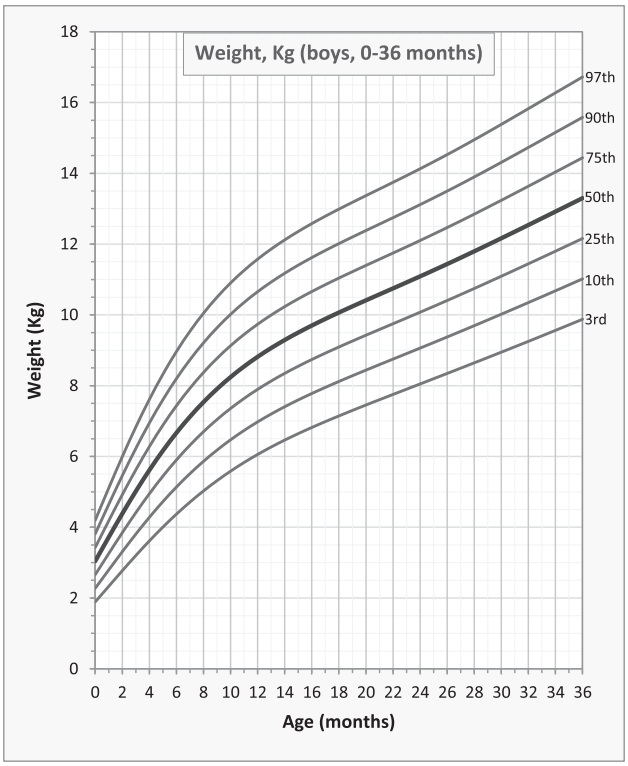

Fig. 1. Weight-for-age percentile curves for Brazilian boys with Down syndrome from birth to 36 months of age. Age is reported in months.

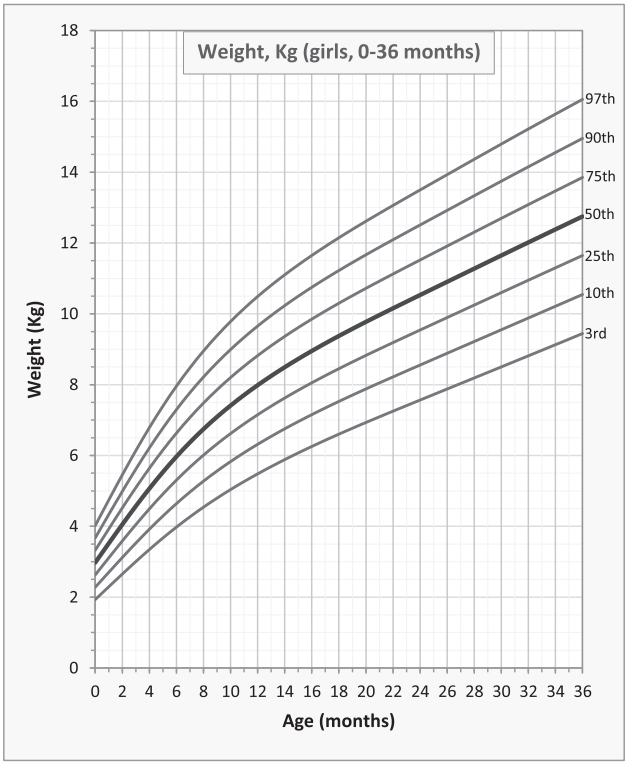

Fig. 2. Weight-for-age percentile curves for Brazilian girls with Down syndrome from birth to 36 months of age. Age is reported in months.

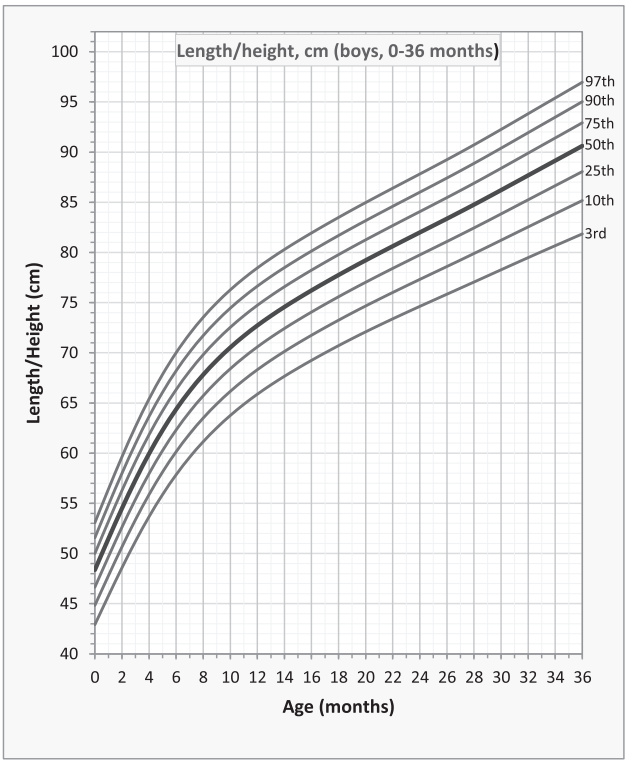

Fig. 3. Length/height-for-age percentile curves for Brazilian boys with Down syndrome from birth to 36 months of age. Age is reported in months.

