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## NORMATIVE GROWTH CHARTS FOR SHWACHMAN-DIAMOND SYNDROME IN CHILDREN 0 TO 8 YEARS OLD.

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3 NORMATIVE GROWTH CHARTS FOR SHWACHMAN-DIAMOND SYNDROME IN  
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5 CHILDREN 0 TO 8 YEARS OLD.

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## Abstract

### Objectives.

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder. The predominant manifestations of the syndrome include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities. Patients frequently present failure to thrive, susceptibility to short stature.

Average birth weight is at the 25th percentile; by the first birthday >50% of patients have dropped below the 3<sup>rd</sup> percentile for height and weight.

The study aims to estimate the growth charts for patients affected by SDS to give a reference tool helpful in the medical care and for growth surveillance throughout childhood of patients.

### Setting and participants.

This retrospective, observational study includes 106 patients (64 M) with available information from birth to 8 years, among the 122 patients included in the Italian National Registry of SDS, born between 1975 and 2016. Gender, birth date and auxological parameters at repeated assessment times are collected. General Additive Model for Location Scale and Shape method was applied to build the growth charts. A set of different distributions were used and the more appropriate were selected in accordance to the criterion of the smallest Akaike's information criterion.

### Results.

A total of 408 measurements were collected and analyzed. The median number of observations per patient was 3, range 1-11. In accordance with the methods described, specific SDS growth charts were built for weight, height and body mass index, separately in males and females.

The 50th and 3rd percentiles of weight and height of the healthy population (WHO standard-references) correspond to the 97th and 50th percentiles, respectively, of the SDS population (SDS specific growth charts), whilst for the BMI the difference is less evident.

## Conclusions.

Specific SDS growth charts obtained from our analysis allow a more appropriate classification of patients based on the auxological parameters, representing a useful reference tool for evaluating their grow-up during childhood.

## Article summary

- Specific SDS growth charts were built for weight, height and BMI, separately for males and females: the 50th and 3rd percentiles of weight and height of the healthy population corresponded to the 97th and 50th percentiles, respectively, of the SDS population.
- The data used for the growth charts do not represent the natural development of the disease but the growth development of SDS subjects receiving medical care. Even if the data in constructing growth charts should ideally come from prospective, longitudinal studies on large groups, this approach cannot be used when considering rare syndromes.
- Specific SDS growth charts obtained from our analysis allow a more appropriate classification of patients based on the auxological parameters, representing a useful reference tool for evaluating their grow-up during childhood.

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3 Data sharing statement

4 We are not interested in participating in study at the Queensland University of Technology (QUT)  
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6 in Australia.  
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11 Competing interests' statement

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13 There are no competing interests for any author.  
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## Introduction

Shwachman–Diamond syndrome (SDS) (OMIM 260400) is a rare autosomal recessive disorder first described in 1964.<sup>1</sup> The predominant manifestations of the syndrome include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities.<sup>2-5</sup> Patients frequently present failure to thrive, susceptibility to infections and short stature.<sup>1-4</sup>

Pancreas insufficiency is present in the first days after birth and it is characterized by replacement of exocrine components with fatty tissue and preserved islets of Langerhans and ductal architecture. During childhood, almost 50% of patients present spontaneous improvement in pancreatic function, discontinuing pancreatic enzyme supplements.<sup>2,4,6-8</sup>

A persistent or intermittent neutropenia occurs in 88–100% of patients.<sup>1,2,7-10</sup> Bone marrow biopsy usually reveals a hypoplastic specimen with varying degrees of hypoplasia and fat infiltration.<sup>2,10</sup>

Up to one third of the patients may develop myelodysplastic syndrome and acute myeloid leukemia.<sup>11-14</sup>

In 2002, the gene (*SBDS*) involved in the syndrome has been identified on chromosome 7q11,<sup>15</sup> although mutation in the *DNAJC21* gene have also been associated to a SDS phenotype, as, possibly, mutations of *EFL1* and *SRP54* genes.<sup>16-18</sup> The *SBDS* is expressed ubiquitously in all mammalian tissue, and other organs may be involved such as teeth and oral cavity, liver, heart, kidneys and skin.<sup>5-7</sup>

In spite of new *SBDS* mutations identified in later years, until now up to 10% of patients with clinical features of SDS lack *SBDS* mutations.<sup>15,19</sup> The negative gene test does not, however, exclude the diagnosis, and an accurate evaluation of clinical signs is compulsory to diagnose the presence of the syndrome.

Cognitive impairment has been noted in the majority of these patients, albeit with intragroup variability,<sup>20-22</sup> this has a serious impact on quality of life, limiting independence and quality of

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3 life.<sup>22</sup> Neuroimaging studies<sup>23-25</sup> reported diffuse brain alterations in the brain structure and  
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5 connectivity.

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7 Several clinical studies reported growth failure with malnutrition as a common feature in the first  
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9 year of life particularly prior to diagnosis. This condition is attributable to various factors, including  
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11 inadequate nutrient intake with or without feeding difficulties, pancreatic insufficiency, and  
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13 recurrent infections.<sup>1,2,4,7,26</sup> The average birth weight is at the 25<sup>th</sup> percentile, by the first birthday  
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15 over half of patients have dropped below the 3<sup>rd</sup> percentile for both height and weight. After  
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17 diagnosis and the start of appropriate therapy, most children show normal growth velocity, but  
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19 remain consistently below the 3<sup>rd</sup> percentile for height and weight.<sup>2,4,8,26</sup> These alterations are not  
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21 related to a pancreatic insufficiency or to an inappropriate caloric intake but seem to be linked  
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23 directly to biallelic mutations of the SBDS gene and the growth of these patients result different  
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25 from that of healthy children.  
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29 Up to date there are no specific SDS growth charts available as for other disorders with marked  
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31 growth retardation such as Down syndrome, Turner syndrome, Ellis-van Creveld syndrome,  
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33 achondroplasia.<sup>27-30</sup> Indeed disease-specific charts are a helpful tool in medical care, monitoring  
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35 growth more accurately, and for research.  
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38 The aim of this retrospective, multicentre, observational study is to estimate the growth chart for  
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40 patients affected by SDS in order to provide a reference tool to monitor the growth of children with  
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42 this disease throughout childhood.  
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## Method

This study includes patients who are part of the Italian National Registry of SDS for whom height, weight and the main demographic characteristic were available in their first 8 years of life. In the Registry, all the 122 patients have a SDS diagnosis confirmed by genetic analysis. For each subject the following characteristics have been collected: gender, birth date, height, weight, assessment date, available clinic information. Measurements have been recorded in accordance with standard criteria by age period. A total of 645 observations on 122 patients were recorded, but data beyond 8 years of age were not included in the analysis because they were available for a too small number of patients in limited data points. Sixteen patients had only information beyond 8 years of age and were not included in the analysis, thus 408 observations on 106 patients with assessments in their first 8 years of life were analyzed,

The primary endpoint is to estimate percentiles for height, weight and BMI for males and females. The protocol was approved by the local Ethics Committee (CE n 1944). All patients signed an informed consent to be included in the Registry.

### *Patient and Public Involvement*

Patients were not involved in the design, recruitment and conduct of this study.

### *Statistical analysis and Growth charts generation*

Data were initially prepared using the statistical software SAS, and then analyzed by the software R for growth curve estimation<sup>31</sup>. A 3-month window was used for each of the three anthropomorphic measures; in case of multiple assessments the average of the values available inside the window was considered. We constructed growth curves for weight, height and BMI from birth to 8 years, each with 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles for age. Data from male and female individuals were analyzed separately.

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2 Normative data for growth parameters were obtained from tables published from Cacciari et al.<sup>32</sup>

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4 The Italian normative data were limited to ages 2–8 years, thus for ages 0-2 WHO data were used.<sup>33</sup>

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6 To model the growth charts, the GAMLSS (General Additive Model for Location Scale and Shape)  
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8 package for the R statistical program was used. This tool allows all the parameters of the  
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10 distribution of the response variable to be modelled as linear/non-linear or smooth functions of the  
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12 explanatory variables<sup>34-36</sup>.

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15 The distribution of height, weight and BMI was modelled by four parameters representing location,  
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17 scale, skewness and kurtosis, using cubic penalized smoothing lines. A set of different distributions  
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19 were used and the more appropriate were selected in accordance to the criterion of the smallest  
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21 AIC. Worm plots and q-q plots were used for the analysis of residuals.

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24 With a sample size of 60 patients the 50<sup>th</sup>, 25<sup>th</sup>/75<sup>th</sup> and 3<sup>rd</sup>/97<sup>th</sup> centiles could be estimated reaching  
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26 a standard error of about 0.8, 0.9 and 1.3, respectively.  
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## Results

A total of 106 patients (64 males and 42 females) were considered eligible for the analysis, with a total of 408 measurements collected from 1975 to 2016, with a median number of 3 observations per patient, range 1-11 (Table 1). All patients were Caucasian, with a median age at diagnosis of 13.8 months, range 0 days- 35.6 years. The median gestational age was 39 weeks, range 29-42 and the median weight at birth was 2.8 kg (0.85-4.2). Pancreas insufficiency was observed in 91 patients (86%). Six patients were treated with growth hormone (GH), 5 after their first 8 years of life and 1 at age 7.5.

Main patients' characteristics and mutations are reported in Table 2 and Table 3.

In accordance with the methods described, specific SDS growth charts were built for weight, height and BMI, separately for males and females. Each subject had the same number of observations for each growth parameter included in the database.

Figure 1 shows growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and females. Table 4 shows the 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles: from birth to 2 years, the centiles are estimated every 3 months, from 2 to 6 years every 6 months, and once a year from 6 to 8 years.

In Figure 2 the estimated SDS growth charts are shown together with Italian reference curves.

Compared to typically developing individuals (standard population), the values of 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles, respectively. At 8 years, the 50<sup>th</sup> centiles for height in SDS patients corresponds to the 3<sup>rd</sup> centile and to the -2 SD value in the healthy population. For the BMI centiles the difference is less evident, meaning that the growth retardation is harmonic.

## Discussion

SDS is a rare disease with a not well defined prevalence. Severe growth retardation (particularly in length/height) is one of the typical features and it is conceivable that it is linked to the genetic cause of the disease.

At present, no growth charts have been validated for SDS; the charts we show here represent the first set of normative curves for SDS children 0- 8 years. As in healthy children specific charts for SDS are important tools in monitoring treatment efficacy and for routine medical follow up.

In this study we used data from all children included in the Italian SDS registry, with available assessments from birth to 8 years. All patients had SDS diagnosis confirmed by genetic mutations on both alleles, although up to 10% of subjects with SDS diagnosis described in literature do not present mutations of the *SBDS* gene. In this way we tried to reduce bias in our dataset.

In spite of the rarity of the disease we had the possibility to generate separate charts for males and females until the age of 8. When compared to normal (regular) growth charts, the SDS charts do not differ in form for this period of age. The 50<sup>th</sup> percentile of SDS charts for weight and height is positioned on 3<sup>rd</sup> percentile of regular charts, both for males and females. The low percentile at birth for length and weight indicates that prenatal retardation occurs, then continuing in the postnatal period.

BMI curves are similar both for normal and SDS population, indicating that also in SDS the weight and height trend is harmonic. These results as a whole suggest these growth curves are influenced by the genetic defect rather than from a malabsorption/malnutrition or inherited factors.

For SDS subjects these specific growth-charts can be used in managing problems related to growth, and specifically may be useful to recognize patients to be investigated with regard to GH activity and any possibility of specific treatment. These specific growth charts are also extremely useful to address nutritional counselling. The parents of the SDS patients regularly ask for the best diet to increase the growth of their children. Sometimes an overfeeding behaviour has been

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3 reported with the aim to influence the height. This erroneous interpretation of the growth problems  
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5 in SDS may cause obesity and negative consequences on skeletal apparatus.  
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7 Given the small number of observations beyond 8 years, the growth charts were curtailed at age 8.

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9 Several associated manifestations of the syndrome, such as heart, renal or skeletal alteration could  
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11 theoretically influence the growth of the patients. In our set we did not identify co-morbidity risk  
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13 factors able to influence growth retardation. In any case, in consideration of the rarity of the disease  
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15 and the consequent small sample size, we did not exclude children with medical problems as  
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17 already considered in other similar works.<sup>37-38</sup>  
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20 We have to consider some limitations in our study; one is that data used for the growth charts do not  
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22 represent the natural development of the disease but the growth development of SDS subjects  
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24 receiving medical care. We are aware that the data in constructing growth charts should ideally  
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26 come from prospective, longitudinal studies on large groups, however when we are considering rare  
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28 syndromes, this approach cannot be used.  
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31 In Italy, as well as in many Northern European countries, the secular trend slowed down or even  
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33 reached a plateau since the 1980s/1990s. Since only less than 3% of measurements included in this  
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35 study were collected before 1980, we did not consider any correction for secular trend.<sup>39-40</sup>  
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38 Furthermore, our curves do not quite grasp the age of puberty and we do not have definitive  
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40 information on what affects the final height. In any case, in literature some SDS patients older than  
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42 18 are described with percentiles remaining in the low average or below the 3<sup>rd</sup> percentile for both  
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44 weight and height<sup>3,4</sup> indicating that the growth spurt does not affect a substantial change in the  
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46 trend of growth.  
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49 The present growth charts can be used to compare growth of SDS individual (height, weight, BMI)  
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51 and general population but also to compare growth of an individual child with peers of the same  
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53 age and sex with the syndrome.

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55 SDS is a worldwide disease with patients diagnosed in every part of the world; the present growth-  
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57 charts should be used with caution when studying SDS individuals of other ethnic backgrounds;  
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3 as presented, the curves reflect an accurate picture of the Italian SDS population.

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5 Our efforts will be to collect more data to improve our knowledge on the syndrome and to  
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7 construct growth-charts until 18 years of age. These tools would allow us to gather more  
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9 information on SDS, especially the influence on the growth of pubertal development, as until now  
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11 we have only sporadic data on this point.

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13 Finally, when similarly to other rare diseases<sup>41</sup>, clinical trials aimed to assess therapies for SDS  
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15 basic defect will be possible, growth chart comparison in treated vs untreated SDS populations  
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17 could be a relevant endpoint.  
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3 **Figure 1** - Growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and  
4 females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each graph.  
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9 **Figure 2** – Estimated SDS growth charts compared to reference Italian curves. The values of 97<sup>th</sup>  
10 and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of the  
11 reference population. For the BMI centiles the difference is less evident.  
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The authors have nothing to disclose.

## AUTHOR CONTRIBUTIONS

Conception and design: MC, PS, TG. Provision of study materials or patients: CM, PS, PE, CS, ME, NE, DC.

Collection and assembly of data: CM, PE. Data analysis: TG, MA. Manuscript writing: All authors. Final approval of manuscript: All authors.



## Reference

1. Shwachman H, Diamond LK, Oski FA, *et al.* The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 1964; 65:645–63.
2. Aggett PJ, Cavanagh NP, Matthew DJ, *et al.* Shwachman's syndrome. A review of 21 cases. *Arch Dis Child* 1980; 55:331-47.
3. Mack DR, Forstner GG, Wilschanski M, *et al.* Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology* 1996;111:1593–602.
4. Cipolli M, D’Orazio C, Delmarco A, *et al.* Shwachman’s Syndrome: pathomorphosis and long-term outcome. *J Pediatr Gastroent Nutr* 1999;29:265–72.
5. Mäkitie O, Ellis L, Durie PR, *et al.* Skeletal phenotype in patients with Shwachman–Diamond syndrome and mutations in SBDS. *Clin Genet* 2004;65:101–12.
6. Mack DR Shwachman–Diamond syndrome. *J Pediatr* 2002;141:164–5.
7. Cipolli M. Shwachman–Diamond syndrome: clinical phenotypes. *Pancreatology* 2001;1:543-8.
8. Rothbaum R, Perrault J, Vlachos A, *et al.* Shwachman-Diamond syndrome: report from an international conference. *J Pediatr* 2002;141:266-70.
9. Burroughs L, Woolfrey A, Shimamura A. Shwachman–Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am* 2009;23:233–48.
10. Dror Y *et al.* Impaired ability of bone marrow stroma from patients with Shwachman–Diamond syndrome to support hematopoiesis. *Brit J Haematol* 1998;102:161 (Abs P-0638)
11. Dror Y, Squire J, Durie P, *et al.* Malignant myeloid transformation with isochromosome 7q in Shwachman–Diamond syndrome. *Leukemia* 1998;12:1591–5.
12. Maserati E, Minelli A, Pressato B, *et al.* Shwachamn syndrome as mutator phenotype responsible for myeloid dysplasia/neoplasia through karyotype instability and chromosomes 7 and 20 anomalies. *Genes Chromosom Cancer* 2006;45:375–82.

- 1  
2  
3 13. Dror Y, Freedman MH. Shwachman–Diamond syndrome: an inherited preleukemic bone  
4 marrow failure disorder with a clonal hematopoietic progenitor and a  
5 microenvironment. *Blood* 1999;94:3048–54  
6  
7  
8  
9 14. Cesaro S, Oneto R, Messina C, *et al.* Haematopoietic stem cell transplantation for Shwachman-  
10 Diamond disease: a study from the European Group for blood and marrow transplantation. *Br J*  
11 *Haematol* 2005;131:231-6.  
12  
13  
14  
15 15. Boocock GR, Morrison JA, Popovic M, *et al.* Mutations in SBDS are associated with  
16 Shwachman–Diamond syndrome. *Nat Genet* 2003;33:97–101.  
17  
18  
19  
20 16. Dhanraj S, Matveev A, Li H, *et al.* Biallelic mutations in DNAJC21 cause Shwachman-  
21 Diamond syndrome. *Blood* 2017; 129:1557-62.  
22  
23 17. Stepensky P, Chacon-Flores M, Kim KH, *et al.* Mutations in EFL1, an SBDS partner, are  
24 associated with infantile pancytopenia, exocrine pancreatic insufficiency and skeletal anomalies in a  
25 Shwachman-Diamond like syndrome. *J Med Genet* 2017; 54:558-66.  
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27  
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29 18. Carapito R, Konantz M, Paillard C, *et al.* Mutations in signal recognition particle SRP54 cause  
30 syndromic neutropenia with Shwachman-Diamond-like features. *J Clin Invest* 2017; 127:4090-103.  
31  
32  
33  
34 19. Nicolis E, Bonizzato A, Baroukh M, *et al.* Identification of novel mutations in patients with  
35 Shwachman–Diamond syndrome. *Human Mutation* 2005;25:410.  
36  
37  
38  
39 20. Kent A, Murphy GH, Milla P. Psychological characteristics of children with Shwachman  
40 syndrome. *Arch Dis Child* 1990;65:1349-52.  
41  
42  
43 21. Kerr EN, Ellis L, Dupuis A, *et al.* The behavioral phenotype of school-age children with  
44 Shwachman-Diamond Syndrome indicates neurocognitive dysfunction with loss of Shwachman-  
45 Bodian-Diamond syndrome gene function. *J Pediatr* 2010;156: 433–8.  
46  
47  
48  
49 22. Perobelli S, Nicolis E, Assael BM, *et al.* Further characterization of Shwachman-Diamond  
50 syndrome: psychological functioning and quality of life in adult and young patients. *Am J Med*  
51 *Genet A.* 2012;158A:567-73.  
52  
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2  
3 23. Toiviainen-Salo S, Mäkitie O, Mannerkoski M, *et al.* Shwachman-Diamond syndrome is  
4 associated with structural brain alterations on MRI. *Am J Med Genet A* 2008;146A:1558-64.  
5  
6  
7 24. Booij J, Reneman L, Alders M, *et al.* Increase in central striatal dopamine transporters in  
8 patients with Shwachman–Diamond syndrome: additional evidence of a brain phenotype. *Am J Med*  
9  
10  
11  
12  
13 25. Perobelli S, Alessandrini F, Zoccatelli G, *et al.* Diffuse alterations in grey and white matter  
14 associated with cognitive impairment in Shwachman–Diamond syndrome: Evidence from a  
15 multimodal approach. *Neuroimage Clin* 2015;7:721-31.  
16  
17  
18 26. Dror Y, Donadieu J, Koglmeyer J, *et al.* Draft consensus guidelines for diagnosis and treatment  
19 of Shwachman-Diamond syndrome. *Ann N Y Acad Sci.* 2011;1242:40-55.  
20  
21  
22 27. Zemel BS, Papanicolaou M, Stallings VA, *et al.* Growth charts for children with Down syndrome in the  
23 United States. *Pediatrics* 2015;136:e1-e8.  
24  
25  
26 28. Verbeek S, Eilers PH, Lawrence K, *et al.* Growth charts for children with Ellis–van Creveld  
27 syndrome, *Eur J Pediatr* 2011;170:207–211.  
28  
29  
30 29. Gawlik A, Gawlik T, Augustyn M, *et al.* Validation of growth charts for girls with Turner  
31 syndrome. *Int J Clin Pract* 2006; 60:150–5.  
32  
33  
34 30. Tofts L, Das S, Collins F, *et al.* Growth charts for Australian children with achondroplasia. *Am J*  
35  
36  
37  
38  
39  
40  
41 31. R version 3.3.3 (2017-03-06), The R Foundation for Statistical Computing  
42  
43  
44 32. Cacciari E, Milani S, Balsamo A, *et al.* Italian cross-sectional growth charts for height, weight  
45 and BMI (2 to 20 yr), *J Endocrinol Invest* 2006;29:581-93.  
46  
47  
48 33. De Onis M, Garza C, Victoria CG, *et al.* The WHO multicentre growth reference study:  
49 planning, study design and methodology. *Food Nutr Bull* 2004;25:15-26.  
50  
51  
52 34. Cole TJ. The LMS method for constructing normalized growth standards, *Eur J Clin Nutr* 1990;  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 35. Cole TJ and Green PJ. Smoothing reference centile curves: the LMS method and penalized  
4 likelihood. *Stat Med* 1992;11:1305-19.  
5  
6  
7 36. Rigby RA, Stasinopoulos DM. Generalized Additive Models for Location Scale and Shape  
8 (GAMLSS) in R, *J Stat Softw.* 2007; 23:1-46.  
9  
10  
11 37. Beets L, Rodriguez-Fonseca C, Hennekam RC. Growth charts for individuals with Rubinstein-  
12 Taybi syndrome. *Am J Med Genet A* 2014;164A:2300-9  
13  
14  
15 38. Su X, Lau JT, Yu CM, Chow, et al. Growth charts for Chinese Down syndrome children from  
16 birth to 14 years. *Arch Dis Child* 2014;99:824-9.  
17  
18  
19 39. Larnkaer A, Attrup Schrøder S, Schmidt IM, et al. Secular change in adult stature has come to a  
20 halt in northern Europe and Italy. *Acta Paediatr* 2006;95:754-5.  
21  
22  
23 40. Bonthuis M, van Stralen KJ, Verrina E, Use of National and International Growth Charts for  
24 Studying Height in European Children: Development of Up-To-Date European Height-For-Age  
25 Charts. *PLoS One* 2012;7:e42506.  
26  
27  
28 41. Harman K, Dobra R, Davies JC. Disease-modifying drug therapy in cystic fibrosis. *Paediatr*  
29  
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**Table 1 - Number of patients and assessments:**