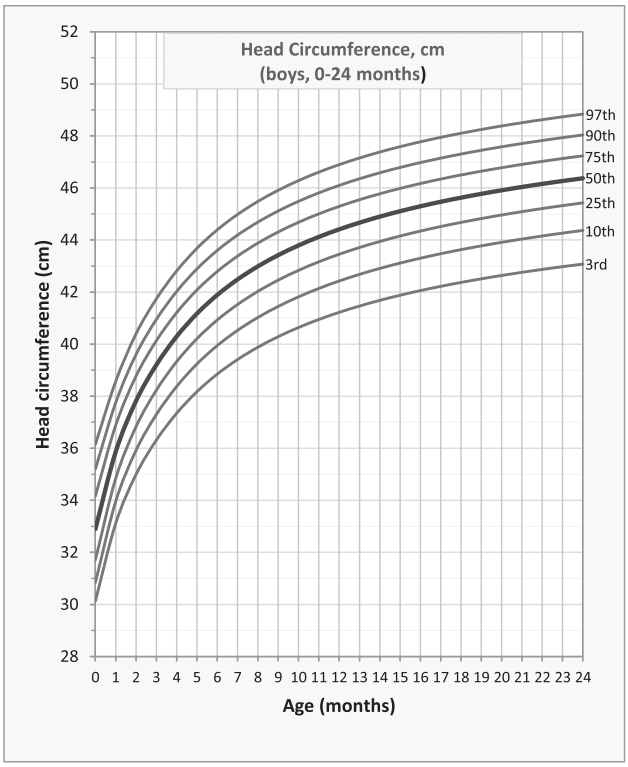

Fig. 5. Head circumference-for-age percentile curves for Brazilian boys with Down syndrome from 0 to 24 years of age. Age is reported in months.

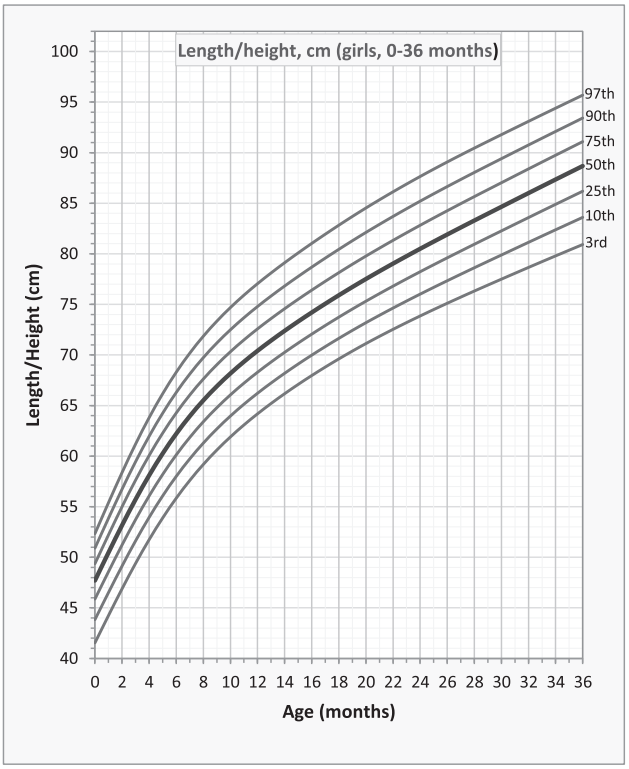

Fig. 4. Length/height-for-age percentile curves for Brazilian girls with Down syndrome from birth to 36 months of age. Age is reported in months.

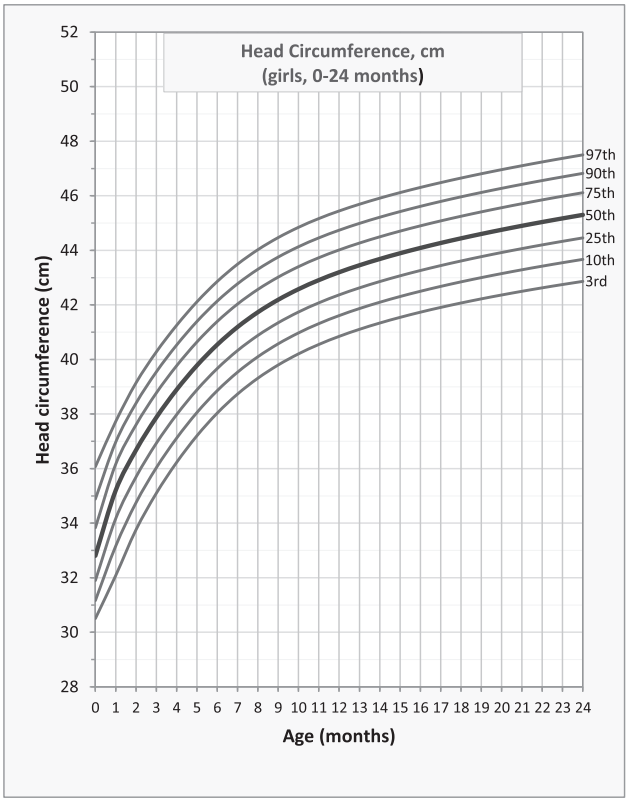

Fig. 6. Head circumference-for-age percentile curves for Brazilian girls with Down syndrome from 0 to 24 years of age. Age is reported in months.

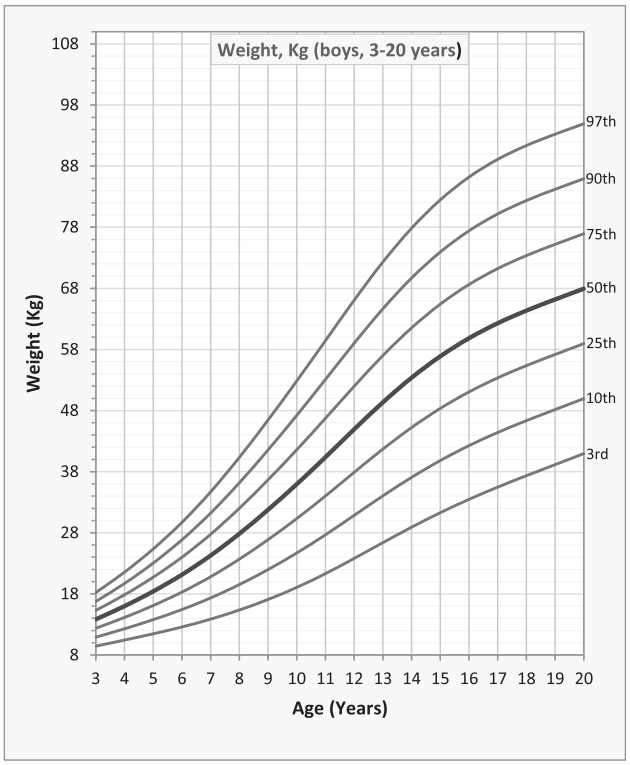

Fig. 7. Weight-for-age percentile curves for Brazilian boys with Down syndrome from 3 to 20 years of age. Age is reported in years.

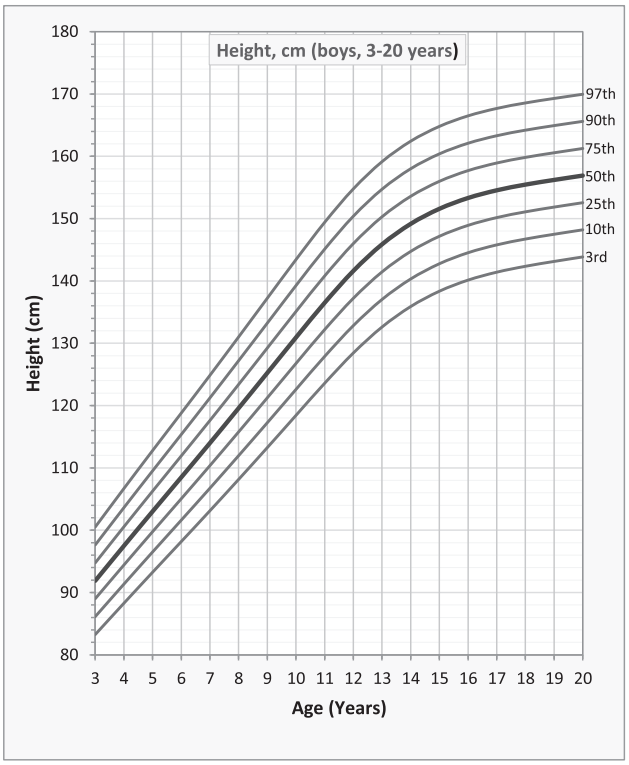

Fig. 9. Height-for-age percentile curves for Brazilian boys with Down syndrome from 3 to 20 years of age. Age is reported in years.

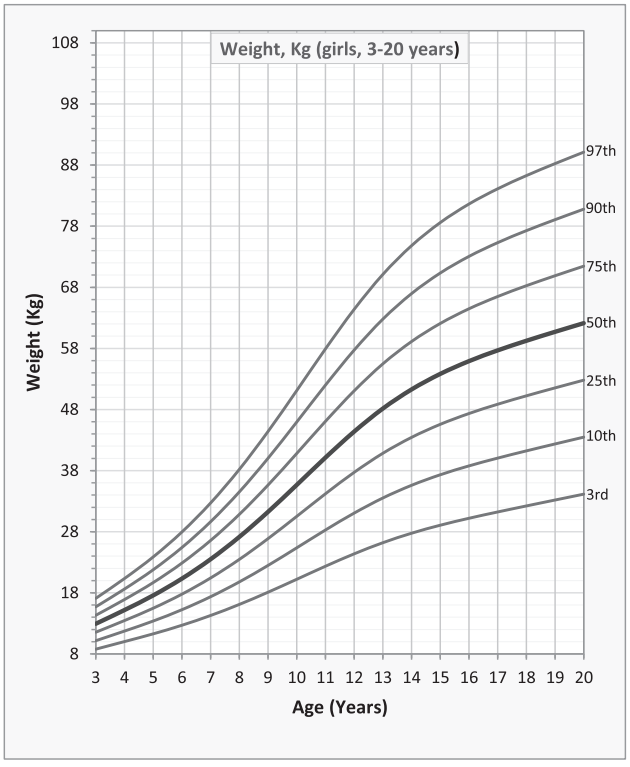

Fig. 8. Weight-for-age percentile curves for Brazilian girls with Down syndrome from 3 to 20 years of age. Age is reported in years.