a) for each age class the number of patients with available assessments is reported, separately for male and female;

b), c) and d) for each age class the number of assessments for weight, height and BMI, respectively, is reported for male and female.

a)		Number of patients		
Variable	Age (years)	F	M	Total
	0-2	36	58	94
	3-4	23	37	60
	5-6	20	27	47
	7-8	18	27	45
b)		Number of assessments		
	Age (years)	F	M	Total
Weight	0-2	91	141	232
	3-4	27	44	71
	5-6	29	41	70
	7-8	17	18	35
	Total	164	244	408
c)		Number of assessments		
	Age (years)	F	M	Total
Height	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377
d)		Number of assessments		
	Age (years)	F	M	Total
Body mass index	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377

**Table 2 - Main demographic and clinical characteristics of patients**

Variables	N (%)
Total	106
Gender	
Male	64 (60)
Female	42 (40)
Age at diagnosis (months)	
Median (range)	13.8 months (0-35.6 years)
Gestational age (weeks)	
Median (range)	39 (29-42)
Pancreatic status	
Pancreas sufficiency	15 (14)
Pancreas insufficiency	91 (86)
Heart problems	
No	99 (93)
Yes	7 (7)
Bone lesions at diagnosis	
No	59 (56)
Yes	47 (44)
Bone lesions during the first 8 years	
No	74 (70)
Yes	32 (30)
GH *	
No	100 (94)
Yes	6 (6)

\* in 5 cases after the first 8 years of life, in 1 case at 7.5 years

**Table 3 – Mutations of SDS patients**

Mutations		N	%
258+2T>C	183-184TA>CT	61	57.5
258+2T>C	183-184TA>CT+258+2T>C	16	15.1
258+2T>C	258+2T>C	9	8.5
258+2T>C	c.258+533 459+403del	4	3.8
258+2T>C	101A>T	1	0.9
258+2T>C	107delT	1	0.9
258+2T>C	187G>T	1	0.9
258+2T>C	212C>T	1	0.9
258+2T>C	289-292del	1	0.9
258+2T>C	300delAC	1	0.9
258+2T>C	307-308delCA	1	0.9
258+2T>C	352A>G	1	0.9
258+2T>C	356G>A	1	0.9
258+2T>C	624+1G>C	1	0.9
258+2T>C	92-93GC>AG	1	0.9
258+2T>C	G63C	1	0.9
258+2T>C	IVS1-71del83bp	1	0.9
258+2T>C	R218X	1	0.9
258+2T>C	Y32C	1	0.9
523C>T	523C>T	1	0.9

**Table 4** – 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported for SDS patients from birth to 8 years: the estimates are reported every 3 months from birth to 2 years, every 6 months from 2 to 6 years, once a year from 6 to 8 years.

a) centiles for height

Height										
Age	Male					Female				
	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	41.8	46.2	48.6	51.1	55.5	38.1	44.3	46.8	48.8	51.8
0.25	47.0	51.9	54.7	57.4	62.3	43.0	49.3	52.0	54.3	57.7
0.50	51.7	57.2	60.2	63.1	68.4	47.8	54.2	57.0	59.5	63.4
0.75	55.9	61.8	65.0	68.1	73.7	52.3	58.7	61.8	64.5	68.8
1.00	59.6	65.8	69.2	72.5	78.4	56.5	62.9	66.1	69.0	73.8
1.25	62.8	69.3	72.8	76.3	82.3	60.2	66.6	69.9	73.0	78.2
1.50	65.5	72.3	75.9	79.5	85.7	63.3	69.8	73.2	76.5	81.9
1.75	68.0	74.9	78.7	82.3	88.7	66.0	72.5	76.0	79.3	85.1
2.00	70.1	77.2	81.0	84.8	91.2	68.3	74.8	78.4	81.8	87.8
2.50	73.8	81.2	85.2	89.0	95.6	72.2	78.8	82.4	86.0	92.4
3.00	77.1	84.8	88.8	92.7	99.4	75.8	82.6	86.3	90.0	96.6
3.50	79.7	87.6	91.7	95.6	102.3	79.2	86.2	90.1	93.9	100.6
4.00	82.1	90.1	94.3	98.2	104.9	82.3	89.7	93.7	97.5	104.3
4.50	84.9	93.1	97.3	101.3	108.0	85.1	92.9	97.0	100.9	107.6
5.00	87.9	96.3	100.5	104.6	111.2	87.2	95.7	99.9	103.8	110.2
5.50	90.6	99.2	103.5	107.6	114.2	88.8	98.0	102.3	106.2	112.4
6.00	93.4	102.1	106.5	110.6	117.3	90.5	100.4	104.8	108.7	114.7
7.00	98.3	107.3	111.7	115.8	122.4	95.1	105.6	110.1	114.1	120.1
8.00	103.0	112.2	116.6	120.7	127.3	100.7	110.6	115.1	119.1	125.5



## b) centiles for weight

Weight										
	Male					Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	1.5	2.6	2.9	3.3	4.0	1.6	2.3	2.7	3.1	3.7
0.25	2.4	3.8	4.3	4.8	5.8	2.2	3.2	3.7	4.2	5.1
0.50	3.2	4.9	5.5	6.1	7.3	2.9	4.1	4.7	5.4	6.4
0.75	3.9	5.8	6.6	7.3	8.6	3.6	5.0	5.7	6.5	7.7
1.00	4.6	6.6	7.5	8.3	9.7	4.3	5.8	6.7	7.5	9.0
1.25	5.2	7.3	8.3	9.2	10.8	5.0	6.6	7.6	8.5	10.2
1.50	5.8	7.9	9.0	10.0	11.7	5.6	7.3	8.3	9.4	11.2
1.75	6.4	8.5	9.6	10.7	12.6	6.1	8.0	9.0	10.1	12.1
2.00	6.9	9.0	10.2	11.4	13.5	6.6	8.6	9.7	10.8	13.0
2.50	7.8	10.0	11.3	12.6	15.1	7.5	9.5	10.7	12.0	14.4
3.00	8.6	10.9	12.3	13.7	16.5	8.3	10.4	11.6	13.0	15.6
3.50	9.2	11.5	13.0	14.6	17.8	9.0	11.1	12.5	13.9	16.9
4.00	9.8	12.1	13.7	15.4	19.0	9.7	11.9	13.3	14.9	18.1
4.50	10.4	12.8	14.4	16.2	20.3	10.3	12.6	14.1	15.8	19.5
5.00	11.0	13.4	15.1	17.1	21.8	10.9	13.3	14.9	16.7	20.8
5.50	11.6	14.0	15.8	17.9	23.4	11.5	13.9	15.6	17.6	22.1
6.00	12.3	14.7	16.5	18.8	25.2	12.1	14.6	16.4	18.5	23.5
7.00	13.6	16.1	18.1	20.9	30.0	13.4	16.1	18.0	20.5	26.8
8.00	15.5	18.1	20.3	23.6	37.2	15.2	18.0	20.2	23.0	31.2

## c) centiles for body mass index (BMI)

Age	BMI									
	Male					Female				
	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	9.6	11.9	12.7	13.6	16.0	8.7	11.6	12.5	13.5	18.3
0.25	10.3	12.5	13.4	14.3	16.9	9.8	12.3	13.3	14.2	18.4
0.50	10.9	13.1	14.0	15.0	17.6	10.8	13.1	14.0	14.9	18.7
0.75	11.3	13.6	14.5	15.5	18.3	11.6	13.7	14.6	15.6	19.0
1.00	11.7	14.0	14.9	15.9	18.8	12.3	14.2	15.1	16.1	19.2
1.25	12.0	14.3	15.2	16.2	19.1	12.9	14.6	15.5	16.4	19.4
1.50	12.3	14.4	15.4	16.3	19.4	13.3	14.9	15.8	16.7	19.5
1.75	12.4	14.6	15.5	16.4	19.5	13.6	15.1	15.9	16.8	19.5
2.00	12.6	14.6	15.5	16.5	19.7	13.8	15.2	16.0	16.8	19.4
2.50	12.8	14.7	15.6	16.6	19.9	13.8	15.1	15.8	16.6	19.0
3.00	12.9	14.8	15.6	16.6	20.0	13.6	14.8	15.5	16.3	18.5
3.50	12.9	14.7	15.6	16.5	20.1	13.5	14.6	15.2	16.0	18.3
4.00	12.8	14.6	15.4	16.4	20.2	13.4	14.4	15.1	15.9	18.3
4.50	12.7	14.4	15.3	16.3	20.3	13.4	14.4	15.1	15.9	18.5
5.00	12.6	14.2	15.1	16.1	20.4	13.4	14.4	15.1	16.0	19.0
5.50	12.5	14.0	14.9	16.0	20.5	13.3	14.3	15.0	16.0	19.4
6.00	12.4	14.0	14.8	15.9	20.7	13.1	14.2	14.9	15.9	19.8
7.00	12.4	14.0	14.9	16.1	21.5	13.0	14.0	14.8	15.9	20.5
8.00	12.7	14.2	15.2	16.5	22.4	13.2	14.4	15.2	16.4	21.3

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3 Legend

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5 **Figure 1** - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and  
6 F) for males and females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each  
7 graph.  
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10 **Figure 2** – Estimated SDS growth charts compared to reference Italian curves. The values of 97<sup>th</sup>  
11 and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of the  
12 reference population. For the body mass index (BMI) centiles the difference is less evident.  
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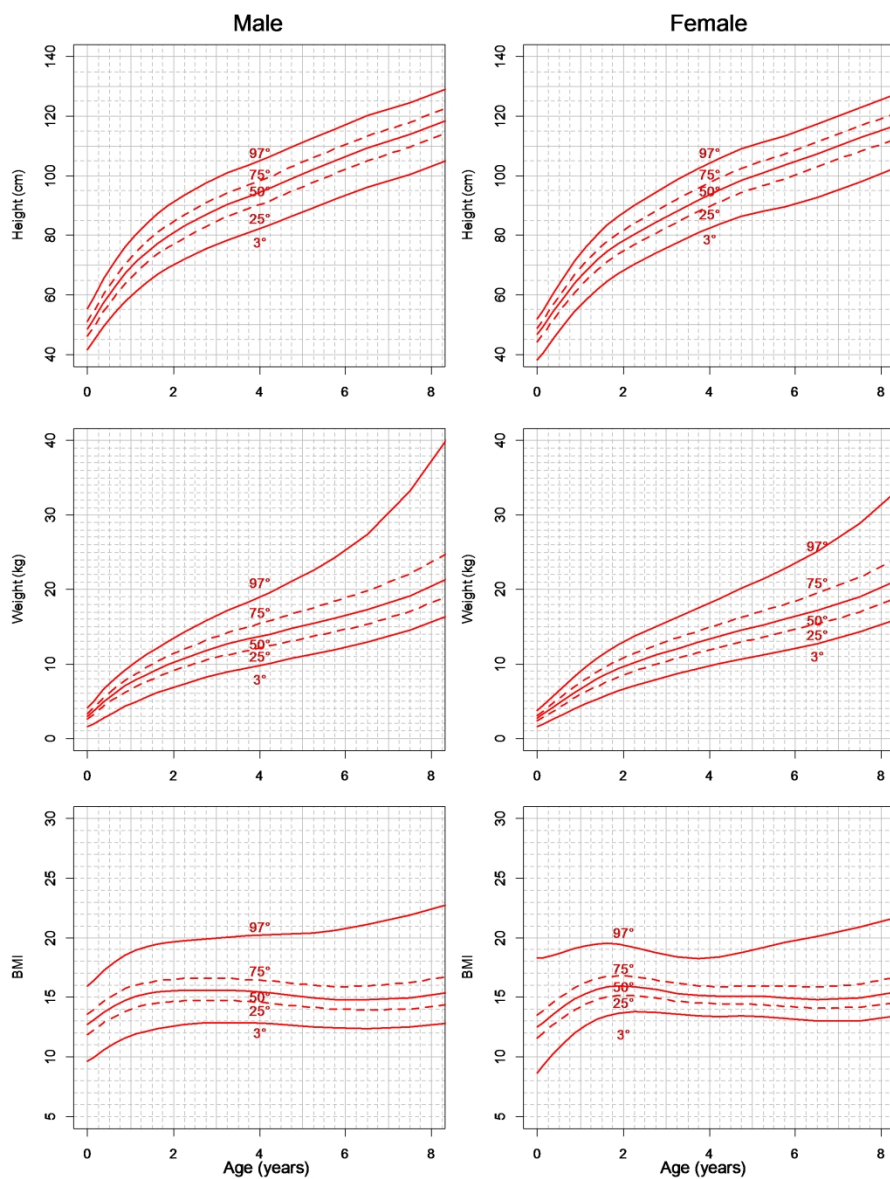


Figure 1 - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and F) for males and females (SDS patient). Curves for 3rd, 25th, 50th, 75th and 97th are reported in each graph.

814x1083mm (72 x 72 DPI)

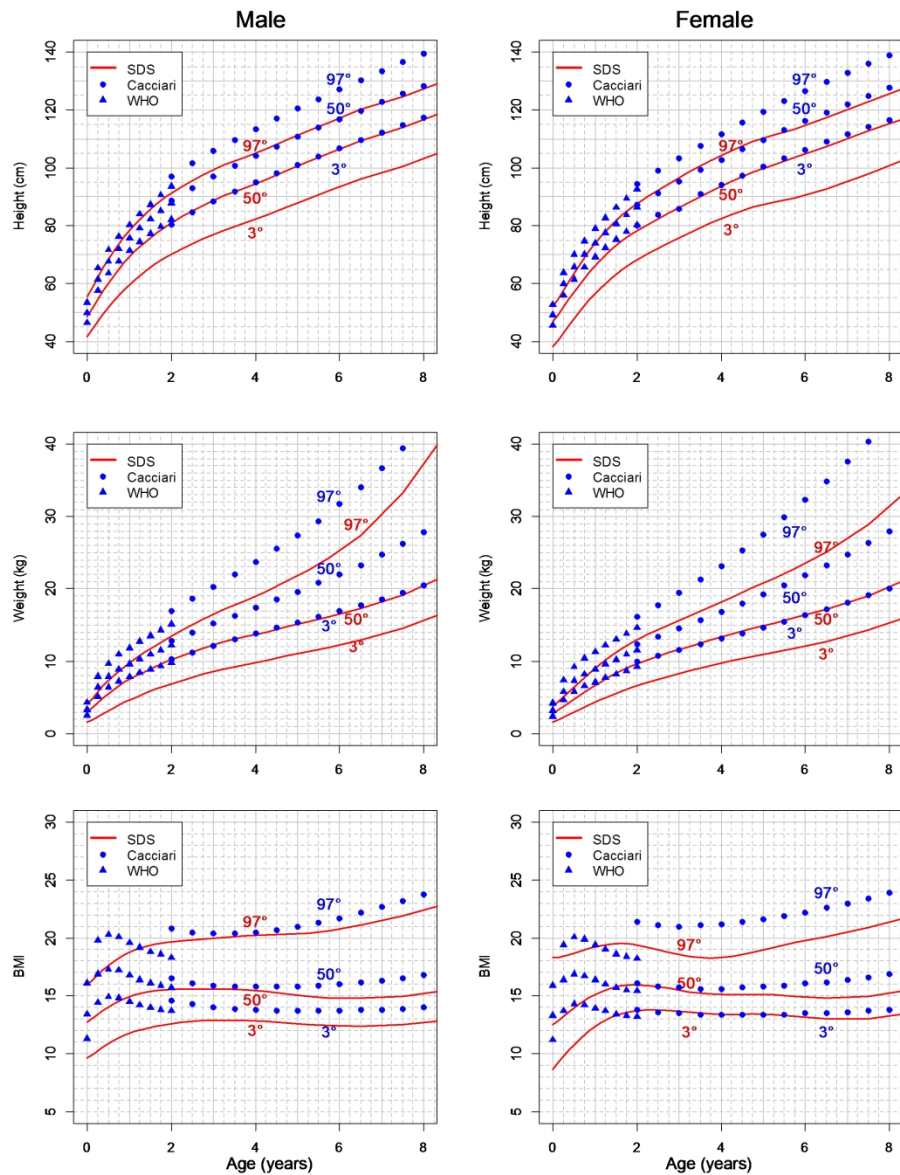


Figure 2 – Estimated SDS growth charts compared to reference Italian curves. The values of 97th and 50th centiles for height and weight of SDS patients are located on the 50th and 3rd centiles of the reference population. For the body mass index (BMI) centiles the difference is less evident.

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# BMJ Open

## NORMATIVE GROWTH CHARTS FOR SHWACHMAN-DIAMOND SYNDROME IN CHILDREN 0 TO 8 YEARS OLD.

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Secondary Subject Heading:	Paediatrics
Keywords:	Shwachman–Diamond syndrome, growth charts, Genetics < TROPICAL MEDICINE

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Manuscripts

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3 NORMATIVE GROWTH CHARTS FOR SHWACHMAN-DIAMOND SYNDROME IN  
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5 CHILDREN 0 TO 8 YEARS OLD.

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7 Cipolli M<sup>1,2</sup>, Tridello G<sup>1</sup>, Micheletto A<sup>1</sup>, Perobelli S<sup>1</sup>, Pintani E<sup>1</sup>, Cesaro S<sup>3</sup>, Maserati E<sup>4</sup>, Nicolis  
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## Abstract

### Objectives.

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder. Its predominant manifestations include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities. Patients frequently present failure to thrive and susceptibility to short stature. Average birth weight is at the 25th percentile; by the first birthday, >50% of patients drop below the 3<sup>rd</sup> percentile for height and weight.