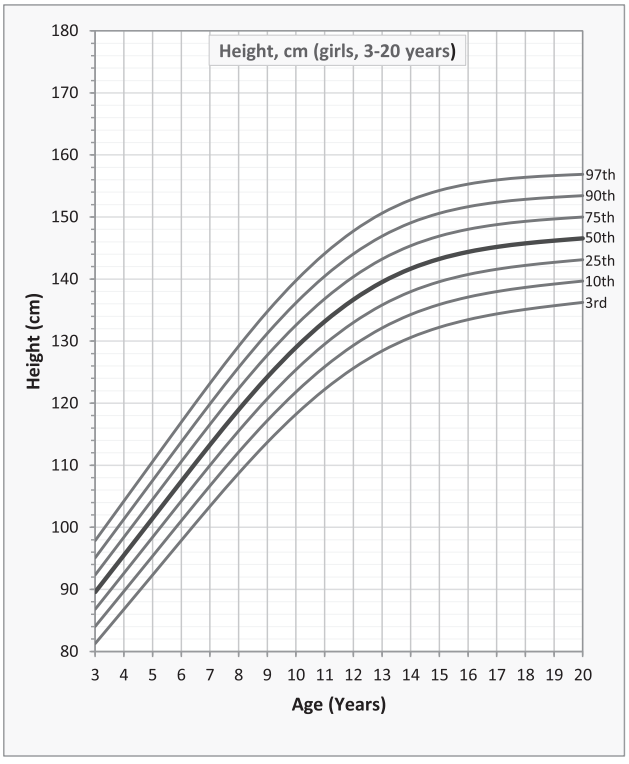

Fig. 10. Height-for-age percentile curves for Brazilian girls with Down syndrome from 3 to 20 years of age. Age is reported in years.

however, there was no difference in height z-scores ($p = 0.73$). We found a non-significant effect of year of birth on growth of children with DS ($p > 0.05$). The growth patterns of children with DS born 33–36 weeks of gestation were not significantly different than those children born ≥37 weeks ($p > 0.05$). Growth of healthy children with DS and those with congenital heart defects and hypothyroidism showed no difference in mean height, weight, or head circumference Z-scores ($p > 0.05$). Fig. 11 shows the differences in length/height of Brazilian youth with DS that ranged from −1.1 to −3.2 z-scores compared to WHO standards, and −1.7 to +1.3 z-scores compared to children with DS of other studies. The average differences between our sample and WHO standards were 3 cm for birth and 20 cm for final height. Fig. 12 shows the differences in mean weight that ranged from −0.8 to −1.4 z-scores compared to WHO standards, and −0.8 to +1.0 compared to children with DS of other studies. Head circumference z-scores ranged from −1.0 to −1.9 compared to WHO standards, and −1.0 to +1.2 compared to children with DS of other studies (Fig. 13).

Discussion

In this study, we developed length/height, weight, and head circumference growth charts for Brazilian youth with DS aged 0–20 years. We also found differences in length/height, weight, and head circumferences z-scores between our sample, WHO standards, and specific growth charts for youth with DS of other studies. These results have implications for monitoring growth in Brazilian youth with DS.

The growth levels of the present youths with DS were well below those described by WHO standards at all developmental phases: fetal, infant, childhood, and pubertal. Different results were expected, but the extent was unknown. The growth restriction is possibly linked to genetic factors. This proposition is supported by ultrasound bone measurements at 11–14 weeks of gestation showing short femur lengths in fetuses with trisomy 21.[24] Abnormal bone development in trisomy 21 is thought to originate from genotype–phenotype interaction during embryonic development.[5] The differences between our sample and the WHO norms varied by age, with a large standard deviation score occurring during the first months of life. The divergence in the average of height-for-age was pronounced at 12–15 years and continued to increase, reaching its greatest level at 17–19 years, resulting in a mean 20 cm below that of the general population. These findings are supported by previous research showing that individuals with DS grow more slowly compared to individuals without DS.[7,9] It has been suggested that growth restriction in adolescents with DS may result from differences in bone age[25]; however, the pubertal growth — an important period of human development[26] — is not known for youth with DS. In summary, the Brazilian youth with DS composing our sample were shorter in comparison to WHO standards for youth without DS. Although genotype–phenotype interaction has been suggested to contribute to the growth of children with DS, its mechanisms remains unknown.

The present boys and girls with DS who were younger than 15 months had lower weights than those predicted by the WHO standards. Length restriction and feeding difficulties may explain these lighter weights of infants with DS in this developmental

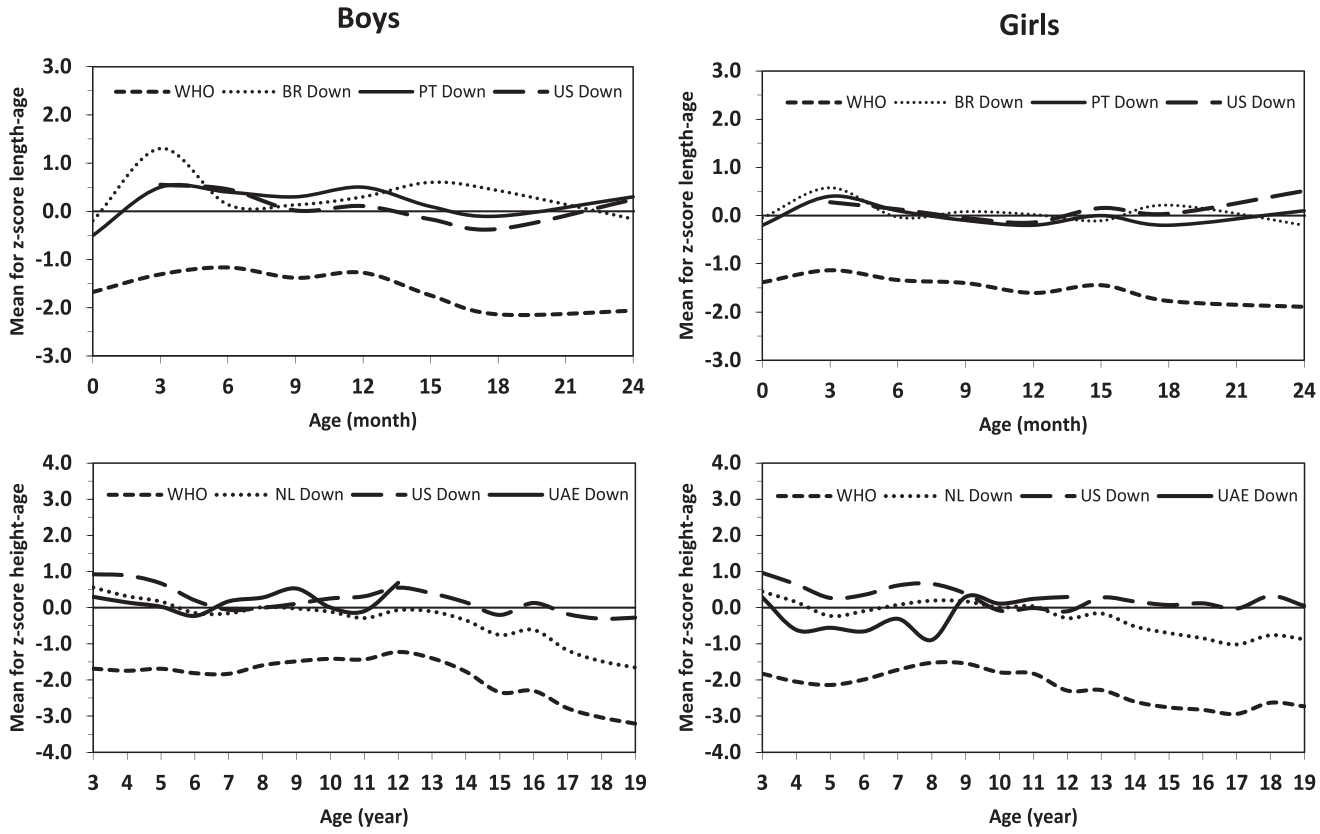

Fig. 11. Mean length/height z-scores of the present Brazilian boys and girls with Down syndrome in comparison to WHO standards and previously published growth charts for Down syndrome from Portugal (PT), Netherlands (NL), Brazil (BR), United States (US), and United Arab Emirates (UAE). The top panels cover 0–24 months of age. The bottom panels cover 3–19 years of age. Negative z-scores indicate that the present sample had lower scores compared to growth data from the other studies.

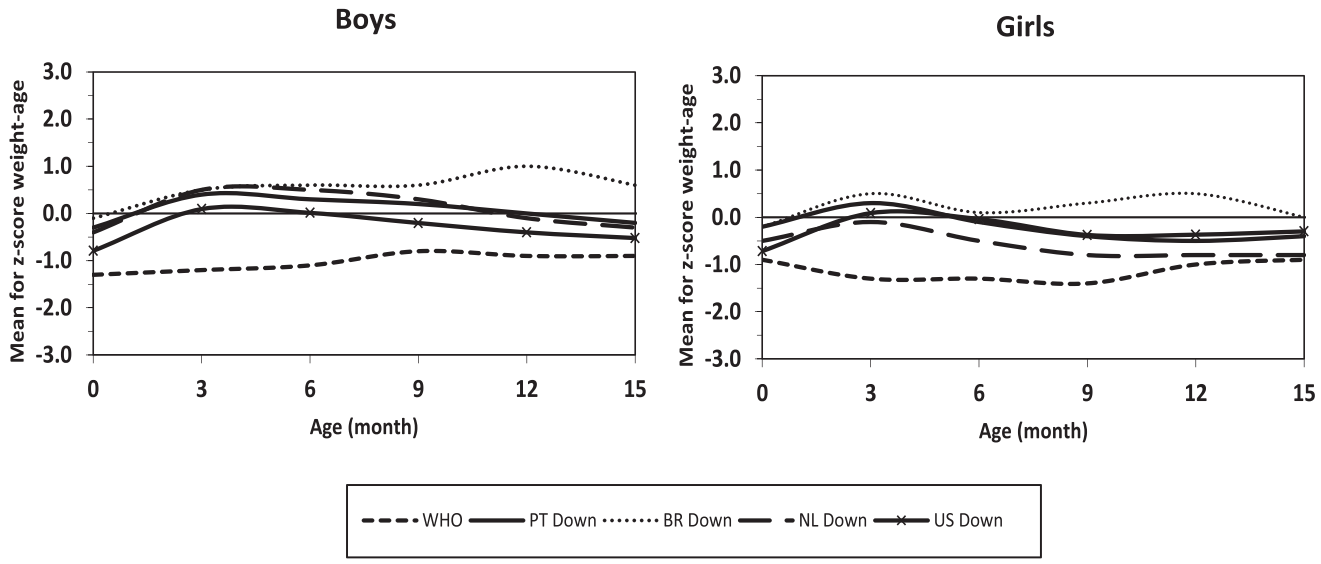

Fig. 12. Mean weight z-scores of the present Brazilian boys and girls with Down syndrome aged 0–15 months in comparison to WHO standards and previously published growth charts for Down syndrome from Portugal (PT), Netherlands (NL), Brazil (BR), and United States (US). Negative z-scores indicate that the present sample had lower scores compared to growth data from the other studies.