The study aims at estimating the growth charts for patients affected by SDS in order to give a reference tool helpful for medical care and growth surveillance through the first 8 years of patient's life.

### Setting and participants.

This retrospective observational study includes 106 patients (64 M) with available information from birth to 8 years, selected among the 122 patients included in the Italian National Registry of SDS and born between 1975 and 2016. Gender, birth date and auxological parameters at repeated assessment times were collected. The General Additive Model for Location Scale and Shape method was applied to build the growth charts. A set of different distributions was used, and the more appropriate were selected in accordance with the smallest Akaike's information criterion.

### Results.

A total of 408 measurements was collected and analyzed. The median number of observations per patient amounted to 3, range 1-11. In accordance with the methods described, specific SDS growth charts were built for weight, height and body mass index, separately in males and females.



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3 The 50<sup>th</sup> and 3<sup>rd</sup> percentiles of weight and height of the healthy population (WHO standard-  
4 references) respectively correspond to the 97<sup>th</sup> and 50<sup>th</sup> percentiles of the SDS population (SDS  
5 specific growth charts), whilst the difference is less evident for the BMI.  
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## 10 11 **Conclusions.**

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13 Specific SDS growth charts obtained through our analysis enable a more appropriate classification  
14 of patients based on auxological parameters, representing a useful reference tool for evaluating their  
15 growth during childhood.  
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## 29 **Article summary**

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33 • Specific SDS growth charts were built for weight, height and BMI, separately for males and  
34 females: the 50<sup>th</sup> and 3<sup>rd</sup> percentiles of weight and height of the healthy population  
35 respectively corresponded to the 97<sup>th</sup> and 50<sup>th</sup> percentiles of the SDS population.  
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39 • The data used for the growth charts does not represent the natural development of the  
40 disease, but rather the growth development of SDS subjects receiving medical care. Even  
41 though the data used in constructing growth charts should ideally come from prospective  
42 longitudinal studies on large groups, this approach cannot be used when considering rare  
43 syndromes.  
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47 • Specific SDS growth charts obtained from our analysis enable a more appropriate  
48 classification of patients based on auxological parameters, representing a useful reference  
49 tool for evaluating their growth during childhood.  
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3 Competing interests' statement

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5 There are no competing interests for any author.  
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## Introduction

Shwachman–Diamond syndrome (SDS) (OMIM 260400) is a rare autosomal recessive disorder first described in 1964.<sup>1</sup> The predominant manifestations of the syndrome include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities.<sup>2-5</sup> Patients frequently present failure to thrive, susceptibility to infections and short stature.<sup>1-4</sup>

Pancreatic insufficiency is present in the first days after birth, and it is characterized by the replacement of exocrine components with fatty tissue and preserved islets of Langerhans and ductal architecture. During childhood, almost 50% of patients present spontaneous improvements in the pancreatic function, discontinuing pancreatic enzyme supplements.<sup>2,4,6-8</sup>

A persistent or intermittent neutropenia occurs in 88–100% of patients.<sup>1,2,7-10</sup> Bone marrow biopsy usually reveals a hypoplastic specimen with varying degrees of hypoplasia and fat infiltration.<sup>2,10</sup>

Up to one third of the patients may develop myelodysplastic syndrome and acute myeloid leukemia.<sup>11-14</sup>

In 2002, the gene (*SBDS*) involved in the syndrome was identified on chromosome 7q11,<sup>15</sup> although mutations in the *DNAJC21* gene have also been associated to a SDS phenotype, as well as, possibly, mutations of *EFL1* and *SRP54* genes.<sup>16-18</sup> The SBDS is expressed ubiquitously in all mammalian tissue, and other organs such as teeth and oral cavity, liver, heart, kidneys and skin may be involved.<sup>5-7</sup>

In spite of the new SBDS mutations identified in later years, until now up to 10% of patients with clinical features of SDS have lacked SBDS mutations.<sup>15,19</sup> However, the negative gene test does not exclude the diagnosis, and an accurate evaluation of clinical signs is compulsory to diagnose the presence of the syndrome.

Cognitive impairment has been noted in the majority of these patients, albeit with intragroup variability,<sup>20-22</sup> this has a serious impact on the patient, limiting independence and quality of life.<sup>22</sup>

Neuroimaging studies<sup>23-25</sup> reported diffuse brain alterations in the brain structure and connectivity.

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3 Several clinical studies reported growth failure with malnutrition as a common feature in the first  
4 year of life, particularly prior to diagnosis. This condition is attributable to various factors,  
5 including inadequate nutrient intake with or without feeding difficulties, pancreatic insufficiency,  
6 and recurrent infections.<sup>1,2,4,7,26</sup> The average weight at birth is at the 25<sup>th</sup> percentile, and over half of  
7 the patients drop below the 3<sup>rd</sup> percentile for both height and weight by the first birthday. After  
8 diagnosis and the start of an appropriate therapy, most children show normal growth velocity, but  
9 remain consistently below the 3<sup>rd</sup> percentile for height and weight.<sup>2,4,8,26</sup> These alterations are not  
10 related to a pancreatic insufficiency or an inappropriate caloric intake, but seem to be directly linked  
11 to biallelic mutations of the SBDS gene, and the growth of these patients differs from that of  
12 healthy children.  
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16 To date, there are no specific SDS growth charts available as to other disorders with marked growth  
17 retardation such as Down syndrome, Turner syndrome, Ellis-van Creveld syndrome,  
18 achondroplasia.<sup>27-30</sup> Indeed, disease-specific charts are a helpful tool in medical care, monitoring  
19 growth more accurately, and for research.  
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23 The aim of this retrospective multicentre observational study is to build the growth chart for  
24 patients affected by SDS in order to provide a reference tool to monitor the growth of children with  
25 this disease throughout childhood.  
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## Method

This study includes patients who are part of the Italian National Registry of SDS whose height, weight and main demographic characteristic were available in their first 8 years of life. In the Registry, all 122 patients have a SDS diagnosis confirmed by genetic analysis. For each subject, the following characteristics were collected: gender, birth date, height, weight, assessment date, available clinic information. Measurements were recorded in accordance with the standard criteria by age period. A total of 645 observations on 122 patients was recorded, but data beyond 8 years of age was not included in the analysis owing to its being available for a too small number of patients in limited data points. Sixteen patients only had information beyond 8 years of age, and were not included in the analysis; thus, 408 observations on 106 patients with assessments in their first 8 years of life were analyzed.

The primary endpoint was to estimate percentiles for height, weight and BMI for males and females.

The protocol was approved by the local Ethics Committee (CE n 1944). All patients signed an informed consent to be included in the Registry.

### *Patient and Public Involvement*

Patients were not involved in the design, recruitment and conduct of this study.

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Data was initially prepared using the statistical software SAS and then analyzed by the software R for growth curve estimation<sup>31</sup>. A 3-month window was used for each of the three anthropomorphic measures; in case of multiple assessments, the average of the values available inside the window was considered. Growth curves for weight, height and BMI from birth to 8 years were constructed,

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3 each with 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles for age. Data from male and female individuals was  
4  
5 analyzed separately.

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7 Normative data for growth parameters was obtained from tables published by Cacciari et al.<sup>32</sup> The  
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9 Italian normative data was limited to 2–8 years, thus WHO data was used for ages 0–2.<sup>33</sup> To model  
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11 the growth charts, the GAMLSS (General Additive Model for Location Scale and Shape) package  
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13 for the R statistical program was used. This tool enables all the parameters of the distribution of the  
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15 response variable to be modelled as linear/non-linear or smooth functions of the explanatory  
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17 variables<sup>34–36</sup>.

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20 The distribution of height, weight and BMI was modelled by use of four parameters representing  
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22 location, scale, skewness and kurtosis, using cubic penalized smoothing lines. A set of different  
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24 distributions was used, and the more appropriate were selected in accordance with the criterion of  
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26 the smallest AIC. Worm plots and q-q plots were used for the analysis of residuals.

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28 With a sample size of 60 patients, the 50<sup>th</sup>, 25<sup>th</sup>/75<sup>th</sup> and 3<sup>rd</sup>/97<sup>th</sup> centiles could be estimated reaching  
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30 a standard error of about 0.8, 0.9 and 1.3, respectively.  
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## Results

A total of 106 patients (64 males and 42 females) was considered eligible for the analysis, with a total of 408 measurements collected from 1975 to 2016, with a median number of 3 observations per patient, range 1-11 (Table 1). All patients were Caucasian and of Italian origin, with a median age at diagnosis of 13.8 months, range 0 days-35.6 years. The median gestational age was 39 weeks, range 29-42, and the median weight at birth was 2.8 kg (0.85-4.2). Pancreatic insufficiency was observed in 91 patients (86%), all of them were on treatment with pancreatic enzymes. Six patients were treated with growth hormone (GH), 5 after their first 8 years of life and 1 at age 7.5. Twelve patients out of 106 underwent hematopoietic stem cell transplantation, 8 out of 12 under eight years of age.

The main patients' characteristics and mutations are reported in Table 2 and Table 3.

In accordance with the methods described, specific SDS growth charts were built for weight, height and BMI, separately for males and females. Each subject had the same number of observations for each growth parameter included in the database.

Figure 1 shows a growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and females. Table 4 shows the 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles: the centiles are estimated every 3 months from birth to 2 years, every 6 months from 2 to 6 years, and once a year from 6 to 8 years.

In Figure 2, the estimated SDS growth charts are shown together with Italian reference curves.

Compared to typically developing individuals (standard population), the values of the 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles, respectively.

At 8 years, the 50<sup>th</sup> centile for height in SDS patients corresponds to the 3<sup>rd</sup> centile and to the -2 SD value in the healthy population. The difference is less evident for the BMI centiles, meaning that the growth retardation is harmonic.

## Discussion

SDS is a rare disease without a well-defined prevalence. Severe growth retardation (particularly in length/height) is one of its typical features, which can be alleged to be linked to the genetic cause of the disease.

At present, no growth charts have been validated for SDS; the charts we show here represent the first set of normative curves for SDS children 0-8 years. As in healthy children, specific charts for SDS are important tools in monitoring treatment efficacy and for routine medical follow up.

In this study, we used data from all children included in the Italian SDS registry with available assessments from birth to 8 years. All patients had SDS diagnosis confirmed by genetic mutations on both alleles, although up to 10% of subjects with SDS diagnosis described in the literature do not present mutations of the *SBDS* gene. In this way, we tried to reduce bias in our dataset.

In spite of the rarity of the disease, we had the possibility to generate separate charts for males and females until the age of 8. When compared to normal (regular) growth charts, the SDS charts do not differ in form for this period of age. The 50<sup>th</sup> percentile of SDS charts for weight and height is positioned on the 3<sup>rd</sup> percentile of regular charts, both for males and females. The low percentile at birth for length and weight indicates that prenatal retardation occurs, then continuing in the postnatal period.

BMI curves are similar both for normal and SDS population, indicating that the weight and height trend is harmonic also in SDS. These results as a whole suggest these growth curves are influenced by the genetic defect rather than malabsorption/malnutrition or inherited factors.

For SDS subjects, these specific growth-charts can be used in managing problems related to growth, and may be specifically useful to recognize patients to be investigated with regard to GH activity and any possibility of specific treatment. These specific growth charts are also extremely useful to address nutritional counselling. The parents of SDS patients regularly ask for the best diet to increase the growth of their children. Sometimes, an overfeeding behaviour has been reported



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3 with the aim of influencing height. This erroneous interpretation of growth problems in SDS may  
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5 cause obesity and negative consequences on the skeletal apparatus.  
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7 Moreover, since there has been no growth chart available for SDS patients until now, the growth  
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9 charts developed in this study provide a significant impact in understanding physical trends in  
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11 these subjects.  
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13 Given the small number of observations beyond 8 years, the growth charts were curtailed at age 8.  
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15 Several associated manifestations of the syndrome, such as heart, renal or skeletal alteration could  
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17 theoretically influence the growth of the patients. In our set, co-morbidity risk factors able to  
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19 influence growth retardation were not identified. In any case, given the rarity of the disease and the  
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21 consequent small sample size, children with medical problems were not excluded, as already done  
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23 in other similar works.<sup>37-38</sup>  
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25 It is also well-known that SDS subjects may be recognized by the presence of typical clinical  
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27 features, but variable penetrance and expressivity are common, which, together with the rarity of  
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29 these patients, makes a correlation genotype-phenotype difficult.  
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32 A few limitations in our study are to be taken into account; one is that the data used for the growth  
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34 charts does not represent the natural development of the disease, but rather the growth development  
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36 of SDS subjects receiving medical care. We are aware that the data used in constructing growth  
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38 charts should ideally come from prospective longitudinal studies on large groups, however, when  
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40 considering rare syndromes, this approach cannot be used.  
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43 In Italy, as well as in many Northern European countries, the secular trend has slowed down or  
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45 even reached a plateau since the 1980s/1990s. Since only less than 3% of measurements included  
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47 in this study were collected before 1980, no correction for the secular trend was considered.<sup>39-40</sup>  
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50 Furthermore, the present curves do not quite grasp the age of puberty, and definitive information  
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52 on what affects the final height could not be obtained. In any case, the literature includes some  
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54 SDS patients older than 18 with percentiles remaining in the low average or below the 3<sup>rd</sup>  
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3 percentile for both weight and height<sup>3,4</sup>, indicating that the growth spurt does not lead to a  
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5 substantial change in the trend of growth.  
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7 The number of older patients at the moment is small, therefore the charts may not be sufficiently  
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9 reliable at the ages over eight years. This is a typical limitation in presence of small numbers of  
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11 patients, and is shared by other reference charts for rare diseases.  
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13 The present growth charts can be used to compare the growth of SDS individual (height, weight,  
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15 BMI) and the general population, but also to compare the growth of an individual child with that of  
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17 peers of the same age and sex with the syndrome.  
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19 SDS is a worldwide disease with patients diagnosed in every part of the world; the present growth-  
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21 charts should be used with caution when studying SDS individuals of other ethnic backgrounds;  
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23 as presented, the curves show an accurate picture of the Italian SDS population.  
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25 Future efforts will aim at collecting more data to improve knowledge on the syndrome and  
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27 construct growth-charts until 18 years of age. These tools would enable the gathering of more  
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29 information on SDS, first and foremost the influence of pubertal development on growth, as only  
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31 sporadic data on this point is currently available.  
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34 Finally, when clinical trials aimed at assessing therapies for SDS basic defect are possible,  
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36 similarly to other rare diseases<sup>41</sup>, growth chart comparison in treated vs untreated SDS populations  
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38 could be a relevant endpoint.  
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3 **Figure 1** - Growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and  
4 females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each graph.  
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9 **Figure 2** – Estimated SDS growth charts compared to the reference Italian curves. The values of  
10 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of  
11 the reference population. The difference is less evident for the BMI centiles.  
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The authors have nothing to disclose.

## AUTHOR CONTRIBUTIONS

Conception and design: MC, PS, TG. Provision of study materials or patients: CM, PS, PE, CS, ME, NE, DC.

Collection and assembly of data: CM, PE. Data analysis: TG, MA. Manuscript writing: All authors. Final approval of manuscript: All authors.

## References

1. Shwachman H, Diamond LK, Oski FA, *et al.* The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 1964; 65:645–63.
2. Aggett PJ, Cavanagh NP, Matthew DJ, *et al.* Shwachman's syndrome. A review of 21 cases. *Arch Dis Child* 1980; 55:331-47.
3. Mack DR, Forstner GG, Wilschanski M, *et al.* Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology* 1996;111:1593–602.
4. Cipolli M, D’Orazio C, Delmarco A, *et al.* Shwachman’s Syndrome: pathomorphosis and long-term outcome. *J Pediatr Gastroent Nutr* 1999;29:265–72.
5. Mäkitie O, Ellis L, Durie PR, *et al.* Skeletal phenotype in patients with Shwachman–Diamond syndrome and mutations in SBDS. *Clin Genet* 2004;65:101–12.
6. Mack DR Shwachman–Diamond syndrome. *J Pediatr* 2002;141:164–5.
7. Cipolli M. Shwachman–Diamond syndrome: clinical phenotypes. *Pancreatology* 2001;1:543-8.
8. Rothbaum R, Perrault J, Vlachos A, *et al.* Shwachman-Diamond syndrome: report from an international conference. *J Pediatr* 2002;141:266-70.
9. Burroughs L, Woolfrey A, Shimamura A. Shwachman–Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am* 2009;23:233–48.
10. Dror Y *et al.* Impaired ability of bone marrow stroma from patients with Shwachman–Diamond syndrome to support hematopoiesis. *Brit J Haematol* 1998;102:161 (Abs P-0638)
11. Dror Y, Squire J, Durie P, *et al.* Malignant myeloid transformation with isochromosome 7q in Shwachman–Diamond syndrome. *Leukemia* 1998;12:1591–5.
12. Maserati E, Minelli A, Pressato B, *et al.* Shwachamn syndrome as mutator phenotype responsible for myeloid dysplasia/neoplasia through karyotype instability and chromosomes 7 and 20 anomalies. *Genes Chromosom Cancer* 2006;45:375–82.