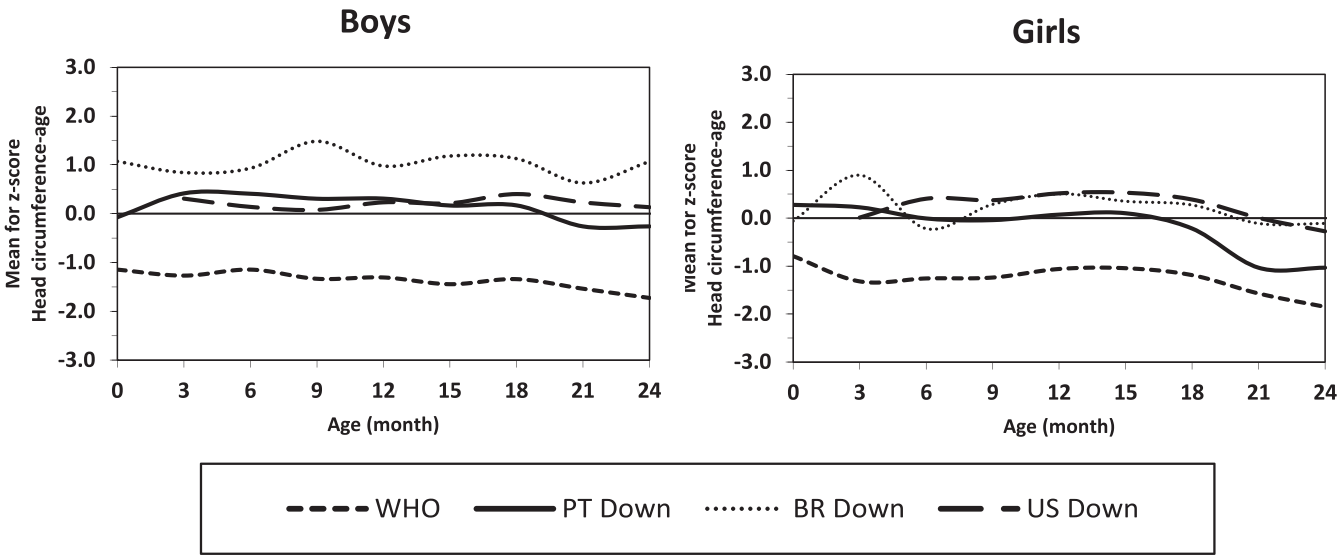

Fig. 13. Mean head circumference z-scores of the present Brazilian boys and girls with Down syndrome aged 0–24 months in comparison to WHO standards and previously published growth charts for Down syndrome from Brazil (BR), Portugal (PT), and United States (US). Negative z-scores indicate that the present sample had lower scores compared to growth data from the other studies.

stage. In a retrospective cohort study, fetuses with DS who had isolated short femur were more likely to have low birth weight.[27] Examining birth weights of 8825 infants with DS born in England and Wales between 1989 and 2010, Morris et al[28] reported that babies with DS were lighter than those without DS. Increased risks of low birthweight are known to be mediated by a number of risk factors, such as poor placentation due to maternal age older than 35 years.[29] It is also possible that the mean weight of infants with DS might be affected by early feeding difficulties associated to hypotonia, chronically open mouth, and oral motor dysfunction.[30,31] Overall, infants with DS were lighter than infants without DS, and this restricted weight may be linked to length faltering and feeding difficulties.

This study found differences in mean length/height, weight, and head circumference compared to youth with DS of other studies. We found that the mean length z-scores were close to zero between studies during the first 24 months. Two other studies have also examined the growth patterns of children with DS from the different countries in the first months of life. A study carried out with 434 Egyptian children with DS aged 0–36 months found that the mean length of those children was not significantly different from that previously reported for Egyptian children with DS.[3] Another large longitudinal study found that Turkish children with DS had no significant difference in length compared to Portuguese children with DS aged 0–3 years.[4] The slight difference in mean length z-scores between our sample and those from other studies suggests that genetic factors may have a small influence on linear growth of those individuals with DS in the first months of life. We also found that the height of children with DS aged 3–13 years in our sample was slightly different from that of children with DS from

the other studies. However, our study showed that the mean height of Brazilian boys and girls was well below that of their Dutch counterparts aged 14–19 years. Style et al[32] also found a similar growth pattern among children with DS from different countries across age. They reported that height centiles between British and American children with DS were slightly different at ages 3–12 years, and children with DS from the United States aged >12 years had lower height those from the United Kingdom. In contrast, we found that the mean height z-scores of our sample were close to zero when compared to American adolescents with DS at ages 12–19 years. The differences between our sample and Dutch adolescents with DS could be attributed to genetic variations. It has been suggested that the height of Dutch children with DS is likely to be higher than those of children with DS of other countries.[22]

The main difference between our data and those previously published by Mustacchi[10] on Brazilian children was that our sample of boys had higher weight during the first months of life. We also found that the mean head circumference of our sample of boys was higher than Mustacchi charts. The difference between our data and those of Mustacchi is likely due to issues related to study design. The Mustacchi charts were developed in a sample of children with DS exclusively born before 2000. Although we could not find any effect of birthyear on growth in the current study, further research is needed to examine secular trend in growth between populations with DS. Studies around the world show a secular trend in growth, especially for weight status[12,13] — the probability exists that youth with DS who live in the same environment have followed this trend. In addition, the previous charts by Mustacchi were developed with a relatively small sample using exclusively retrospective growth data from a single community. In summary, the differences in growth between our sample and those from the other studies cannot be directly inferred from the present results; however, it may partly be due to issues related to study design as well as genetic and environmental differences between studies.

These gender-specific growth charts have clinical implications for monitoring growth in Brazilian youth with DS aged 0–20 years. The Brazilian Ministry of Health[11] recommends using the charts by Mustacchi[10] for Brazilian infants with DS aged 0–24 months, and, for youth aged 2–18 years, it recommends the growth charts by Cronk et al,[14] which were originally developed for American youth with DS. However, these charts may not be representative of the growth of Brazilian youth with DS. For example, the Mustacchi chart[10] would classify a 3 months-old male infant with a length of 56 cm at the 50th percentile, whereas our chart would classify this infant at the 25th percentile. Furthermore, graphical inspection of the height percentiles chart by Cronk et al[14] indicates similar performance. For example, a 36 months-old boy with a height of 86 cm would be classified at the 50th percentile by the Cronk chart[14] but below the 25th percentile based on our chart for height. Such discrepancies could be avoided by using the present growth charts, which also allow for continuous monitoring from 0 to 20 years of age. Therefore, the new charts will allow clinicians and families to monitor the growth of Brazilian youth with DS throughout the developmental years.

The following limitations of this study should be considered. First, the data from medical records were not obtained with standardized techniques, and this could lead to measurement errors. Second, we did not recruit participants from sites throughout Brazil, but from a single state. It should be considered, however, that the State of São Paulo has a population composition similar to the total population of Brazil in terms of racial and ethnic backgrounds. Finally, these growth charts do not accurately reflect the full genetic growth potential of children with DS because they are not based exclusively on a healthy sample of youth. This study also had strengths. First, we had a large sample size. Second, we had data for youth aged 0–20 years, thus covering the full range of development. Finally, we conducted a thorough cleaning process for measurements errors and influential observations.

Conclusion

In conclusion, the growth of Brazilian youth with DS differs from growth references established by WHO, and from the growth of youth with DS described in other studies. These new specific growth charts may guide clinicians and parents in the evaluation and management of the growth of Brazilian children and adolescents with DS.

Acknowledgements

Fabio Bertapelli's scholarship was funded by the CAPES foundation (BEX 3546/15-2), Ministry of Education of Brazil. Maira Rossmann Machado and Raísa do Val Roso were supported by an undergraduate scholarship from the National Council for Scientific and Technological Development (CNPq), (2014/118104-4; 2014/118369-8). The authors acknowledge Roberto A. Soares (FEAPAES/SP), João F. Cosmo, Alessandra C.P.D. Costa, and Eliane T. Nogueira (APAE/CAMPINAS), Fabio Crozara (FSD), and Célia de Oliveira and Maria A. C. Pacheco (CEESD) for their excellent technical assistance. They also acknowledge the children and their families, clinicians, AIEP/FCM/UNICAMP, DGM/FCM/UNICAMP, CIPED/FCM/UNICAMP, FEAPAES/SP, Fundação Síndrome de Down, CEESD, and APAES/SP (Américo Brasiliense, Araçatuba, Araraquara, Arujá, Assis, Cabreúva, Campinas, Candido Motta, Caraguatatuba, Catanduva, Cordeirópolis, Cravinhos, Diadema, Dracena, Ferraz de Vasconcelos, General Salgado, Guaíra, Guaratinguetá, Ibitinga, Itapevi, Itápolis, Jaguariúna, José Bonifácio, Marília, Matão, Mogi das Cruzes, Monte Alto, Nhandeara, Nova Odessa, Novo Horizonte, Ourinhos, Palmital, Piedade, Pirassununga, Poá, Pompeia, Porto Feliz, São José do Rio Preto, Salto, Salto Grande, São Caetano do Sul, Santo André, Santa Bárbara d'Oeste, Sumaré, Taquaritinga, Taquarituba, Votuporanga, and Xavantes) for their collaboration in this study.