- 1  
2  
3 13. Dror Y, Freedman MH. Shwachman–Diamond syndrome: an inherited preleukemic bone  
4 marrow failure disorder with a borronnt hematopoietic progenitors and pultry marrow  
5  
6 microenvironment. *Blood* 1999;94:3048–54  
7  
8  
9 14. Cesaro S, Oneto R, Messina C, *et al.* Haematopoietic stem cell transplantation for Shwachman-  
10 Diamond disease: a study from the European Group for blood and marrow transplantation. *Br J*  
11 *Haematol* 2005;131:231-6.  
12  
13  
14 15. Boocock GR, Morrison JA, Popovic M, *et al.* Mutations in SBDS are associated with  
15 Shwachman–Diamond syndrome. *Nat Genet* 2003;33:97–101.  
16  
17  
18 16. Dhanraj S, Matveev A, Li H, *et al.* Biallelic mutations in DNAJC21 cause Shwachman-  
19 Diamond syndrome. *Blood* 2017; 129:1557-62.  
20  
21  
22 17. Stepensky P, Chacon-Flores M, Kim KH, *et al.* Mutations in EFL1, an SBDS partner, are  
23 associated with infantile pancytopenia, exocrine pancreatic insufficiency and skeletal anomalies in a  
24 Shwachman-Diamond like syndrome. *J Med Genet* 2017; 54:558-66.  
25  
26  
27 18. Carapito R, Konantz M, Paillard C, *et al.* Mutations in signal recognition particle SRP54 cause  
28 syndromic neutropenia with Shwachman-Diamond-like features. *J Clin Invest* 2017; 127:4090-103.  
29  
30  
31 19. Nicolis E, Bonizzato A, Baroukh M, *et al.* Identification of novel mutations in patients with  
32 Shwachman–Diamond syndrome. *Human Mutation* 2005;25:410.  
33  
34  
35 20. Kent A, Murphy GH, Milla P. Psychological characteristics of children with Shwachman  
36 syndrome. *Arch Dis Child* 1990;65:1349-52.  
37  
38  
39 21. Kerr EN, Ellis L, Dupuis A, *et al.* The behavioral phenotype of school-age children with  
40 Shwachman-Diamond Syndrome indicates neurocognitive dysfunction with loss of Shwachman-  
41 Bodian-Diamond syndrome gene function. *J Pediatr* 2010;156: 433–8.  
42  
43  
44 22. Perobelli S, Nicolis E, Assael BM, *et al.* Further characterization of Shwachman-Diamond  
45 syndrome: psychological functioning and quality of life in adult and young patients. *Am J Med*  
46 *Genet A.* 2012;158A:567-73.  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 23. Toiviainen-Salo S, Mäkitie O, Mannerkoski M, *et al.* Shwachman-Diamond syndrome is  
4 associated with structural brain alterations on MRI. *Am J Med Genet A* 2008;146A:1558-64.  
5  
6  
7 24. Booij J, Reneman L, Alders M, *et al.* Increase in central striatal dopamine transporters in  
8 patients with Shwachman–Diamond syndrome: additional evidence of a brain phenotype. *Am J Med*  
9  
10  
11  
12  
13 25. Perobelli S, Alessandrini F, Zoccatelli G, *et al.* Diffuse alterations in grey and white matter  
14 associated with cognitive impairment in Shwachman–Diamond syndrome: Evidence from a  
15 multimodal approach. *Neuroimage Clin* 2015;7:721-31.  
16  
17  
18 26. Dror Y, Donadieu J, Koglmeyer J, *et al.* Draft consensus guidelines for diagnosis and treatment  
19 of Shwachman-Diamond syndrome. *Ann N Y Acad Sci.* 2011;1242:40-55.  
20  
21  
22 27. Zemel BS, Pipan M, Stallings VA, *et al.* Growth charts for children with Down syndrome in the  
23 United States. *Pediatrics* 2015;136:e1-e8.  
24  
25  
26 28. Verbeek S, Eilers PH, Lawrence K, *et al.* Growth charts for children with Ellis–van Creveld  
27 syndrome, *Eur J Pediatr* 2011;170:207–211.  
28  
29  
30 29. Gawlik A, Gawlik T, Augustyn M, *et al.* Validation of growth charts for girls with Turner  
31 syndrome. *Int J Clin Pract* 2006; 60:150–5.  
32  
33  
34 30. Tofts L, Das S, Collins F, *et al.* Growth charts for Australian children with achondroplasia. *Am J*  
35  
36  
37  
38  
39  
40  
41 31. R version 3.3.3 (2017-03-06), The R Foundation for Statistical Computing  
42  
43  
44 32. Cacciari E, Milani S, Balsamo A, *et al.* Italian cross-sectional growth charts for height, weight  
45 and BMI (2 to 20 yr), *J Endocrinol Invest* 2006;29:581-93.  
46  
47  
48 33. De Onis M, Garza C, Victoria CG, *et al.* The WHO multicentre growth reference study:  
49 planning, study design and methodology. *Food Nutr Bull* 2004;25:15-26.  
50  
51  
52 34. Cole TJ. The LMS method for constructing normalized growth standards, *Eur J Clin Nutr* 1990;  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 35. Cole TJ and Green PJ. Smoothing reference centile curves: the LMS method and penalized  
4 likelihood. *Stat Med* 1992;11:1305-19.  
5  
6  
7 36. Rigby RA, Stasinopoulos DM. Generalized Additive Models for Location Scale and Shape  
8 (GAMLSS) in R, *J Stat Softw.* 2007; 23:1-46.  
9  
10  
11 37. Beets L, Rodriguez-Fonseca C, Hennekam RC. Growth charts for individuals with Rubinstein-  
12 Taybi syndrome. *Am J Med Genet A* 2014;164A:2300-9  
13  
14  
15 38. Su X, Lau JT, Yu CM, Chow, et al. Growth charts for Chinese Down syndrome children from  
16 birth to 14 years. *Arch Dis Child* 2014;99:824-9.  
17  
18  
19 39. Larnkaer A, Attrup Schrøder S, Schmidt IM, et al. Secular change in adult stature has come to a  
20 halt in northern Europe and Italy. *Acta Paediatr* 2006;95:754-5.  
21  
22  
23 40. Bonthuis M, van Stralen KJ, Verrina E, Use of National and International Growth Charts for  
24 Studying Height in European Children: Development of Up-To-Date European Height-For-Age  
25 Charts. *PLoS One* 2012;7:e42506.  
26  
27  
28 41. Harman K, Dobra R, Davies JC. Disease-modifying drug therapy in cystic fibrosis. *Paediatr*  
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**Table 1 - Number of patients and assessments:**

a) for each age class, the number of patients with available assessments is reported, separately for male and female;

b), c) and d) for each age class, the number of assessments for weight, height and BMI, respectively, is reported for male and female.

a)		Number of patients		
Variable	Age (years)	F	M	Total
	0-2	36	58	94
	3-4	23	37	60
	5-6	20	27	47
	7-8	18	27	45
b)		Number of assessments		
	Age (years)	F	M	Total
Weight	0-2	91	141	232
	3-4	27	44	71
	5-6	29	41	70
	7-8	17	18	35
	Total	164	244	408
c)		Number of assessments		
	Age (years)	F	M	Total
Height	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377
d)		Number of assessments		
	Age (years)	F	M	Total
Body mass index	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377

**Table 2 - Main demographic and clinical characteristics of patients**

Variables	N (%)
Total	106
Gender	
Male	64 (60)
Female	42 (40)
Age at diagnosis (months)	
Median (range)	13.8 months (0-35.6 years)
Gestational age (weeks)	
Median (range)	39 (29-42)
Pancreatic status	
Pancreatic sufficiency	15 (14)
Pancreatic insufficiency	91 (86)
Heart problems	
No	99 (93)
Yes	7 (7)
Bone lesions at diagnosis	
No	59 (56)
Yes	47 (44)
Bone lesions during the first 8 years	
No	74 (70)
Yes	32 (30)
GH *	
No	100 (94)
Yes	6 (6)

\* in 5 cases after the first 8 years of life, in 1 case at 7.5 years

**Table 3 – Mutations of SDS patients**

Mutations		N	%
258+2T>C	183-184TA>CT	61	57.5
258+2T>C	183-184TA>CT+258+2T>C	16	15.1
258+2T>C	258+2T>C	9	8.5
258+2T>C	c.258+533 459+403del	4	3.8
258+2T>C	101A>T	1	0.9
258+2T>C	107delT	1	0.9
258+2T>C	187G>T	1	0.9
258+2T>C	212C>T	1	0.9
258+2T>C	289-292del	1	0.9
258+2T>C	300delAC	1	0.9
258+2T>C	307-308delCA	1	0.9
258+2T>C	352A>G	1	0.9
258+2T>C	356G>A	1	0.9
258+2T>C	624+1G>C	1	0.9
258+2T>C	92-93GC>AG	1	0.9
258+2T>C	G63C	1	0.9
258+2T>C	IVS1-71del83bp	1	0.9
258+2T>C	R218X	1	0.9
258+2T>C	Y32C	1	0.9
523C>T	523C>T	1	0.9

**Table 4** – 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported for SDS patients from birth to 8 years: the estimates are reported every 3 months from birth to 2 years, every 6 months from 2 to 6 years and once a year from 6 to 8 years.

a) centiles for height

Height										
	Male					Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	41.8	46.2	48.6	51.1	55.5	38.1	44.3	46.8	48.8	51.8
0.25	47.0	51.9	54.7	57.4	62.3	43.0	49.3	52.0	54.3	57.7
0.50	51.7	57.2	60.2	63.1	68.4	47.8	54.2	57.0	59.5	63.4
0.75	55.9	61.8	65.0	68.1	73.7	52.3	58.7	61.8	64.5	68.8
1.00	59.6	65.8	69.2	72.5	78.4	56.5	62.9	66.1	69.0	73.8
1.25	62.8	69.3	72.8	76.3	82.3	60.2	66.6	69.9	73.0	78.2
1.50	65.5	72.3	75.9	79.5	85.7	63.3	69.8	73.2	76.5	81.9
1.75	68.0	74.9	78.7	82.3	88.7	66.0	72.5	76.0	79.3	85.1
2.00	70.1	77.2	81.0	84.8	91.2	68.3	74.8	78.4	81.8	87.8
2.50	73.8	81.2	85.2	89.0	95.6	72.2	78.8	82.4	86.0	92.4
3.00	77.1	84.8	88.8	92.7	99.4	75.8	82.6	86.3	90.0	96.6
3.50	79.7	87.6	91.7	95.6	102.3	79.2	86.2	90.1	93.9	100.6
4.00	82.1	90.1	94.3	98.2	104.9	82.3	89.7	93.7	97.5	104.3
4.50	84.9	93.1	97.3	101.3	108.0	85.1	92.9	97.0	100.9	107.6
5.00	87.9	96.3	100.5	104.6	111.2	87.2	95.7	99.9	103.8	110.2
5.50	90.6	99.2	103.5	107.6	114.2	88.8	98.0	102.3	106.2	112.4
6.00	93.4	102.1	106.5	110.6	117.3	90.5	100.4	104.8	108.7	114.7
7.00	98.3	107.3	111.7	115.8	122.4	95.1	105.6	110.1	114.1	120.1
8.00	103.0	112.2	116.6	120.7	127.3	100.7	110.6	115.1	119.1	125.5

## b) centiles for weight

Weight										
Male						Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	1.5	2.6	2.9	3.3	4.0	1.6	2.3	2.7	3.1	3.7
0.25	2.4	3.8	4.3	4.8	5.8	2.2	3.2	3.7	4.2	5.1
0.50	3.2	4.9	5.5	6.1	7.3	2.9	4.1	4.7	5.4	6.4
0.75	3.9	5.8	6.6	7.3	8.6	3.6	5.0	5.7	6.5	7.7
1.00	4.6	6.6	7.5	8.3	9.7	4.3	5.8	6.7	7.5	9.0
1.25	5.2	7.3	8.3	9.2	10.8	5.0	6.6	7.6	8.5	10.2
1.50	5.8	7.9	9.0	10.0	11.7	5.6	7.3	8.3	9.4	11.2
1.75	6.4	8.5	9.6	10.7	12.6	6.1	8.0	9.0	10.1	12.1
2.00	6.9	9.0	10.2	11.4	13.5	6.6	8.6	9.7	10.8	13.0
2.50	7.8	10.0	11.3	12.6	15.1	7.5	9.5	10.7	12.0	14.4
3.00	8.6	10.9	12.3	13.7	16.5	8.3	10.4	11.6	13.0	15.6
3.50	9.2	11.5	13.0	14.6	17.8	9.0	11.1	12.5	13.9	16.9
4.00	9.8	12.1	13.7	15.4	19.0	9.7	11.9	13.3	14.9	18.1
4.50	10.4	12.8	14.4	16.2	20.3	10.3	12.6	14.1	15.8	19.5
5.00	11.0	13.4	15.1	17.1	21.8	10.9	13.3	14.9	16.7	20.8
5.50	11.6	14.0	15.8	17.9	23.4	11.5	13.9	15.6	17.6	22.1
6.00	12.3	14.7	16.5	18.8	25.2	12.1	14.6	16.4	18.5	23.5
7.00	13.6	16.1	18.1	20.9	30.0	13.4	16.1	18.0	20.5	26.8
8.00	15.5	18.1	20.3	23.6	37.2	15.2	18.0	20.2	23.0	31.2

## c) centiles for body mass index (BMI)

Age	BMI									
	Male					Female				
	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	9.6	11.9	12.7	13.6	16.0	8.7	11.6	12.5	13.5	18.3
0.25	10.3	12.5	13.4	14.3	16.9	9.8	12.3	13.3	14.2	18.4
0.50	10.9	13.1	14.0	15.0	17.6	10.8	13.1	14.0	14.9	18.7
0.75	11.3	13.6	14.5	15.5	18.3	11.6	13.7	14.6	15.6	19.0
1.00	11.7	14.0	14.9	15.9	18.8	12.3	14.2	15.1	16.1	19.2
1.25	12.0	14.3	15.2	16.2	19.1	12.9	14.6	15.5	16.4	19.4
1.50	12.3	14.4	15.4	16.3	19.4	13.3	14.9	15.8	16.7	19.5
1.75	12.4	14.6	15.5	16.4	19.5	13.6	15.1	15.9	16.8	19.5
2.00	12.6	14.6	15.5	16.5	19.7	13.8	15.2	16.0	16.8	19.4
2.50	12.8	14.7	15.6	16.6	19.9	13.8	15.1	15.8	16.6	19.0
3.00	12.9	14.8	15.6	16.6	20.0	13.6	14.8	15.5	16.3	18.5
3.50	12.9	14.7	15.6	16.5	20.1	13.5	14.6	15.2	16.0	18.3
4.00	12.8	14.6	15.4	16.4	20.2	13.4	14.4	15.1	15.9	18.3
4.50	12.7	14.4	15.3	16.3	20.3	13.4	14.4	15.1	15.9	18.5
5.00	12.6	14.2	15.1	16.1	20.4	13.4	14.4	15.1	16.0	19.0
5.50	12.5	14.0	14.9	16.0	20.5	13.3	14.3	15.0	16.0	19.4
6.00	12.4	14.0	14.8	15.9	20.7	13.1	14.2	14.9	15.9	19.8
7.00	12.4	14.0	14.9	16.1	21.5	13.0	14.0	14.8	15.9	20.5
8.00	12.7	14.2	15.2	16.5	22.4	13.2	14.4	15.2	16.4	21.3

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3 Legend

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5 **Figure 1** - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and  
6 F) for males and females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each  
7 graph.  
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10 **Figure 2** – Estimated SDS growth charts compared to reference Italian curves. The values of 97<sup>th</sup>  
11 and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of the  
12 reference population. The difference is less evident for the body mass index (BMI) centiles.  
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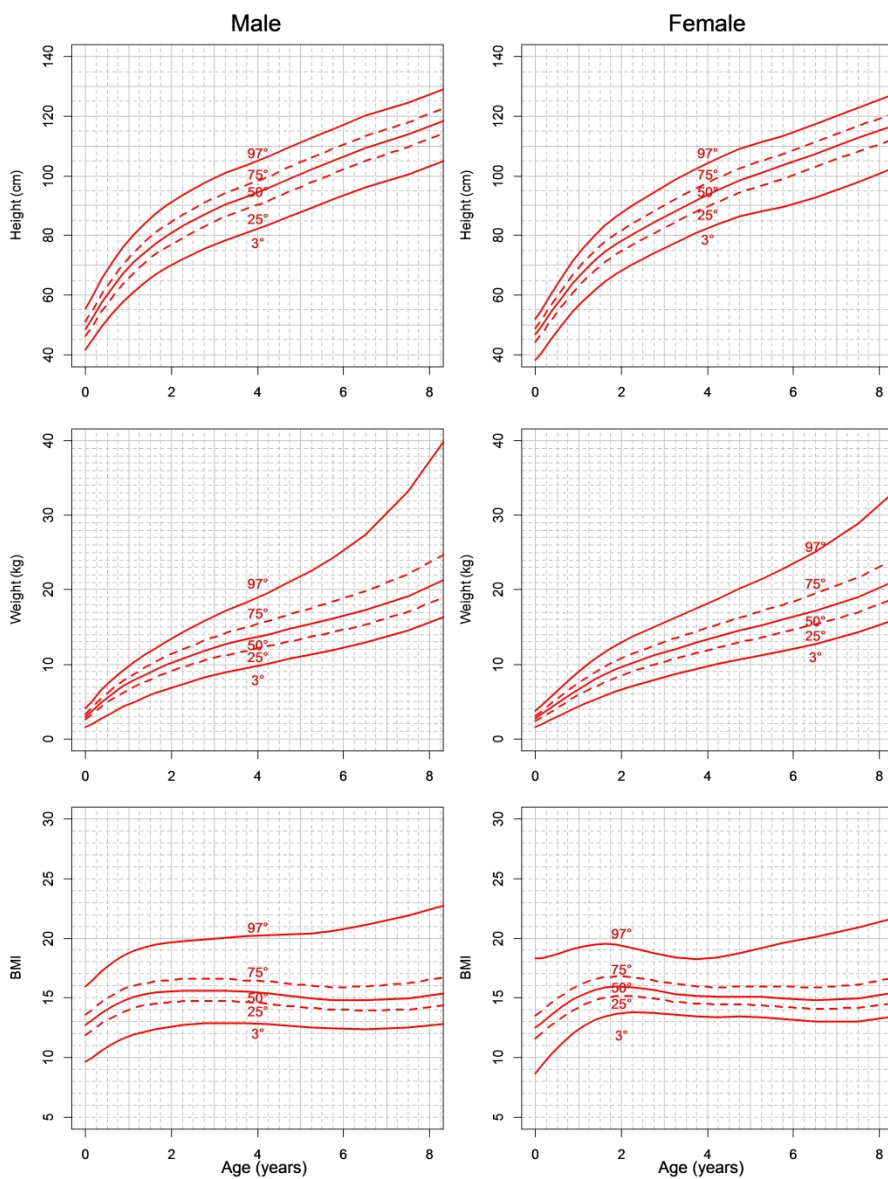


Figure 1 - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and F) for males and females (SDS patient). Curves for 3rd, 25th, 50th, 75th and 97th are reported in each graph.



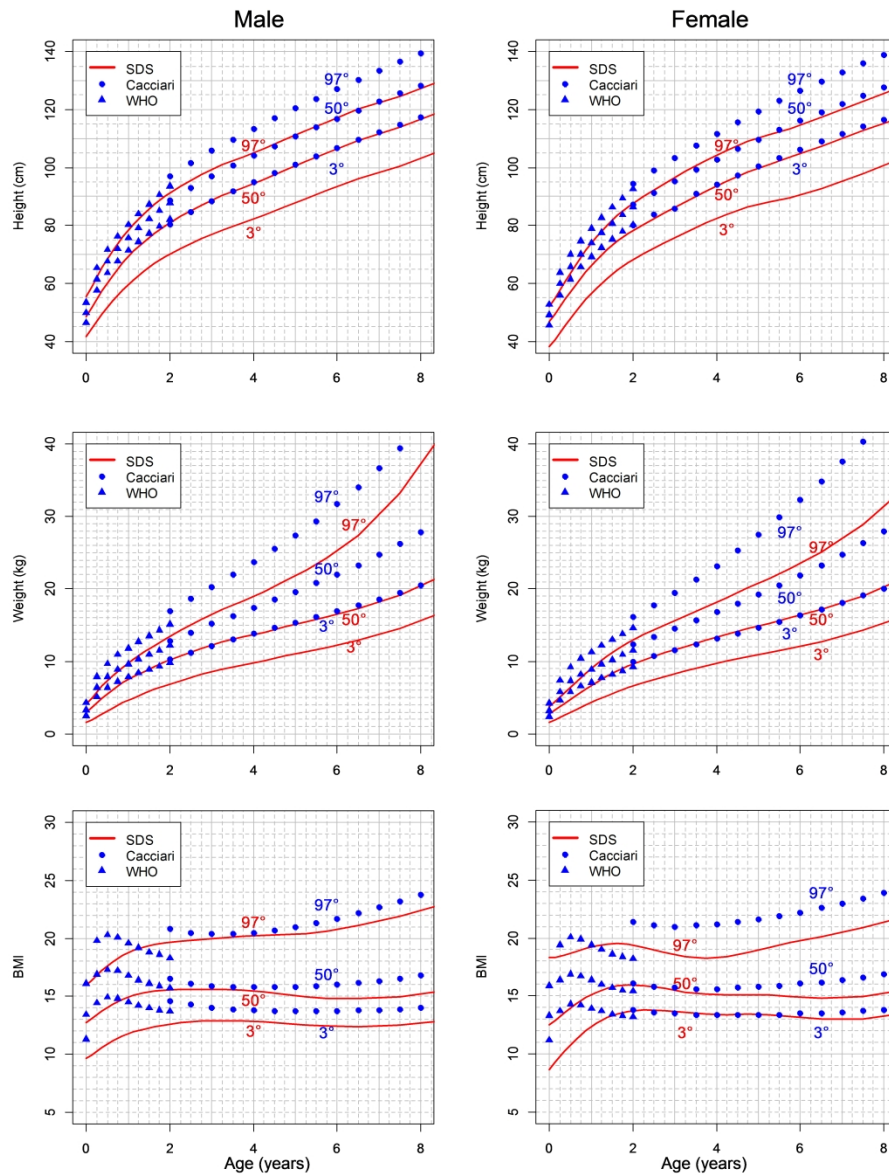


Figure 2 – Estimated SDS growth charts compared to reference Italian curves. The values of 97th and 50th centiles for height and weight of SDS patients are located on the 50th and 3rd centiles of the reference population. The difference is less evident for the body mass index (BMI) centiles.

# BMJ Open

## NORMATIVE GROWTH CHARTS FOR SHWACHMAN – DIAMOND SYNDROME FROM ITALIAN COHORT 0 TO 8 YEARS OLD

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Manuscripts

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3 NORMATIVE GROWTH CHARTS FOR SHWACHMAN –DIAMOND SYNDROME FROM  
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5 ITALIAN COHORT 0 TO 8 YEARS OLD  
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## Abstract

### Objectives.

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder. Its predominant manifestations include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities. Patients frequently present failure to thrive and susceptibility to short stature. Average birth weight is at the 25th percentile; by the first birthday, >50% of patients drop below the 3<sup>rd</sup> percentile for height and weight.