References

1. Presson AP, Partyka G, Jensen KM, et al. Current estimate of Down syndrome population prevalence in the United States. *J Pediatr*. 2013;163:1163–1168.
2. de Graaf G, Vis JC, Haveman M, et al. Assessment of prevalence of persons with Down syndrome: a theory-based demographic model. *J Appl Res Intellect Disabil*. 2011;24:247–262.
3. Afifi HH, Aglan MS, Zaki ME, Thomas MM, Tosson AM. Growth charts of Down syndrome in Egypt: a study of 434 children 0–36 months of age. *Am J Med Genet Part A*. 2012;158A:2647–2655.
4. Tuysuz B, Goknar NT, Ozturk B. Growth charts of Turkish children with Down syndrome. *Am J Med Genet Part A*. 2012;58A:2656–2664.
5. Blazek JD, Malik AM, Tischbein M, Arbones ML, Moore CS, Roper RJ. Abnormal mineralization of the Ts65Dn Down syndrome mouse appendicular skeleton begins during embryonic development in a Dyrk1a-independent manner. *Mech Dev*. 2015;136:133–142.
6. Bertapelli F, Martin JE, Goncalves EM, de Oliveira Barbeta VJ, Guerra-Junior G. Growth curves in Down syndrome: implications for clinical practice. *Am J Med Genet Part A*. 2014;164A:844–847.
7. Aburawi EH, Nagelkerke N, Deeb A, Abdulla S, Abdulrazzaq YM. National growth charts for United Arab Emirates children with Down syndrome from birth to 15 years of age. *J Epidemiol*. 2015;25:20–29.
8. Su X, Lau JT, Yu CM, et al. Growth charts for Chinese Down syndrome children from birth to 14 years. *Arch Dis Child*. 2014;99:824–829.
9. Zemel BS, Pipan M, Stallings VA, et al. Growth charts for children with Down syndrome in the United States. *Pediatrics*. 2015;136:e1204–e1211.
10. Mustacchi Z. *Growth Charts for Individuals with Down Syndrome Living in Urban Area of São Paulo City*. São Paulo: University of São Paulo; 2002:192 (Curvas padrão pondero-estatural de portadores de síndrome de Down procedentes da região urbana da cidade de São Paulo. São Paulo: Universidade de São Paulo. 192 p.).
11. Brasil, Ministério da Saúde, Secretaria de Atenção à Saúde, Departamento de Ações Programáticas Estratégicas. *Health Care Guidelines for the Person with Down Syndrome*. Ministry of health of Brazil; 2012:58–60 (Diretrizes de

atenção à pessoa com Síndrome de Down. Brasília: Ministério da Saúde. 2012; p. 58–60).
12. de Onis M, Blossner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr*. 2010;92:1257–1264.
13. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384: 766–781.
14. Cronk C, Crocker AC, Pueschel SM, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. *Pediatrics*. 1988;81:102–110.
15. Bull MJ. American Academy of Pediatrics Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics*. 2011;128:393–406.
16. Victora CG, Rivera JA. Optimal child growth and the double burden of malnutrition: research and programmatic implications. *Am J Clin Nutr*. 2014;100, 1611S–12S.
17. Brasil. Ministério da Saúde, Secretaria de Atenção à Saúde, Departamento de Atenção Básica. *Food and Nutrition Surveillance System – Sisvan. Anthropometry: How to Weigh and Measure*. Ministry of Health of Brazil; 2004:62 (Vigilância alimentar e nutricional- Sisvan: antropometria: como pesar e medir. Brasília: Ministério da Saúde. 2004; p. 62).
18. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2016. https://www.r-project.org/. Accessed 10.02.2015.
19. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med*. 1992;11:1305–1319.
20. WHO Multicentre growth reference study Group. WHO child growth standards based on length/height, weight and age. *Acta Paediatr Suppl*. 2006;450:76–85.
21. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85:660–667.
22. Van Gameren-Oosterom HB, Van Dommelen P, Oudesluys-Murphy AM, Buitendijk SE, Van Buuren S, Van Wouwe JP. Healthy growth in children with Down syndrome. *PLoS One*. 2012;7:e31079.
23. Fernandes A, Mourato AP, Xavier MJ, Andrade D, Fernandes C, Palha M. Characterization of the somatic evolution of Portuguese children with Trisomy 21-Preliminary results. *Down Syndr Res Pract*. 2001;6:134–138.
24. Longo D, DeFigueiredo D, Cicero S, Sacchini C, Nicolaides KH. Femur and humerus length in trisomy 21 fetuses at 11–14 weeks of gestation. *Ultrasound Obstet Gynecol*. 2004;23:143–147.
25. de Moraes ME, Tanaka JL, de Moraes LC, Filho EM, de Melo Castilho JC. Skeletal age of individuals with Down syndrome. *Spec Care Dent*. 2008;28:101–106.
26. Silventoinen K, Haukka J, Dunkel L, Tynelius P, Rasmussen F. Genetics of pubertal timing and its associations with relative weight in childhood and adult height: the Swedish Young Male Twins Study. *Pediatrics*. 2008;121:e885–e891.
27. Weisz B, David AL, Chitty L, et al. Association of isolated short femur in the midtrimester fetus with perinatal outcome. *Ultrasound Obstet Gynecol*. 2008;31: 512–516.
28. Morris JK, Cole TJ, Springett AL, Dennis J. Down syndrome birth weight in England and Wales: implications for clinical practice. *Am J Med Genet Part A*. 2015;167:3070–3075.
29. Restrepo-Mendez MC, Lawlor DA, Horta BL, et al. The association of maternal age with birthweight and gestational age: a cross-cohort comparison. *Paediatr Perinat Epidemiol*. 2015;29:31–40.
30. Cooper-Brown L, Copeland S, Dailey S, et al. Feeding and swallowing dysfunction in genetic syndromes. *Dev Disabil Res Rev*. 2008;14:147–157.
31. Frazier JB, Friedman B. Swallow function in children with Down syndrome: a retrospective study. *Dev Med Child Neurol*. 1996;38:695–703.
32. Styles M, Cole T, Dennis J, Preece M. New cross sectional stature, weight, and head circumference references for Down's syndrome in the UK and Republic of Ireland. *Arch Dis Child*. 2002;87:104–108.