The study aims at estimating the growth charts for patients affected by SDS in order to give a reference tool helpful for medical care and growth surveillance through the first 8 years of patient's life.

### Setting and participants.

This retrospective observational study includes 106 patients (64 M) with available information from birth to 8 years, selected among the 122 patients included in the Italian National Registry of SDS and born between 1975 and 2016. Gender, birth date and auxological parameters at repeated assessment times were collected. The General Additive Model for Location Scale and Shape method was applied to build the growth charts. A set of different distributions was used, and the more appropriate were selected in accordance with the smallest Akaike's information criterion.

### Results.

A total of 408 measurements was collected and analyzed. The median number of observations per patient amounted to 3, range 1-11. In accordance with the methods described, specific SDS growth charts were built for weight, height and body mass index, separately for males and females.

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3 The 50<sup>th</sup> and 3<sup>rd</sup> percentiles of weight and height of the healthy population (WHO standard-references)  
4 respectively correspond to the 97<sup>th</sup> and 50<sup>th</sup> percentiles of the SDS population (SDS specific growth  
5 charts), whilst the difference is less evident for the BMI.  
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## 11 **Conclusions.**

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14 Specific SDS growth charts obtained through our analysis enable a more appropriate classification of  
15 patients based on auxological parameters, representing a useful reference tool for evaluating their  
16 growth during childhood.  
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## 31 **Strengths and limitations**

- 32 • These growth charts represent the first set of normative curves for SDS children 0 to 8 years old
- 33 • The 50<sup>th</sup> and 3<sup>rd</sup> percentiles of weight and height of the healthy population respectively correspond
- 34 to the 97<sup>th</sup> and 50<sup>th</sup> percentiles of the SDS population
- 35 • These charts can be principally used to compare the growth between SDS subjects of the same age
- 36 and sex and also to recognize patients to investigate for GH deficiency
- 37 • The data used for the growth charts do not represent the natural development of the disease, but
- 38 rather the growth development of SDS subjects receiving medical care
- 39 • The present growth-charts should be used with caution when studying SDS individuals of other
- 40 ethnic backgrounds, as they show an accurate picture of the Italian SDS population.
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### Competing interests

None declared

### Data sharing

All the available data were included in the analysis. The data may be available by contacting the authors.

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## Introduction

Shwachman–Diamond syndrome (SDS) (OMIM 260400) is a rare autosomal recessive disorder first described in 1964.<sup>1</sup> The predominant manifestations of the syndrome include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities.<sup>2-5</sup> Patients frequently present failure to thrive, susceptibility to infections and short stature.<sup>1-4</sup>

Pancreatic insufficiency is present in the first days after birth, and it is characterized by the replacement of exocrine components with fatty tissue and preserved islets of Langerhans and ductal architecture. During childhood, almost 50% of patients present spontaneous improvements in the pancreatic function, discontinuing pancreatic enzyme supplements.<sup>2,4,6-8</sup>

A persistent or intermittent neutropenia occurs in 88–100% of patients.<sup>1,2,7-10</sup> Bone marrow biopsy reveals a hypoplastic “marrow” with varying degrees of fat infiltration.<sup>2,10</sup> Up to one third of the patients may develop myelodysplastic syndrome and acute myeloid leukemia.<sup>11-14</sup>

In 2002, the gene (*SBDS*) involved in the syndrome was identified on chromosome 7q11,<sup>15</sup> although mutations in the *DNAJC21* gene have also been associated to a SDS phenotype, as well as, possibly, mutations of *EFL1* and *SRP54* genes.<sup>16-18</sup> The *SBDS* is expressed ubiquitously in all mammalian tissues, and other organs such as teeth and oral cavity, liver, heart, kidneys and skin may be involved.<sup>5-7</sup>

In spite of the new *SBDS* mutations identified in later years, until now up to 10% of patients with clinical features of SDS have lacked *SBDS* mutations.<sup>15,19</sup> However, the negative gene test does not exclude the diagnosis, and an accurate evaluation of clinical signs is important to diagnose the presence of the syndrome.

Cognitive impairment has been noted in the majority of these patients, albeit with intragroup variability,<sup>20-22</sup> this has a serious impact on the patient, limiting independence and quality of life.<sup>22</sup>

Neuroimaging studies<sup>23-25</sup> reported diffuse brain alterations in the brain structure and connectivity.

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3 Several clinical studies reported growth failure with malnutrition as a common feature in the first year  
4 of life, particularly prior to diagnosis. This condition is attributable to various factors, including  
5 inadequate nutrient intake with or without feeding difficulties, pancreatic insufficiency, and recurrent  
6 infections.<sup>1,2,4,7,26</sup> The average weight at birth is at the 25<sup>th</sup> percentile, and over half of the patients drop  
7 below the 3<sup>rd</sup> percentile for both height and weight by the first birthday. After diagnosis and the start of  
8 an appropriate therapy, most children show normal growth velocity, but remain consistently below the  
9 3<sup>rd</sup> percentile for height and weight.<sup>2,4,8,26</sup> These alterations are not related to a pancreatic insufficiency  
10 or an inappropriate caloric intake, but seem to be directly linked to biallelic mutations of the SBDS  
11 gene, and the growth of these patients differs from that of healthy children.  
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14 To date, there are no specific SDS growth charts available unlike other disorders with marked growth  
15 retardation such as Down syndrome, Turner syndrome, Ellis-van Creveld syndrome, achondroplasia.<sup>27-</sup>  
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17 <sup>30</sup> Indeed, disease-specific charts are a helpful tool in medical care, monitoring growth more accurately,  
18 and for research.  
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21 The aim of this retrospective multicentre observational study is to develop the growth chart for patients  
22 affected by SDS in order to provide a reference tool to monitor the growth of children with this disease  
23 throughout childhood.  
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## Method

This study includes patients who are part of the Italian National Registry of SDS whose height, weight and main demographic characteristic were available in their first 8 years of life. In the Registry, all 122 patients have a SDS diagnosis confirmed by genetic analysis. For each subject, the following characteristics were collected: gender, birth date, height, weight, assessment date, available clinic information. Measurements were recorded in accordance with the standard criteria by age period. A total of 645 observations on 122 patients was recorded, but data beyond 8 years of age was not included in the analysis owing to its being available for only 16 patients and at limited data points; thus, 408 observations on 106 patients with assessments in their first 8 years of life were analyzed.

The primary endpoint was to estimate percentiles for height, weight and BMI for males and females.

The protocol was approved by the local Ethics Committee (CE n 1944). All patients signed an informed consent to be included in the Registry.

### *Patient and Public Involvement*

Patients were not involved in the design, recruitment and conduct of this study.

Data was initially prepared using the statistical software SAS and then analyzed by the software R for growth curve estimation<sup>31</sup>. A 3-month window was used for each of the three anthropomorphic measures; in case of multiple assessments, the average of the values available inside the window was considered. Growth curves for weight, height and BMI from birth to 8 years were constructed, each with 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles for age. Data from male and female individuals was analyzed separately.

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3 Normative data for growth parameters was obtained from tables published by Cacciari et al.<sup>32</sup> The  
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5 Italian normative data was limited to 2–8 years, thus WHO data was used for ages 0–2.<sup>33</sup> To model the  
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7 growth charts, the GAMLSS (General Additive Model for Location Scale and Shape) package for the R  
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9 statistical program was used. This tool enables all the parameters of the distribution of the response  
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11 variable to be modelled as linear/non-linear or smooth functions of the explanatory variables<sup>34–36</sup>.  
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14 The distribution of height, weight and BMI was modelled by use of four parameters representing  
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16 location, scale, skewness and kurtosis, using cubic penalized smoothing lines. A set of different  
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18 distributions was used, and the more appropriate were selected in accordance with the criterion of the  
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20 smallest AIC. Worm plots and q-q plots were used for the analysis of residuals.  
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24 With a sample size of 60 patients, the 50<sup>th</sup>, 25<sup>th</sup>/75<sup>th</sup> and 3<sup>rd</sup>/97<sup>th</sup> centiles could be estimated reaching a  
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26 standard error of about 0.8, 0.9 and 1.3, respectively.  
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## Results

A total of 106 patients (64 males and 42 females) were considered eligible for the analysis, with a total of 408 measurements collected from 1975 to 2016, with a median number of 3 observations per patient, range 1-11 (Table 1). All patients were Caucasian and of Italian origin, with a median age at diagnosis of 13.8 months, range 0 days-35.6 years. The median gestational age was 39 weeks, range 29-42, and the median weight at birth was 2.8 kg (0.85-4.2). Pancreatic insufficiency was observed in 91 patients (86%), all of them were on treatment with pancreatic enzymes. Six patients were treated with growth hormone (GH), 5 after their first 8 years of life and 1 at age 7.5. Twelve patients out of 106 underwent hematopoietic stem cell transplantation, 8 out of 12 under eight years of age.

The main patient characteristics and mutations are reported in Table 2 and Table 3.

In accordance with the methods described, specific SDS growth charts were built for weight, height and BMI, separately for males and females. Each subject had the same number of observations for each growth parameter included in the database.

Figure 1 shows a growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and females. Table 4 shows the 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles: the centiles are estimated every 3 months from birth to 2 years, every 6 months from 2 to 6 years, and once a year from 6 to 8 years.

In Figure 2, the estimated SDS growth charts are shown together with Italian reference curves.

Compared to typically developing individuals (standard population), the values of the 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles, respectively. At 8 years, the 50<sup>th</sup> centile for height in SDS patients corresponds to the 3<sup>rd</sup> centile and to the -2 SD value in the healthy population. The difference is less evident for the BMI centiles, meaning that the growth retardation is harmonic.

## Discussion

SDS is a rare disease without a well-defined prevalence. Severe growth retardation (particularly in length/height) is one of its typical features, which can be alleged to be linked to the genetic cause of the disease.

At present, no growth charts have been validated for SDS; the charts we show here represent the first set of normative curves for SDS children 0-8 years. As in healthy children, specific charts for SDS are important tools in monitoring treatment efficacy and for routine medical follow up.

In this study, we used data from all children included in the Italian SDS registry with available assessments from birth to 8 years. All patients had SDS diagnosis confirmed by genetic mutations on both alleles, although up to 10% of subjects with SDS diagnosis described in the literature do not present mutations of the *SBDS* gene. In this way, we tried to reduce bias in our dataset.

In spite of the rarity of the disease, we had the possibility to generate separate charts for males and females until the age of 8. When compared to normal (regular) growth charts, the SDS charts do not differ in form for this period of age. The 50<sup>th</sup> percentile of SDS charts for weight and height is positioned on the 3<sup>rd</sup> percentile of regular charts, both for males and females. The low percentile at birth for length and weight indicates that prenatal retardation occurs, then continuing in the postnatal period.

BMI curves are similar both for normal and SDS population, indicating that the weight and height trend is harmonic also in SDS. These results as a whole suggest these growth curves are influenced by the genetic defect rather than malabsorption/malnutrition or inherited factors.

The SDS-specific growth-charts can be used in managing problems related to growth, and may be useful to recognize patients who need investigations for GH deficiency and for the possibility of specific treatment. These specific growth charts are also extremely useful to address nutritional

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3 counselling. The parents of SDS patients regularly ask for the best diet to increase the growth of their  
4 children. Sometimes, an overfeeding behaviour has been reported with the aim of influencing height.  
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6 This erroneous interpretation of growth problems in SDS may cause obesity and negative  
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8 consequences on the skeletal apparatus.  
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12 Moreover, since there has been no growth chart available for SDS patients until now, the growth  
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14 charts developed in this study provide a significant impact in understanding physical trends in these  
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16 subjects.  
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19 Given the small number of observations beyond 8 years, the growth charts were curtailed at age 8.  
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22 Several associated manifestations of the syndrome, such as heart, renal or skeletal alteration could  
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24 theoretically influence the growth of the patients. In our set, co-morbidity risk factors able to influence  
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26 growth retardation were not identified. In any case, given the rarity of the disease and the consequent  
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28 small sample size, children with medical problems were not excluded, as already done in other similar  
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30 works.<sup>37-38</sup>  
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33 It is also well-known that SDS subjects may be recognized by the presence of typical clinical features,  
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35 but variable penetrance and expressivity are common, which, together with the rarity of these patients,  
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37 makes a correlation genotype-phenotype difficult.  
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40 A few limitations in our study are to be taken into account; one is that the data used for the growth  
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42 charts does not represent the natural development of the disease, but rather the growth development of  
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44 SDS subjects receiving medical care. We are aware that the data used in constructing growth charts  
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46 should ideally come from prospective longitudinal studies on large groups, however, when considering  
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48 rare syndromes, this approach cannot be used.  
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51 In Italy, as well as in many Northern European countries, the secular trend has slowed down or even  
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53 reached a plateau since the 1980s/1990s. Since only less than 3% of measurements included in this  
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55 study were collected before 1980, no correction for the secular trend was considered.<sup>39-40</sup>  
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3 Furthermore, the present curves do not quite grasp the age of puberty, and definitive information on  
4 what affects the final height could not be obtained. In any case, the literature includes some SDS  
5 patients older than 18 with percentiles remaining in the low average or below the 3<sup>rd</sup> percentile for  
6 both weight and height<sup>3,4</sup>, indicating that the growth spurt does not lead to a substantial change in the  
7 trend of growth.  
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12 The number of older patients at the moment is small, therefore the charts may not be sufficiently  
13 reliable at the ages over eight years. This is a typical limitation in presence of small numbers of  
14 patients, and is shared by other reference charts for rare diseases.  
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19 The present growth charts can be used to compare the growth of SDS individual (height, weight, BMI)  
20 and the general population, and also to compare the growth of an individual child with that of peers of  
21 the same age and sex with the syndrome.  
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26 SDS is a worldwide disease with patients diagnosed in every part of the world; the present growth-  
27 charts should be used with caution when studying SDS individuals of other ethnic backgrounds;  
28 as presented, the curves show an accurate picture of the Italian SDS population.  
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33 Future efforts will aim at collecting more data to improve knowledge on the syndrome and construct  
34 growth-charts until 18 years of age. These tools would enable the gathering of more information on  
35 SDS, especially the influence of pubertal development on growth, as only sporadic data on this point  
36 is currently available.  
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41 Finally, when clinical trials aimed at assessing therapies for SDS basic defect are possible, similarly to  
42 other rare diseases<sup>41</sup>, growth chart comparison in treated vs untreated SDS populations could be a  
43 relevant endpoint.  
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3 **Figure 1** - Growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and  
4 females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each graph.  
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10 **Figure 2** – Estimated SDS growth charts compared to the reference Italian curves. The values of 97<sup>th</sup>  
11 and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of the  
12 reference population. The difference is less evident for the BMI centiles.  
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## AUTHOR CONTRIBUTIONS

Conception and design: MC, PS, TG. Provision of study materials or patients: CM, PS, PE, CS, ME, NE, DC. Collection and assembly of data: CM, PE. Data analysis: TG, MA. Manuscript writing: All authors. Final approval of manuscript: All authors.



## References

1. Shwachman H, Diamond LK, Oski FA, *et al.* The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 1964; 65:645–63.
2. Aggett PJ, Cavanagh NP, Matthew DJ, *et al.* Shwachman's syndrome. A review of 21 cases. *Arch Dis Child* 1980; 55:331-47.
3. Mack DR, Forstner GG, Wilschanski M, *et al.* Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology* 1996;111:1593–602.
4. Cipolli M, D'Orazio C, Delmarco A, *et al.* Shwachman's Syndrome: pathomorphosis and long-term outcome. *J Pediatr Gastroent Nutr* 1999;29:265–72.
5. Mäkitie O, Ellis L, Durie PR, *et al.* Skeletal phenotype in patients with Shwachman–Diamond syndrome and mutations in SBDS. *Clin Genet* 2004;65:101–12.
6. Mack DR Shwachman–Diamond syndrome. *J Pediatr* 2002;141:164–5.
7. Cipolli M. Shwachman-Diamond syndrome: clinical phenotypes. *Pancreatology* 2001;1:543-8.
8. Rothbaum R, Perrault J, Vlachos A, *et al.* Shwachman-Diamond syndrome: report from an international conference. *J Pediatr* 2002;141:266-70.
9. Burroughs L, Woolfrey A, Shimamura A. Shwachman–Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am* 2009;23:233–48.
10. Dror Y *et al.* Impaired ability of bone marrow stroma from patients with Shwachman–Diamond syndrome to support hematopoiesis. *Brit J Haematol* 1998;102:161 (Abs P-0638)
11. Dror Y, Squire J, Durie P, *et al.* Malignant myeloid transformation with isochromosome 7q in Shwachman–Diamond syndrome. *Leukemia* 1998;12:1591–5.

- 1  
2  
3 12. Maserati E, Minelli A, Pressato B, *et al.* Shwachamn syndrome as mutator phenotype responsible  
4 for myeloid dysplasia/neoplasia through karyotype instability and chromosomes 7 and 20 anomalies.  
5  
6 *Genes Chromosom Cancer* 2006;45:375–82.  
7  
8  
9  
10 13. Dror Y, Freedman MH. Shwachman–Diamond syndrome: an inherited preleukemic bone marrow  
11 failure disorder with a borrront hematopoietic progenitors and pulty marrow icroenvironment. *Blood*  
12  
13 1999;94:3048–54  
14  
15  
16 14. Cesaro S, Oneto R, Messina C, *et al.* Haematopoietic stem cell transplantation for Shwachman-  
17  
18 Diamond disease: a study from the European Group for blood and marrow transplantation. *Br J*  
19  
20 *Haematol* 2005;131:231-6.  
21  
22  
23 15. Boocock GR, Morrison JA, Popovic M, *et al.* Mutations in SBDS are associated with Shwachman–  
24  
25 Diamond syndrome. *Nat Genet* 2003;33:97–101.  
26  
27  
28 16. Dhanraj S, Matveev A, Li H, *et al.* Biallelic mutations in DNAJC21 cause Shwachman-Diamond  
29  
30 syndrome. *Blood* 2017; 129:1557-62.  
31  
32 17. Stepensky P, Chacon-Flores M, Kim KH, *et al.* Mutations in EFL1, an SBDS partner, are  
33  
34 associated with infantile pancytopenia, exocrine pancreatic insufficiency and skeletal anomalies in a  
35  
36 Shwachman-Diamond like syndrome. *J Med Genet* 2017; 54:558-66.  
37  
38  
39 18. Carapito R, Konantz M, Paillard C, *et al.* Mutations in signal recognition particle SRP54 cause  
40  
41 syndromic neutropenia with Shwachman-Diamond-like features. *J Clin Invest* 2017; 127:4090-103.  
42  
43  
44 19. Nicolis E, Bonizzato A, Baroukh M, *et al.* Identification of novel mutations in patients with  
45  
46 Shwachman–Diamond syndrome. *Human Mutation* 2005;25:410.  
47  
48 20. Kent A, Murphy GH, Milla P. Psychological characteristics of children with Shwachman  
49  
50 syndrome. *Arch Dis Child* 1990;65:1349-52.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 21. Kerr EN, Ellis L, Dupuis A, *et al.* The behavioral phenotype of school-age children with  
4  
5 Shwachman-Diamond Syndrome indicates neurocognitive dysfunction with loss of Shwachman-  
6  
7 Bodian-Diamond syndrome gene function. *J Pediatr* 2010;156: 433–8.  
8  
9  
10 22. Perobelli S, Nicolis E, Assael BM, *et al.* Further characterization of Shwachman-Diamond  
11  
12 syndrome: psychological functioning and quality of life in adult and young patients. *Am J Med Genet*  
13  
14 *A.* 2012;158A:567-73.  
15  
16  
17 23. Toiviainen-Salo S, Mäkitie O, Mannerkoski M, *et al.* Shwachman-Diamond syndrome is associated  
18  
19 with structural brain alterations on MRI. *Am J Med Genet A* 2008;146A:1558-64.  
20  
21  
22 24. Booij J, Reneman L, Alders M, *et al.* Increase in central striatal dopamine transporters in patients  
23  
24 with Shwachman–Diamond syndrome: additional evidence of a brain phenotype. *Am J Med Genet A*  
25  
26 2013;161A:102–7.  
27  
28  
29 25. Perobelli S, Alessandrini F, Zoccatelli G, *et al.* Diffuse alterations in grey and white matter  
30  
31 associated with cognitive impairment in Shwachman–Diamond syndrome: Evidence from a multimodal  
32  
33 approach. *Neuroimage Clin* 2015;7:721-31.  
34  
35  
36 26. Dror Y, Donadieu J, Koglmeyer J, *et al.* Draft consensus guidelines for diagnosis and treatment of  
37  
38 Shwachman-Diamond syndrome. *Ann N Y Acad Sci.* 2011;1242:40-55.  
39  
40  
41 27. Zemel BS, Pipan M, Stallings VA, *et al.* Growth charts for children with Down syndrome in the  
42  
43 United States. *Pediatrics* 2015;136:e1-e8.  
44  
45  
46 28. Verbeek S, Eilers PH, Lawrence K, *et al.* Growth charts for children with Ellis–van Creveld  
47  
48 syndrome, *Eur J Pediatr* 2011;170:207–211.  
49  
50  
51 29. Gawlik A, Gawlik T, Augustyn M, *et al.* Validation of growth charts for girls with Turner  
52  
53 syndrome. *Int J Clin Pract* 2006; 60:150–5.  
54  
55  
56 30. Tofts L, Das S, Collins F, *et al.* Growth charts for Australian children with achondroplasia. *Am J*  
57  
58 *Med Genet* 2017;9999:1-12  
59  
60

- 1  
2  
3 31. R version 3.3.3 (2017-03-06), The R Foundation for Statistical Computing  
4  
5 32. Cacciari E, Milani S, Balsamo A, et al. Italian cross-sectional growth charts for heighth, weigth and  
6  
7 BMI (2 to 20 yr), *J Endocrinol Invest* 2006;29:581-93.  
8  
9 33. De Onis M, Garza C, Victoria CG, et al. The WHO multicentre growth reference study:  
10  
11 planning, study design and methodology. *Food Nutr Bull* 2004;25:15-26.  
12  
13 34. Cole TJ. The LMS method for constructing normalized growth standards, *Eur J Clin Nutr* 1990;  
14  
15 44:45-60.  
16  
17 35. Cole TJ and Green PJ. Smoothing reference centile curves: the LMS method and penalized  
18  
19 likelihood. *Stat Med* 1992;11:1305-19.  
20  
21 36. Rigby RA, Stasinopoulus DM. Generalized Additive Models for Location Scale and Shape  
22  
23 (GAMLSS) in R, *J Stat Softw.*2007; 23:1-46.  
24  
25 37. Beets L, Rodriguez-Fonseca C, Hennekam RC. Growth charts for individuals with Rubinstein-  
26  
27 Taybi syndrome. *Am J Med Genet A* 2014;164A:2300-9  
28  
29 38. Su X, Lau JT, Yu CM, Chow, et al. Growth charts for Chinese Down syndrome children from birth  
30  
31 to 14 years. *Arch Dis Child* 2014;99:824-9.  
32  
33 39. Larnkaer A, Attrup Schrøder S, Schmidt IM, et al. Secular change in adult stature has come to a  
34  
35 halt in northern Europe and Italy. *Acta Paediatr* 2006;95:754-5.  
36  
37 40. Bonthuis M, van Stralen KJ, Verrina E, Use of National and International Growth Charts for  
38  
39 Studying Height in European Children: Development of Up-To-Date European Height-For-Age  
40  
41 Charts. *PLoS One* 2012;7:e42506.  
42  
43 41. Harman K, Dobra R, Davies JC. Disease-modifying drug therapy in cystic fibrosis. *Paediatr Respir*  
44  
45 *Rev* 2017; Mar 14. pii: S1526-0542(17)30031-3.  
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**Table 1 - Number of patients and assessments:**

a) for each age class, the number of patients with available assessments is reported, separately for male and female;

b), c) and d) for each age class, the number of assessments for weight, height and BMI, respectively, is reported for male and female.

a)		Number of patients		
	Age (years)	F	M	Total
	0-2	36	58	94
	3-4	23	37	60
	5-6	20	27	47
	7-8	18	27	45
b)		Number of assessments		
	Age (years)	F	M	Total
Weight	0-2	91	141	232
	3-4	27	44	71
	5-6	29	41	70
	7-8	17	18	35
	Total	164	244	408
c)		Number of assessments		
	Age (years)	F	M	Total
Height	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377
d)		Number of assessments		
	Age (years)	F	M	Total
Body mass index	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377

**Table 2 - Main demographic and clinical characteristics of patients**

Variables	N (%)
Total	106
Gender	
Male	64 (60)
Female	42 (40)
Age at diagnosis (months)	
Median (range)	13.8 months (0-35.6 years)
Gestational age (weeks)	
Median (range)	39 (29-42)
Pancreatic status	
Pancreatic sufficiency	15 (14)
Pancreatic insufficiency	91 (86)
Heart problems	
No	99 (93)
Yes	7 (7)
Bone lesions at diagnosis	
No	59 (56)
Yes	47 (44)
Bone lesions during the first 8 years	
No	74 (70)
Yes	32 (30)
GH *	
No	100 (94)
Yes	6 (6)

\* in 5 cases after the first 8 years of life, in 1 case at 7.5 years

**Table 3 – Mutations of SDS patients**

Mutations		N	%
258+2T>C	183-184TA>CT	61	57.5
258+2T>C	183-184TA>CT+258+2T>C	16	15.1
258+2T>C	258+2T>C	9	8.5
258+2T>C	c.258+533_459+403del	4	3.8
258+2T>C	101A>T	1	0.9
258+2T>C	107delT	1	0.9
258+2T>C	187G>T	1	0.9
258+2T>C	212C>T	1	0.9
258+2T>C	289-292del	1	0.9
258+2T>C	300delAC	1	0.9
258+2T>C	307-308delCA	1	0.9
258+2T>C	352A>G	1	0.9
258+2T>C	356G>A	1	0.9
258+2T>C	624+1G>C	1	0.9
258+2T>C	92-93GC>AG	1	0.9
258+2T>C	G63C	1	0.9
258+2T>C	IVS1-71del83bp	1	0.9
258+2T>C	R218X	1	0.9
258+2T>C	Y32C	1	0.9
523C>T	523C>T	1	0.9

**Table 4** – 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported for SDS patients from birth to 8 years: the estimates are reported every 3 months from birth to 2 years, every 6 months from 2 to 6 years and once a year from 6 to 8 years.

a) centiles for height

Age	Height									
	Male					Female				
	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	41.8	46.2	48.6	51.1	55.5	38.1	44.3	46.8	48.8	51.8
0.25	47.0	51.9	54.7	57.4	62.3	43.0	49.3	52.0	54.3	57.7
0.50	51.7	57.2	60.2	63.1	68.4	47.8	54.2	57.0	59.5	63.4
0.75	55.9	61.8	65.0	68.1	73.7	52.3	58.7	61.8	64.5	68.8
1.00	59.6	65.8	69.2	72.5	78.4	56.5	62.9	66.1	69.0	73.8
1.25	62.8	69.3	72.8	76.3	82.3	60.2	66.6	69.9	73.0	78.2
1.50	65.5	72.3	75.9	79.5	85.7	63.3	69.8	73.2	76.5	81.9
1.75	68.0	74.9	78.7	82.3	88.7	66.0	72.5	76.0	79.3	85.1
2.00	70.1	77.2	81.0	84.8	91.2	68.3	74.8	78.4	81.8	87.8
2.50	73.8	81.2	85.2	89.0	95.6	72.2	78.8	82.4	86.0	92.4
3.00	77.1	84.8	88.8	92.7	99.4	75.8	82.6	86.3	90.0	96.6
3.50	79.7	87.6	91.7	95.6	102.3	79.2	86.2	90.1	93.9	100.6
4.00	82.1	90.1	94.3	98.2	104.9	82.3	89.7	93.7	97.5	104.3
4.50	84.9	93.1	97.3	101.3	108.0	85.1	92.9	97.0	100.9	107.6
5.00	87.9	96.3	100.5	104.6	111.2	87.2	95.7	99.9	103.8	110.2
5.50	90.6	99.2	103.5	107.6	114.2	88.8	98.0	102.3	106.2	112.4
6.00	93.4	102.1	106.5	110.6	117.3	90.5	100.4	104.8	108.7	114.7
7.00	98.3	107.3	111.7	115.8	122.4	95.1	105.6	110.1	114.1	120.1
8.00	103.0	112.2	116.6	120.7	127.3	100.7	110.6	115.1	119.1	125.5



**b) centiles for weight**

Weight										
Male						Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	1.5	2.6	2.9	3.3	4.0	1.6	2.3	2.7	3.1	3.7
0.25	2.4	3.8	4.3	4.8	5.8	2.2	3.2	3.7	4.2	5.1
0.50	3.2	4.9	5.5	6.1	7.3	2.9	4.1	4.7	5.4	6.4
0.75	3.9	5.8	6.6	7.3	8.6	3.6	5.0	5.7	6.5	7.7
1.00	4.6	6.6	7.5	8.3	9.7	4.3	5.8	6.7	7.5	9.0
1.25	5.2	7.3	8.3	9.2	10.8	5.0	6.6	7.6	8.5	10.2
1.50	5.8	7.9	9.0	10.0	11.7	5.6	7.3	8.3	9.4	11.2
1.75	6.4	8.5	9.6	10.7	12.6	6.1	8.0	9.0	10.1	12.1
2.00	6.9	9.0	10.2	11.4	13.5	6.6	8.6	9.7	10.8	13.0
2.50	7.8	10.0	11.3	12.6	15.1	7.5	9.5	10.7	12.0	14.4
3.00	8.6	10.9	12.3	13.7	16.5	8.3	10.4	11.6	13.0	15.6
3.50	9.2	11.5	13.0	14.6	17.8	9.0	11.1	12.5	13.9	16.9
4.00	9.8	12.1	13.7	15.4	19.0	9.7	11.9	13.3	14.9	18.1
4.50	10.4	12.8	14.4	16.2	20.3	10.3	12.6	14.1	15.8	19.5
5.00	11.0	13.4	15.1	17.1	21.8	10.9	13.3	14.9	16.7	20.8
5.50	11.6	14.0	15.8	17.9	23.4	11.5	13.9	15.6	17.6	22.1
6.00	12.3	14.7	16.5	18.8	25.2	12.1	14.6	16.4	18.5	23.5
7.00	13.6	16.1	18.1	20.9	30.0	13.4	16.1	18.0	20.5	26.8
8.00	15.5	18.1	20.3	23.6	37.2	15.2	18.0	20.2	23.0	31.2

## e) centiles for body mass index (BMI)

BMI										
Male						Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	9.6	11.9	12.7	13.6	16.0	8.7	11.6	12.5	13.5	18.3
0.25	10.3	12.5	13.4	14.3	16.9	9.8	12.3	13.3	14.2	18.4
0.50	10.9	13.1	14.0	15.0	17.6	10.8	13.1	14.0	14.9	18.7
0.75	11.3	13.6	14.5	15.5	18.3	11.6	13.7	14.6	15.6	19.0
1.00	11.7	14.0	14.9	15.9	18.8	12.3	14.2	15.1	16.1	19.2
1.25	12.0	14.3	15.2	16.2	19.1	12.9	14.6	15.5	16.4	19.4
1.50	12.3	14.4	15.4	16.3	19.4	13.3	14.9	15.8	16.7	19.5
1.75	12.4	14.6	15.5	16.4	19.5	13.6	15.1	15.9	16.8	19.5
2.00	12.6	14.6	15.5	16.5	19.7	13.8	15.2	16.0	16.8	19.4
2.50	12.8	14.7	15.6	16.6	19.9	13.8	15.1	15.8	16.6	19.0
3.00	12.9	14.8	15.6	16.6	20.0	13.6	14.8	15.5	16.3	18.5
3.50	12.9	14.7	15.6	16.5	20.1	13.5	14.6	15.2	16.0	18.3
4.00	12.8	14.6	15.4	16.4	20.2	13.4	14.4	15.1	15.9	18.3
4.50	12.7	14.4	15.3	16.3	20.3	13.4	14.4	15.1	15.9	18.5
5.00	12.6	14.2	15.1	16.1	20.4	13.4	14.4	15.1	16.0	19.0
5.50	12.5	14.0	14.9	16.0	20.5	13.3	14.3	15.0	16.0	19.4
6.00	12.4	14.0	14.8	15.9	20.7	13.1	14.2	14.9	15.9	19.8
7.00	12.4	14.0	14.9	16.1	21.5	13.0	14.0	14.8	15.9	20.5
8.00	12.7	14.2	15.2	16.5	22.4	13.2	14.4	15.2	16.4	21.3

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3 Legend  
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5 **Figure 1** - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and F)  
6 for males and females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each graph.  
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9  
10 **Figure 2** – Estimated SDS growth charts compared to reference Italian curves. The values of 97<sup>th</sup> and  
11 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of the  
12 reference population. The difference is less evident for the body mass index (BMI) centiles.  
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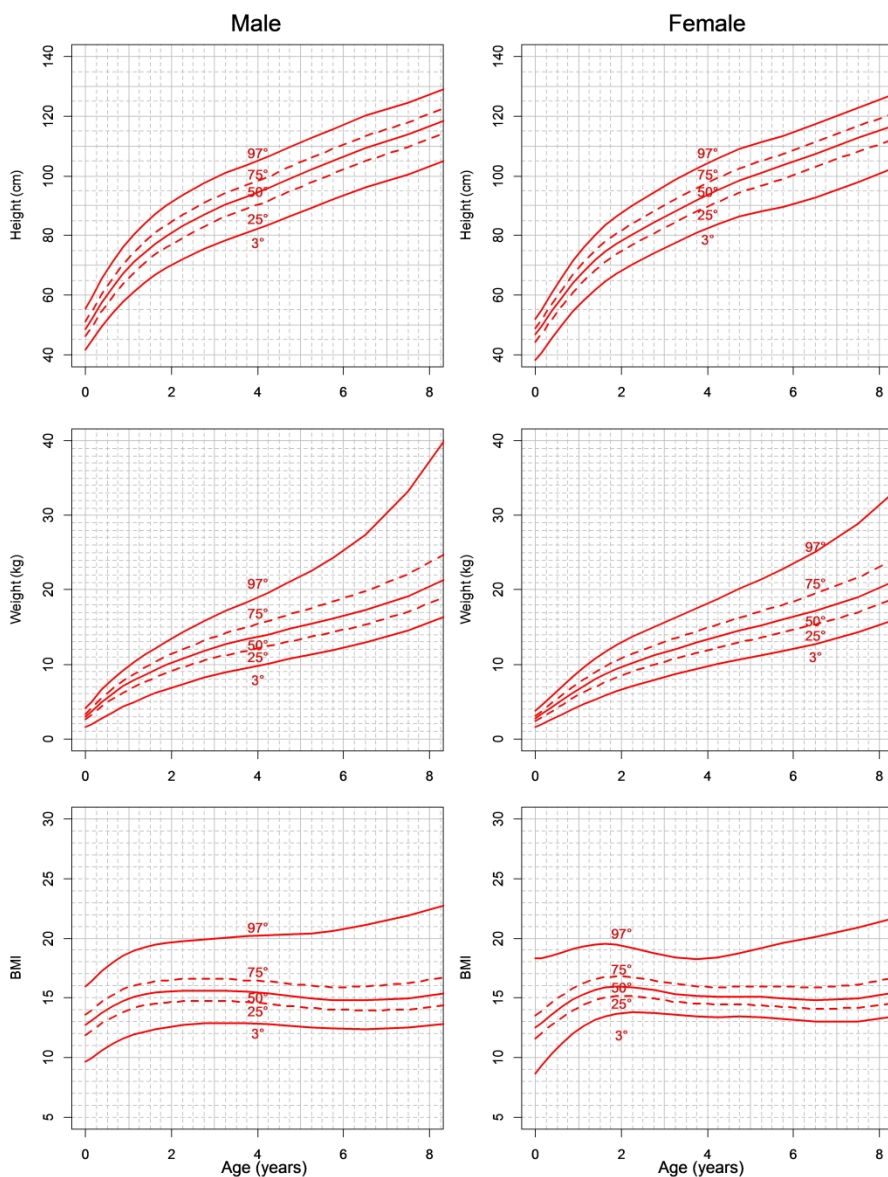


Figure 1 - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and F) for males and females (SDS patient). Curves for 3rd, 25th, 50th, 75th and 97th are reported in each graph.

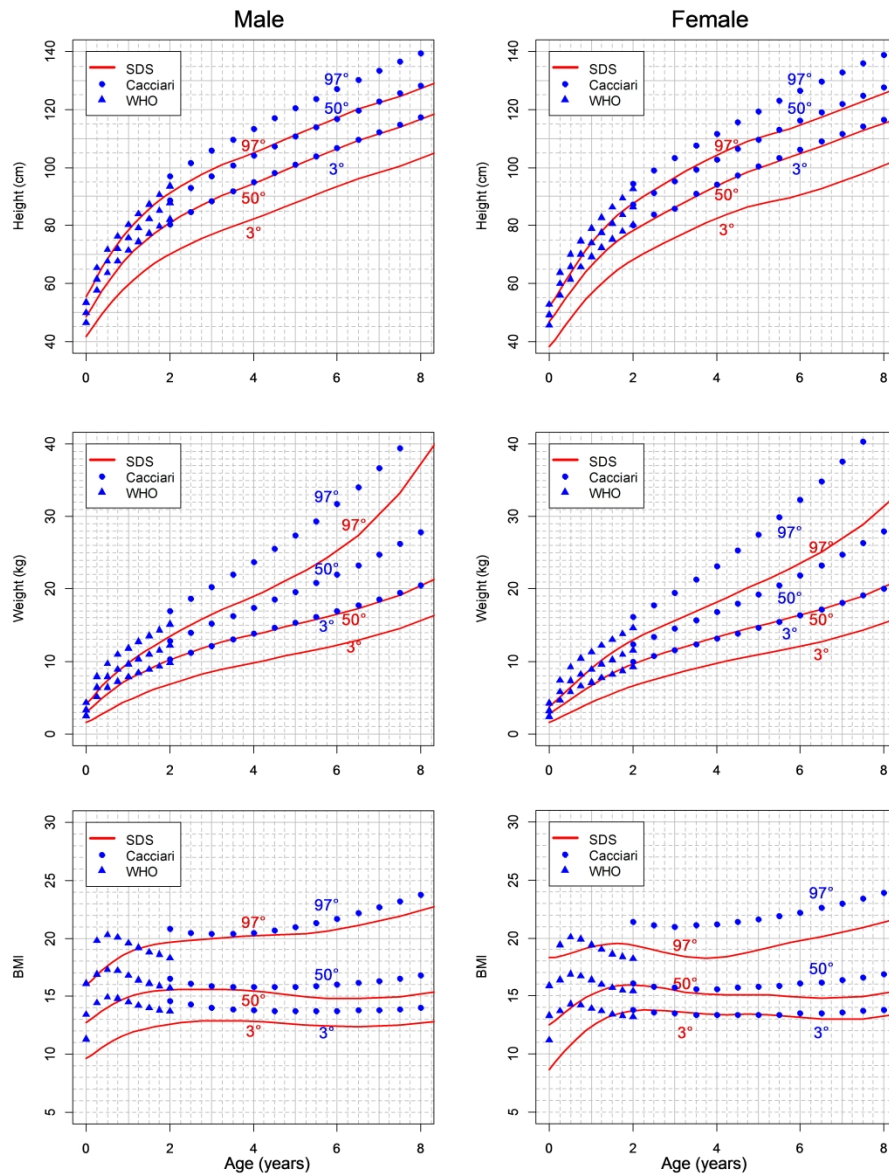


Figure 2 – Estimated SDS growth charts compared to reference Italian curves. The values of 97th and 50th centiles for height and weight of SDS patients are located on the 50th and 3rd centiles of the reference population. The difference is less evident for the body mass index (BMI) centiles.

# BMJ Open

## NORMATIVE GROWTH CHARTS FOR SHWACHMAN – DIAMOND SYNDROME FROM ITALIAN COHORT 0 TO 8 YEARS OLD

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Manuscripts

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3 NORMATIVE GROWTH CHARTS FOR SHWACHMAN –DIAMOND SYNDROME FROM  
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5 ITALIAN COHORT 0 TO 8 YEARS OLD  
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## Abstract

### Objectives.

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive disorder. Its predominant manifestations include exocrine pancreatic insufficiency, bone marrow failure and skeletal abnormalities. Patients frequently present failure to thrive and susceptibility to short stature. Average birth weight is at the 25<sup>th</sup> percentile; by the first birthday, >50% of patients drop below the 3<sup>rd</sup> percentile for height and weight.

The study aims at estimating the growth charts for patients affected by SDS in order to give a reference tool helpful for medical care and growth surveillance through the first 8 years of patient's life.

### Setting and participants.

This retrospective observational study includes 106 patients (64 M) with available information from birth to 8 years, selected among the 122 patients included in the Italian National Registry of SDS and born between 1975 and 2016. Gender, birth date and auxological parameters at repeated assessment times were collected. The General Additive Model for Location Scale and Shape method was applied to build the growth charts. A set of different distributions was used, and the more appropriate were selected in accordance with the smallest Akaike's information criterion.

### Results.

A total of 408 measurements was collected and analyzed. The median number of observations per patient amounted to 3, range 1-11. In accordance with the methods described, specific SDS growth charts were built for weight, height and body mass index, separately for males and females.



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3 The 50<sup>th</sup> and 3<sup>rd</sup> percentiles of weight and height of the healthy population (WHO standard-  
4 references) respectively correspond to the 97<sup>th</sup> and 50<sup>th</sup> percentiles of the SDS population (SDS  
5 specific growth charts), whilst the difference is less evident for the BMI.  
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## 11 **Conclusions.**

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14 Specific SDS growth charts obtained through our analysis enable a more appropriate classification  
15 of patients based on auxological parameters, representing a useful reference tool for evaluating their  
16 growth during childhood.  
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## 31 **Strengths and limitations**

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- These growth charts represent the first set of normative curves for SDS children 0 to 8 years old
  - The 50<sup>th</sup> and 3<sup>rd</sup> percentiles of weight and height of the healthy population respectively correspond to the 97<sup>th</sup> and 50<sup>th</sup> percentiles of the SDS population
  - These charts should be principally used to compare the growth between SDS subjects of the same age and sex and also to recognize patients to investigate for GH deficiency
  - The data used for the growth charts do not represent the natural development of the disease, but rather the growth development of SDS subjects receiving medical care
  - The present growth-charts should be used with caution when studying SDS patients of other ethnic backgrounds, as they show an accurate picture of the Italian SDS population.

### Competing interests

None declared

### Data sharing

All the available data were included in the analysis. The data may be available by contacting the authors.

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## Introduction

Shwachman–Diamond syndrome (SDS) (OMIM 260400) is a rare autosomal recessive disorder first described in 1964<sup>1</sup>, characterized by exocrine pancreas insufficiency, bone marrow failure and bone malformations.<sup>2-5</sup> Failure to thrive, susceptibility to infections and short stature are frequently observed in patients with SDS as well.<sup>1-4,6</sup>

Pancreatic insufficiency early arises and is characterized by replacement of exocrine components with fatty tissue, but preserved islets of Langerhans and ductal architecture. Pancreatic function spontaneously improves over the time in almost 50% of patients.<sup>2,4,7-9</sup>

Almost the totality of patients present persistent or intermittent neutropenia.<sup>1,2,8-11</sup> Bone marrow biopsy reveals a hypoplastic “marrow” with varying degrees of fat infiltration.<sup>2,11</sup> Up to 15-20% of patients develop myelodysplastic syndrome (MDS), with high risk of acute myeloid leukemia (AML) progression.<sup>12-15</sup>

In 2002, the gene (*SBDS*) involved in the syndrome was identified on chromosome 7q11,<sup>16</sup> although mutations in the *DNAJC21* gene have also been associated to a SDS phenotype, as well as, possibly, mutations of *EFL1* and *SRP54* genes.<sup>17-19</sup> *SBDS* is widely expressed in mammalian tissue. In fact, other organs such as teeth and oral cavity, liver, heart, kidneys and skin may be involved.<sup>5,7-8</sup>

Currently, almost 10% of SDS patients with clinical features of SDS have lacked *SBDS* mutations.<sup>16,20</sup> However, the negative genetic test should not exclude the diagnosis. An accurate clinical evaluation is important in order to diagnose the presence of the syndrome.

Cognitive impairment has been noted in the majority of these patients, albeit with intragroup variability;<sup>21-23</sup> this has a serious impact on the patient, limiting independence and quality of life.<sup>23</sup>

Neuroimaging studies<sup>24-26</sup> reported diffuse brain alterations in the brain structure and connectivity.

Several clinical studies reported failure to thrive associated with malnutrition. This is a common feature in early stage of life, in particular prior to diagnosis. Growth failure is mainly due to inadequate nutrient intake in the presence or in the absence of feeding difficulties, pancreatic

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3 insufficiency and recurrent infections.<sup>1,2,4,8,27</sup> The average weight at birth is at the 25<sup>th</sup> percentile,  
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5 and over half of the patients drop below the 3<sup>rd</sup> percentile for both height and weight by the first  
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7 birthday. After diagnosis and the start of an appropriate therapy, growth rate is restored to normal  
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9 level in most of SDS children, even though it consistently remains below the 3<sup>rd</sup> percentile for  
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11 height and weight.<sup>2,4,9,27</sup> These alterations are not related to a pancreatic insufficiency or an  
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13 inappropriate caloric intake, but seem to be directly linked to biallelic mutations of the SBDS gene,  
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15 and the growth of these patients differs from that of healthy children.  
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19 To date, there are no specific SDS growth charts available unlike other disorders with marked  
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21 growth retardation such as Down syndrome, Turner syndrome, Ellis-van Creveld syndrome,  
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23 achondroplasia.<sup>28-31</sup> Indeed, disease-specific charts are a helpful tool in medical care, monitoring  
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25 growth more accurately, and for research.  
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29 The aim of this retrospective multicentre observational study is to develop the growth chart for  
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31 patients affected by SDS in order to provide a reference tool to monitor the growth of children with  
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33 this disease throughout childhood.  
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## Method

This study includes patients who are part of the Italian National Registry of SDS whose height, weight and main demographic characteristic were available in their first 8 years of life. In the Registry, all 122 patients have a SDS diagnosis confirmed by genetic analysis. For each subject, the following characteristics were collected: gender, birth date, height, weight, assessment date, available clinic information. Measurements were recorded in accordance with the standard criteria by age period. A total of 645 observations on 122 patients was recorded, but data beyond 8 years of age was not included in the analysis owing to its being available for only 16 patients and at limited data points; thus, 408 observations on 106 patients with assessments in their first 8 years of life were analyzed.

The primary endpoint was to estimate percentiles for height, weight and BMI for males and females.

The protocol was approved by the local Ethics Committee (CE n 1944). All patients signed an informed consent to be included in the Registry.

### *Patient and Public Involvement*

Patients were not involved in the design, recruitment and conduct of this study.

Data was initially prepared using the statistical software SAS and then analyzed by the software R for growth curve estimation<sup>32</sup>. A 3-month window was used for each of the three anthropomorphic measures; in case of multiple assessments, the average of the values available inside the window was considered. Growth curves for weight, height and BMI from birth to 8 years were constructed, each with 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles for age. Data from male and female individuals was analyzed separately.

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3 Normative data for growth parameters was obtained from tables published by Cacciari et al.<sup>33</sup> The  
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5 Italian normative data was limited to 2–8 years, thus WHO data was used for ages 0-2.<sup>34</sup> To model  
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7 the growth charts, the GAMLSS (General Additive Model for Location Scale and Shape) package  
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9 for the R statistical program was used. This tool enables all the parameters of the distribution of the  
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11 response variable to be modelled as linear/non-linear or smooth functions of the explanatory  
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13 variables<sup>35-37</sup>.  
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17 The distribution of height, weight and BMI was modelled by use of four parameters representing  
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19 location, scale, skewness and kurtosis, using cubic penalized smoothing lines. A set of different  
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21 distributions was used, and the more appropriate were selected in accordance with the criterion of  
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23 the smallest AIC. Worm plots and q-q plots were used for the analysis of residuals.  
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26 With a sample size of 60 patients, the 50<sup>th</sup>, 25<sup>th</sup>/75<sup>th</sup> and 3<sup>rd</sup>/97<sup>th</sup> centiles could be estimated reaching  
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28 a standard error of about 0.8, 0.9 and 1.3, respectively.  
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## Results

A total of 106 patients (64 males and 42 females) were considered eligible for the analysis, with a total of 408 measurements collected from 1975 to 2016, with a median number of 3 observations per patient, range 1-11 (Table 1). All patients were Caucasian and of Italian origin, with a median age at diagnosis of 13.8 months, range 0 days-35.6 years. The median gestational age was 39 weeks, range 29-42, and the median weight at birth was 2.8 kg (0.85-4.2). Pancreatic insufficiency was observed in 91 patients (86%), all of them were on treatment with pancreatic enzymes. Six patients were treated with growth hormone (GH), 5 after their first 8 years of life and 1 at age 7.5. Twelve patients out of 106 underwent hematopoietic stem cell transplantation, 8 out of 12 under eight years of age.

The main patient characteristics and mutations are reported in Table 2 and Table 3.

In accordance with the methods described, specific SDS growth charts were built for weight, height and BMI, separately for males and females. Each subject had the same number of observations for each growth parameter included in the database.

Figure 1 shows a growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and females. Table 4 shows the 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> centiles: the centiles are estimated every 3 months from birth to 2 years, every 6 months from 2 to 6 years, and once a year from 6 to 8 years.

In Figure 2, the estimated SDS growth charts are shown together with Italian reference curves.

Compared to typically developing individuals (standard population), the values of the 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles, respectively. At 8 years, the 50<sup>th</sup> centile for height in SDS patients corresponds to the 3<sup>rd</sup> centile and to the -2 SD value in the healthy population. The difference is less evident for the BMI centiles, meaning that the growth retardation is harmonic.

## Discussion

SDS is a rare disease without a well-defined prevalence. Severe growth retardation (particularly in length/height) is one of its typical features, which can be alleged to be linked to the genetic cause of the disease.

At present, no growth charts have been validated for SDS; the charts we show here represent the first set of normative curves for SDS children 0-8 years. As in healthy children, specific charts for SDS are important tools in monitoring treatment efficacy and for routine medical follow up.

In this study, we used data from all children included in the Italian SDS registry with available assessments from birth to 8 years. All patients had SDS diagnosis confirmed by genetic mutations on both alleles, although up to 10% of subjects with SDS diagnosis described in the literature do not present mutations of the *SBDS* gene. In this way, we tried to reduce bias in our dataset.

In spite of the rarity of the disease, we had the possibility to generate separate charts for males and females until the age of 8. When compared to normal (regular) growth charts, the SDS charts do not differ in form for this period of age. The 50<sup>th</sup> percentile of SDS charts for weight and height is positioned on the 3<sup>rd</sup> percentile of regular charts, both for males and females. The low percentile at birth for length and weight indicates that prenatal retardation occurs, then continuing in the postnatal period.

BMI curves are similar both for normal and SDS population, indicating that the weight and height trend is harmonic also in SDS. These results as a whole suggest these growth curves are influenced by the genetic defect rather than malabsorption/malnutrition or inherited factors.

The SDS-specific growth-charts can be used in managing problems related to growth, and may be useful to recognize patients who need investigations for GH deficiency and for the possibility of specific treatment. These specific growth charts are also extremely useful to address nutritional counselling. The parents of SDS patients regularly ask for the best diet to increase the growth of their children. Sometimes, an overfeeding behaviour has been reported with the aim of influencing



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3 height. This erroneous interpretation of growth problems in SDS may cause obesity and negative  
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5 consequences on the skeletal apparatus.  
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7  
8 Moreover, since there has been no growth chart available for SDS patients until now, the growth  
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10 charts developed in this study provide a significant impact in understanding physical trends in  
11  
12 these subjects.  
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14  
15 Given the small number of observations beyond 8 years, the growth charts were curtailed at age 8.

16  
17 Several associated manifestations of the syndrome, such as heart, renal or skeletal alteration could  
18  
19 theoretically influence the growth of the patients. In our set, co-morbidity risk factors able to  
20  
21 influence growth retardation were not identified. In any case, given the rarity of the disease and the  
22  
23 consequent small sample size, children with medical problems were not excluded, as already done  
24  
25 in other similar works.<sup>38-39</sup>  
26

27  
28 It is also well-known that SDS subjects may be recognized by the presence of typical clinical  
29  
30 features, but variable penetrance and expressivity are common, which, together with the rarity of  
31  
32 these patients, makes a correlation genotype-phenotype difficult.  
33

34  
35 A few limitations in our study are to be taken into account; one is that the data used for the growth  
36  
37 charts does not represent the natural development of the disease, but rather the growth development  
38  
39 of SDS subjects receiving medical care. We are aware that the data used in constructing growth  
40  
41 charts should ideally come from prospective longitudinal studies on large groups, however, when  
42  
43 considering rare syndromes, this approach cannot be used.  
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45

46  
47 In Italy, as well as in many Northern European countries, the secular trend has slowed down or  
48  
49 even reached a plateau since the 1980s/1990s. Since only less than 3% of measurements included  
50  
51 in this study were collected before 1980, no correction for the secular trend was considered.<sup>40-41</sup>  
52

53  
54 Furthermore, the present curves do not quite grasp the age of puberty, and definitive information  
55  
56 on what affects the final height could not be obtained. In any case, the literature includes some  
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58 SDS patients older than 18 with percentiles remaining in the low average or below the 3<sup>rd</sup>  
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3 percentile for both weight and height<sup>3,4</sup>, indicating that the growth spurt does not lead to a  
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5 substantial change in the trend of growth.  
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7  
8 The number of older patients at the moment is small, therefore the charts may not be sufficiently  
9  
10 reliable at the ages over eight years. This is a typical limitation in presence of small numbers of  
11  
12 patients, and is shared by other reference charts for rare diseases.  
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14  
15 The present growth charts can be used to compare the growth of SDS individual (height, weight,  
16  
17 BMI) and the general population, and also to compare the growth of an individual child with that  
18  
19 of peers of the same age and sex with the syndrome.  
20

21  
22 SDS is a worldwide disease with patients diagnosed in every part of the world; the present growth-  
23  
24 charts should be used with caution when studying SDS individuals of other ethnic backgrounds;  
25  
26 as presented, the curves show an accurate picture of the Italian SDS population.  
27

28  
29 Future efforts will aim at collecting more data to improve knowledge on the syndrome and  
30  
31 construct growth-charts until 18 years of age. These tools would enable the gathering of more  
32  
33 information on SDS, especially the influence of pubertal development on growth, as only sporadic  
34  
35 data on this point is currently available.  
36

37  
38 Finally, when clinical trials aimed at assessing therapies for SDS basic defect are possible,  
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40 similarly to other rare diseases<sup>42</sup>, growth chart comparison in treated vs untreated SDS populations  
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42 could be a relevant endpoint.  
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3 **Figure 1** - Growth chart for height (A and B), weight (C and D) and BMI (E and F) for males and  
4 females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each graph.  
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10 **Figure 2** – Estimated SDS growth charts compared to the reference Italian curves. The values of  
11 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of  
12 the reference population. The difference is less evident for the BMI centiles.  
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47  
48 Conception and design: MC, PS, TG. Provision of study materials or patients: CM, PS, PE, CS, ME, NE, DC.

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51 Collection and assembly of data: CM, PE. Data analysis: TG, MA. Manuscript writing: All authors. Final approval of  
52  
53 manuscript: All authors.

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## References

1. Shwachman H, Diamond LK, Oski FA, *et al.* The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 1964; 65:645–63.
2. Aggett PJ, Cavanagh NP, Matthew DJ, *et al.* Shwachman's syndrome. A review of 21 cases. *Arch Dis Child* 1980; 55:331-47.
3. Mack DR, Forstner GG, Wilschanski M, *et al.* Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology* 1996;111:1593–602.
4. Cipolli M, D'Orazio C, Delmarco A, *et al.* Shwachman's Syndrome: pathomorphosis and long-term outcome. *J Pediatr Gastroent Nutr* 1999;29:265–72.
5. Mäkitie O, Ellis L, Durie PR, *et al.* Skeletal phenotype in patients with Shwachman–Diamond syndrome and mutations in SBDS. *Clin Genet* 2004;65:101–12.
6. Dall'oca C, Bondi M, Merlini, *et al.* Shwachman–Diamond syndrome. *Musculoskelet Surg* 2012;96:81-8.
7. Mack DR Shwachman–Diamond syndrome. *J Pediatr* 2002;141:164–5.
8. Cipolli M. Shwachman-Diamond syndrome: clinical phenotypes. *Pancreatology* 2001;1:543-8.
9. Rothbaum R, Perrault J, Vlachos A, *et al.* Shwachman-Diamond syndrome: report from an international conference. *J Pediatr* 2002;141:266-70.
10. Burroughs L, Woolfrey A, Shimamura A. Shwachman–Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am* 2009;23:233–48.
11. Dror Y *et al.* Impaired ability of bone marrow stroma from patients with Shwachman–Diamond syndrome to support hematopoiesis. *Brit J Haematol* 1998;102:161 (Abs P-0638)
12. Dror Y, Squire J, Durie P, *et al.* Malignant myeloid transformation with isochromosome 7q in Shwachman–Diamond syndrome. *Leukemia* 1998;12:1591–5.

13. Maserati E, Minelli A, Pressato B, *et al.* Shwachamn syndrome as mutator phenotype responsible for myeloid dysplasia/neoplasia through karyotype instability and chromosomes 7 and 20 anomalies. *Genes Chromosom Cancer* 2006;45:375–82.
14. Dror Y, Freedman MH. Shwachman–Diamond syndrome: an inherited preleukemic bone marrow failure disorder with a aberrant hematopoietic progenitors and pultly marrow microenvironment. *Blood* 1999;94:3048–54
15. Cesaro S, Oneto R, Messina C, *et al.* Haematopoietic stem cell transplantation for Shwachman–Diamond disease: a study from the European Group for blood and marrow transplantation. *Br J Haematol* 2005;131:231–6.
16. Boocock GR, Morrison JA, Popovic M, *et al.* Mutations in SBDS are associated with Shwachman–Diamond syndrome. *Nat Genet* 2003;33:97–101.
17. Dhanraj S, Matveev A, Li H, *et al.* Biallelic mutations in DNAJC21 cause Shwachman–Diamond syndrome. *Blood* 2017; 129:1557–62.
18. Stepensky P, Chacon-Flores M, Kim KH, *et al.* Mutations in EFL1, an SBDS partner, are associated with infantile pancytopenia, exocrine pancreatic insufficiency and skeletal anomalies in a Shwachman–Diamond like syndrome. *J Med Genet* 2017; 54:558–66.
19. Carapito R, Konantz M, Paillard C, *et al.* Mutations in signal recognition particle SRP54 cause syndromic neutropenia with Shwachman–Diamond-like features. *J Clin Invest* 2017; 127:4090–103.
20. Nicolis E, Bonizzato A, Baroukh M, *et al.* Identification of novel mutations in patients with Shwachman–Diamond syndrome. *Human Mutation* 2005;25:410.
21. Kent A, Murphy GH, Milla P. Psychological characteristics of children with Shwachman syndrome. *Arch Dis Child* 1990;65:1349–52.
22. Kerr EN, Ellis L, Dupuis A, *et al.* The behavioral phenotype of school-age children with Shwachman–Diamond Syndrome indicates neurocognitive dysfunction with loss of Shwachman–Bodian–Diamond syndrome gene function. *J Pediatr* 2010;156: 433–8.

- 1  
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3 23. Perobelli S, Nicolis E, Assael BM, *et al.* Further characterization of Shwachman-Diamond  
4 syndrome: psychological functioning and quality of life in adult and young patients. *Am J Med*  
5  
6  
7 *Genet A.* 2012;158A:567-73.  
8  
9  
10 24. Toiviainen-Salo S, Mäkitie O, Mannerkoski M, *et al.* Shwachman-Diamond syndrome is  
11 associated with structural brain alterations on MRI. *Am J Med Genet A* 2008;146A:1558-64.  
12  
13 25. Booij J, Reneman L, Alders M, *et al.* Increase in central striatal dopamine transporters in  
14 patients with Shwachman–Diamond syndrome: additional evidence of a brain phenotype. *Am J Med*  
15  
16  
17 *Genet A* 2013;161A:102–7.  
18  
19  
20 26. Perobelli S, Alessandrini F, Zoccatelli G, *et al.* Diffuse alterations in grey and white matter  
21 associated with cognitive impairment in Shwachman–Diamond syndrome: Evidence from a  
22  
23  
24 multimodal approach. *Neuroimage Clin* 2015;7:721-31.  
25  
26  
27 27. Dror Y, Donadieu J, Koglmeier J, *et al.* Draft consensus guidelines for diagnosis and treatment  
28 of Shwachman-Diamond syndrome. *Ann N Y Acad Sci.* 2011;1242:40-55.  
29  
30  
31 28. Zemel BS, Pipan M, Stallings VA, *et al.* Growth charts for children with Down syndrome in the  
32 United States. *Pediatrics* 2015;136:e1-e8.  
33  
34  
35 29. Verbeek S, Eilers PH, Lawrence K, *et al.* Growth charts for children with Ellis–van Creveld  
36 syndrome, *Eur J Pediatr* 2011;170:207–211.  
37  
38  
39 30. Gawlik A, Gawlik T, Augustyn M, *et al.* Validation of growth charts for girls with Turner  
40 syndrome. *Int J Clin Pract* 2006; 60:150–5.  
41  
42  
43 31. Tofts L, Das S, Collins F, *et al.* Growth charts for Australian children with achondroplasia. *Am J*  
44  
45  
46 *Med Genet* 2017;9999:1-12  
47  
48  
49 32. R version 3.3.3 (2017-03-06), The R Foundation for Statistical Computing  
50  
51  
52 33. Cacciari E, Milani S, Balsamo A, *et al.* Italian cross-sectional growth charts for height, weight  
53 and BMI (2 to 20 yr), *J Endocrinol Invest* 2006;29:581-93.  
54  
55  
56 34. De Onis M, Garza C, Victoria CG, *et al.* The WHO multicentre growth reference study:  
57  
58  
59 planning, study design and methodology. *Food Nutr Bull* 2004;25:15-26.  
60

- 1  
2  
3 35. Cole TJ. The LMS method for constructing normalized growth standards, *Eur J Clin Nutr* 1990;  
4 44:45-60.  
5  
6  
7 36. Cole TJ and Green PJ. Smoothing reference centile curves: the LMS method and penalized  
8 likelihood. *Stat Med* 1992;11:1305-19.  
9  
10 37. Rigby RA, Stasinopoulos DM. Generalized Additive Models for Location Scale and Shape  
11 (GAMLSS) in R, *J Stat Softw.*2007; 23:1-46.  
12  
13 38. Beets L, Rodriguez-Fonseca C, Hennekam RC. Growth charts for individuals with Rubinstein-  
14 Taybi syndrome. *Am J Med Genet A* 2014;164A:2300-9  
15  
16 39. Su X, Lau JT, Yu CM, Chow, et al. Growth charts for Chinese Down syndrome children from  
17 birth to 14 years. *Arch Dis Child* 2014;99:824-9.  
18  
19 40. Larnkaer A, Attrup Schrøder S, Schmidt IM, et al. Secular change in adult stature has come to a  
20 halt in northern Europe and Italy. *Acta Paediatr* 2006;95:754-5.  
21  
22 41. Bonthuis M, van Stralen KJ, Verrina E, Use of National and International Growth Charts for  
23 Studying Height in European Children: Development of Up-To-Date European Height-For-Age  
24 Charts. *PLoS One* 2012;7:e42506.  
25  
26 42. Harman K, Dobra R, Davies JC. Disease-modifying drug therapy in cystic fibrosis. *Paediatr*  
27 *Respir Rev* 2017; Mar 14. pii: S1526-0542(17)30031-3.  
28  
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**Table 1 - Number of patients and assessments:**

a) for each age class, the number of patients with available assessments is reported, separately for male and female;

b), c) and d) for each age class, the number of assessments for weight, height and BMI, respectively, is reported for male and female.

a)		Number of patients		
Variable	Age (years)	F	M	Total
	0-2	36	58	94
	3-4	23	37	60
	5-6	20	27	47
	7-8	18	27	45
b)		Number of assessments		
	Age (years)	F	M	Total
Weight	0-2	91	141	232
	3-4	27	44	71
	5-6	29	41	70
	7-8	17	18	35
	Total	164	244	408
c)		Number of assessments		
	Age (years)	F	M	Total
Height	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377
d)		Number of assessments		
	Age (years)	F	M	Total
Body mass index	0-2	77	128	205
	3-4	27	42	69
	5-6	28	41	69
	7-8	16	18	34
	Total	148	229	377

**Table 2 - Main demographic and clinical characteristics of patients**

Variables	N (%)
Total	106
Gender	
Male	64 (60)
Female	42 (40)
Age at diagnosis (months)	
Median (range)	13.8 months (0-35.6 years)
Gestational age (weeks)	
Median (range)	39 (29-42)
Pancreatic status	
Pancreatic sufficiency	15 (14)
Pancreatic insufficiency	91 (86)
Heart problems	
No	99 (93)
Yes	7 (7)
Bone lesions at diagnosis	
No	59 (56)
Yes	47 (44)
Bone lesions during the first 8 years	
No	74 (70)
Yes	32 (30)
GH *	
No	100 (94)
Yes	6 (6)

\* in 5 cases after the first 8 years of life, in 1 case at 7.5 years

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**Table 3 – Mutations of SDS patients**

Mutations		N	%
258+2T>C	183-184TA>CT	61	57.5
258+2T>C	183-184TA>CT+258+2T>C	16	15.1
258+2T>C	258+2T>C	9	8.5
258+2T>C	c.258+533_459+403del	4	3.8
258+2T>C	101A>T	1	0.9
258+2T>C	107delT	1	0.9
258+2T>C	187G>T	1	0.9
258+2T>C	212C>T	1	0.9
258+2T>C	289-292del	1	0.9
258+2T>C	300delAC	1	0.9
258+2T>C	307-308delCA	1	0.9
258+2T>C	352A>G	1	0.9
258+2T>C	356G>A	1	0.9
258+2T>C	624+1G>C	1	0.9
258+2T>C	92-93GC>AG	1	0.9
258+2T>C	G63C	1	0.9
258+2T>C	IVS1-71del83bp	1	0.9
258+2T>C	R218X	1	0.9
258+2T>C	Y32C	1	0.9
523C>T	523C>T	1	0.9

**Table 4** – 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported for SDS patients from birth to 8 years: the estimates are reported every 3 months from birth to 2 years, every 6 months from 2 to 6 years and once a year from 6 to 8 years.

a) centiles for height

Height										
	Male					Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	41.8	46.2	48.6	51.1	55.5	38.1	44.3	46.8	48.8	51.8
0.25	47.0	51.9	54.7	57.4	62.3	43.0	49.3	52.0	54.3	57.7
0.50	51.7	57.2	60.2	63.1	68.4	47.8	54.2	57.0	59.5	63.4
0.75	55.9	61.8	65.0	68.1	73.7	52.3	58.7	61.8	64.5	68.8
1.00	59.6	65.8	69.2	72.5	78.4	56.5	62.9	66.1	69.0	73.8
1.25	62.8	69.3	72.8	76.3	82.3	60.2	66.6	69.9	73.0	78.2
1.50	65.5	72.3	75.9	79.5	85.7	63.3	69.8	73.2	76.5	81.9
1.75	68.0	74.9	78.7	82.3	88.7	66.0	72.5	76.0	79.3	85.1
2.00	70.1	77.2	81.0	84.8	91.2	68.3	74.8	78.4	81.8	87.8
2.50	73.8	81.2	85.2	89.0	95.6	72.2	78.8	82.4	86.0	92.4
3.00	77.1	84.8	88.8	92.7	99.4	75.8	82.6	86.3	90.0	96.6
3.50	79.7	87.6	91.7	95.6	102.3	79.2	86.2	90.1	93.9	100.6
4.00	82.1	90.1	94.3	98.2	104.9	82.3	89.7	93.7	97.5	104.3
4.50	84.9	93.1	97.3	101.3	108.0	85.1	92.9	97.0	100.9	107.6
5.00	87.9	96.3	100.5	104.6	111.2	87.2	95.7	99.9	103.8	110.2
5.50	90.6	99.2	103.5	107.6	114.2	88.8	98.0	102.3	106.2	112.4
6.00	93.4	102.1	106.5	110.6	117.3	90.5	100.4	104.8	108.7	114.7
7.00	98.3	107.3	111.7	115.8	122.4	95.1	105.6	110.1	114.1	120.1
8.00	103.0	112.2	116.6	120.7	127.3	100.7	110.6	115.1	119.1	125.5

## b) centiles for weight

Weight										
Male						Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	1.5	2.6	2.9	3.3	4.0	1.6	2.3	2.7	3.1	3.7
0.25	2.4	3.8	4.3	4.8	5.8	2.2	3.2	3.7	4.2	5.1
0.50	3.2	4.9	5.5	6.1	7.3	2.9	4.1	4.7	5.4	6.4
0.75	3.9	5.8	6.6	7.3	8.6	3.6	5.0	5.7	6.5	7.7
1.00	4.6	6.6	7.5	8.3	9.7	4.3	5.8	6.7	7.5	9.0
1.25	5.2	7.3	8.3	9.2	10.8	5.0	6.6	7.6	8.5	10.2
1.50	5.8	7.9	9.0	10.0	11.7	5.6	7.3	8.3	9.4	11.2
1.75	6.4	8.5	9.6	10.7	12.6	6.1	8.0	9.0	10.1	12.1
2.00	6.9	9.0	10.2	11.4	13.5	6.6	8.6	9.7	10.8	13.0
2.50	7.8	10.0	11.3	12.6	15.1	7.5	9.5	10.7	12.0	14.4
3.00	8.6	10.9	12.3	13.7	16.5	8.3	10.4	11.6	13.0	15.6
3.50	9.2	11.5	13.0	14.6	17.8	9.0	11.1	12.5	13.9	16.9
4.00	9.8	12.1	13.7	15.4	19.0	9.7	11.9	13.3	14.9	18.1
4.50	10.4	12.8	14.4	16.2	20.3	10.3	12.6	14.1	15.8	19.5
5.00	11.0	13.4	15.1	17.1	21.8	10.9	13.3	14.9	16.7	20.8
5.50	11.6	14.0	15.8	17.9	23.4	11.5	13.9	15.6	17.6	22.1
6.00	12.3	14.7	16.5	18.8	25.2	12.1	14.6	16.4	18.5	23.5
7.00	13.6	16.1	18.1	20.9	30.0	13.4	16.1	18.0	20.5	26.8
8.00	15.5	18.1	20.3	23.6	37.2	15.2	18.0	20.2	23.0	31.2

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3 **e) centiles for body mass index (BMI)**  
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BMI										
	Male					Female				
Age	C3	C25	C50	C75	C97	C3	C25	C50	C75	C97
0.00	9.6	11.9	12.7	13.6	16.0	8.7	11.6	12.5	13.5	18.3
0.25	10.3	12.5	13.4	14.3	16.9	9.8	12.3	13.3	14.2	18.4
0.50	10.9	13.1	14.0	15.0	17.6	10.8	13.1	14.0	14.9	18.7
0.75	11.3	13.6	14.5	15.5	18.3	11.6	13.7	14.6	15.6	19.0
1.00	11.7	14.0	14.9	15.9	18.8	12.3	14.2	15.1	16.1	19.2
1.25	12.0	14.3	15.2	16.2	19.1	12.9	14.6	15.5	16.4	19.4
1.50	12.3	14.4	15.4	16.3	19.4	13.3	14.9	15.8	16.7	19.5
1.75	12.4	14.6	15.5	16.4	19.5	13.6	15.1	15.9	16.8	19.5
2.00	12.6	14.6	15.5	16.5	19.7	13.8	15.2	16.0	16.8	19.4
2.50	12.8	14.7	15.6	16.6	19.9	13.8	15.1	15.8	16.6	19.0
3.00	12.9	14.8	15.6	16.6	20.0	13.6	14.8	15.5	16.3	18.5
3.50	12.9	14.7	15.6	16.5	20.1	13.5	14.6	15.2	16.0	18.3
4.00	12.8	14.6	15.4	16.4	20.2	13.4	14.4	15.1	15.9	18.3
4.50	12.7	14.4	15.3	16.3	20.3	13.4	14.4	15.1	15.9	18.5
5.00	12.6	14.2	15.1	16.1	20.4	13.4	14.4	15.1	16.0	19.0
5.50	12.5	14.0	14.9	16.0	20.5	13.3	14.3	15.0	16.0	19.4
6.00	12.4	14.0	14.8	15.9	20.7	13.1	14.2	14.9	15.9	19.8
7.00	12.4	14.0	14.9	16.1	21.5	13.0	14.0	14.8	15.9	20.5
8.00	12.7	14.2	15.2	16.5	22.4	13.2	14.4	15.2	16.4	21.3

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### Legend

**Figure 1** - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and F) for males and females (SDS patient). Curves for 3<sup>rd</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 97<sup>th</sup> are reported in each graph.

**Figure 2** – Estimated SDS growth charts compared to reference Italian curves. The values of 97<sup>th</sup> and 50<sup>th</sup> centiles for height and weight of SDS patients are located on the 50<sup>th</sup> and 3<sup>rd</sup> centiles of the reference population. The difference is less evident for the body mass index (BMI) centiles.

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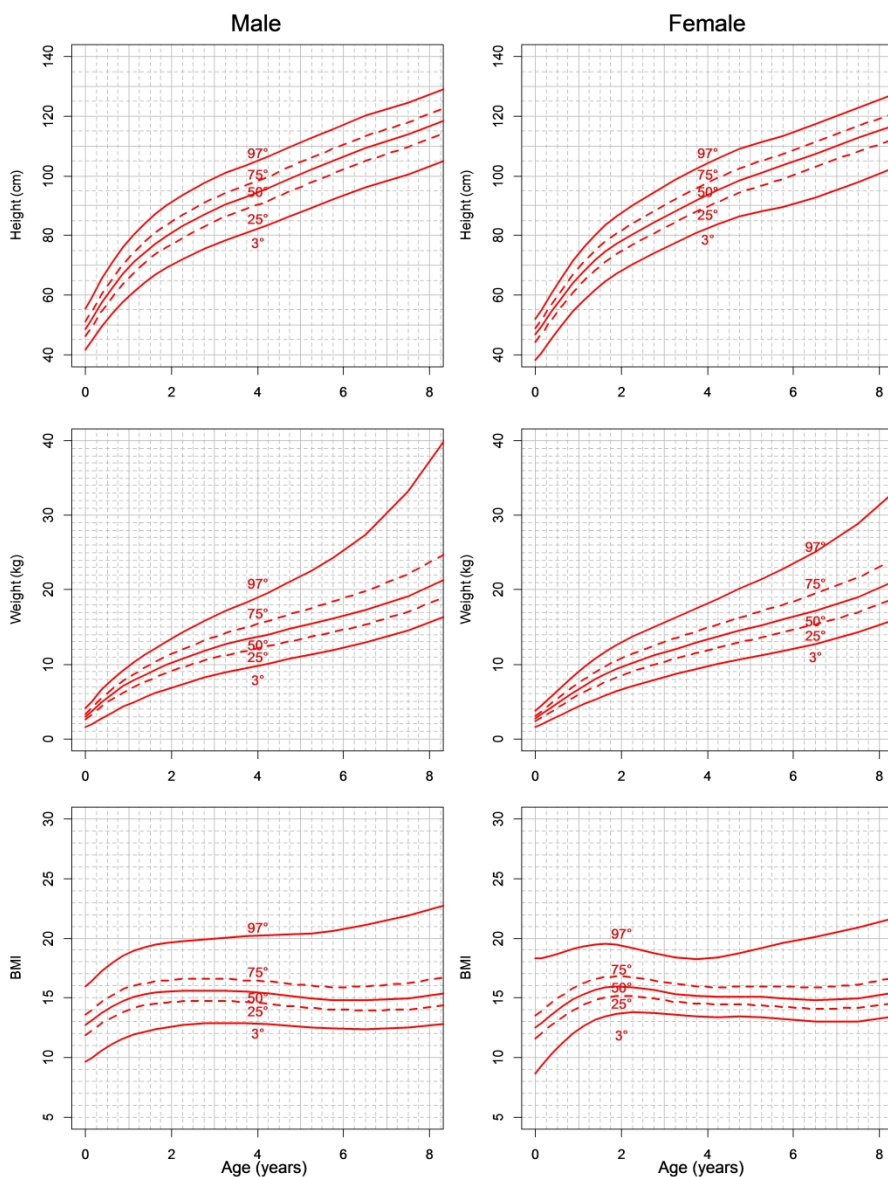


Figure 1 - Growth chart for height (A and B), weight (C and D) and body mass index (BMI) (E and F) for males and females (SDS patient). Curves for 3rd, 25th, 50th, 75th and 97th are reported in each graph.



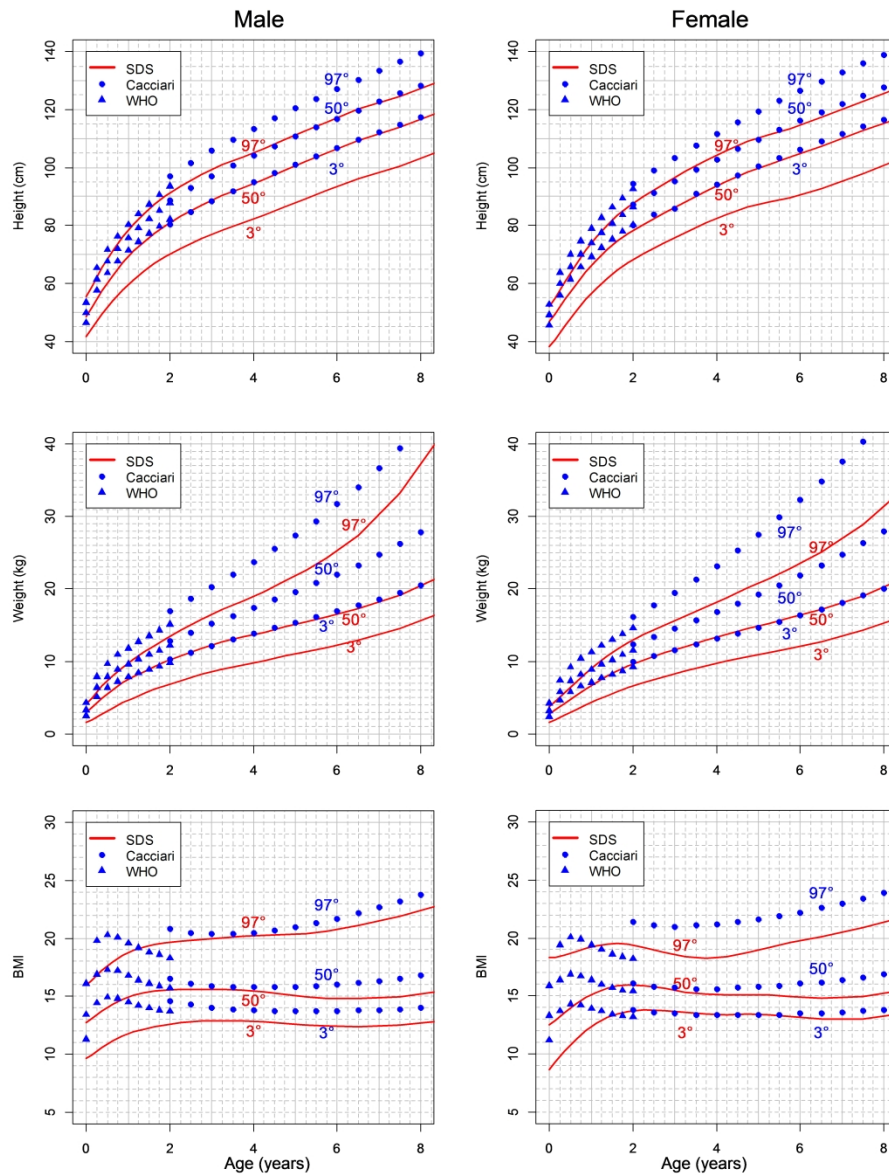


Figure 2 – Estimated SDS growth charts compared to reference Italian curves. The values of 97th and 50th centiles for height and weight of SDS patients are located on the 50th and 3rd centiles of the reference population. The difference is less evident for the body mass index (BMI) centiles.