

Research Article – Basic and Applied Anatomy

Facial soft-tissue volumes in adult Northern Sudanese individuals with Down syndrome

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Abstract

Objective: To investigate dimensions and ratios of soft-tissue facial volumes of adult Northern Sudanese subjects with Down syndrome by using computerized anthropometric measurements. **Design, Setting, and Patients:** The 3D coordinates of soft-tissue facial landmarks were obtained by a computerized digitizer in 26 Northern Sudanese adult subjects with Down syndrome (18 men, 8 women, aged 17-34 years), and in 99 healthy Northern Sudanese controls (48 women, 51 men) of the same age range. From the landmarks, several facial volumes and volume ratios were calculated. Data were compared to those collected in healthy individuals by computing z-scores.

Results: In subjects with Down syndrome, facial volumes were significantly smaller than in control subjects (Student's *t*, $p < 0.05$). The patterns of deviation from the norm were similar in men and women. When compared to controls, subjects with Down syndrome had no differences in nose volume as a fraction of total facial volume and a larger total lip volume as a fraction of total facial volume; within the facial middle third, they had relatively larger upper lip volumes and relatively smaller nose volumes.

Conclusions: The facial soft-tissue structures of subjects with Down syndrome differed from those of normal controls of the same age, sex and ethnic group: a reduced facial size was coupled with specific variations in the nasal and labial regions.

Key words

Anthropometry, Down syndrome, face, soft-tissues, three-dimensional.

Introduction

Down syndrome (DS, Mendelian Inheritance in Man, OMIM #190685: www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) is one of the most common chromosomal causes of intellectual disability, found in 1 in every 691 (Kucik et al., 2013; CDC, 2014) or 733 babies (Zingman, 2013). The genetic cause of the disease, clinically described in 1866 by John Langdon Down, was discovered in 1959 by Jérôme Lejeune (Zingman, 2013). It is caused by a triplicate state (trisomy) of all or a critical portion of chromosome 21.

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In Europe, the prevalence of DS has increased over the last 30 years, largely due to the increasing age of mothers and the increasing genetic analysis of fetal losses, but its live birth prevalence has remained relatively constant, because of the increased use of prenatal screening and subsequent pregnancy terminations (Rankin et al., 2012; Loane et al., 2013).

DS subjects have multiple morphological and functional alterations of their body structures, from cellular organelles to multiorgan systems, with varying degrees of gravity (Roizen and Patterson, 2003; Zingman, 2013). Due to the various congenital anomalies, and to some higher incidence of postnatal diseases, persons with DS had a mortality 5–11 times higher than the general population (Zhu et al., 2013). Surgery (especially correction of congenital heart defects) and medical treatment of DS subjects had modified their life expectancy, and more recent birth cohorts have lower mortality rates than older ones (Rankin et al., 2012). In the USA, recent investigations found survival probability rates of 98% at 1 month of age, 93% at 1 year, 91% at 5 years, 88.9% at 15 years, 88% at 20 years, and 87.5% at 25 years of age (Kucik et al., 2013; Zingman, 2013).

In Italy, approximately 10,500 subjects with DS are aged 0–14 years, 32,000 are between 15 and 44 years, and 5,000 are older than 44 years; most Italian persons with DS are expected to live until 45–46 years, with a 13% survival rate between 45 and 65 years of age (Arosio et al., 2004).

Subjects with DS show several alterations of their body growth and development. In the head and face, almost all structures are altered, and the general dimensions are reduced (Sforza et al., 2012a). Among the others, nasal hypoplasia and slowed or absent ossification of nasal bones are observed already during intrauterine life and are used for ultrasound-based prenatal screening (Sonek, 2003; Tuxen et al., 2003; Persico et al., 2012). Prenatal underdevelopment of the nose is coupled with a general hypoplasia of the facial middle third (Borenstein et al., 2008) and is a typical postnatal marker of persons with DS (Farkas et al., 2001a, b, 2002a, b; Quintanilla et al., 2002; Bagic and Verzak, 2003; Roizen and Patterson, 2003; Ferrario et al., 2004; Sforza et al., 2004, 2011b; Asha et al., 2011).

To better appreciate the modifications in facial dimensions, Sforza et al. (2004, 2012a) estimated some soft-tissue facial volumes in a group of Italian adolescent and adult subjects with DS. When compared to data collected in reference subjects of the same sex, age and ethnic group, both sexes had a general reduction of the volumes of all facial thirds (forehead, maxilla, and mandible). The maxillary region was particularly reduced.

DS can be found in babies from ethnical groups all around the world; a recent report found that mortality risk in subjects with DS is partially influenced by ethnicity, with lower survival rates of non-Hispanic black children compared with non-Hispanic white children living in the same area (Kucik et al., 2013). Some kind of heterogeneity in the expressions of DS alterations in the various ethnic groups may contribute to explain this finding. Indeed, facial characteristics in DS subjects seem to be nearly the same all over the world, but detailed quantitative analyses of the ethnic groups are only partial, with data available only for the United States (Farkas et al., 2001a, b, 2002a, b), Spain (Quintanilla et al., 2002), Croatia (Bagic and Verzak, 2003), Italy (Ferrario et al., 2004; Sforza et al., 2004, 2012a, b), Southern India (Asha et al., 2011) and Northern Sudan (Sforza et al., 2011a, b, 2012b).

We have analyzed a group of Northern Sudanese subjects with DS and compared their facial dimensions with those measured in reference subjects of the same age, sex and ethnicity (Sforza et al., 2011a, b, 2012b). Sudan is one of the largest African countries, hosting a multiethnic population: official estimates declare a population of approximately 33 million people at the beginning of 2011, with an annual growth rate of 2.53 (Republic of Sudan, 2014). About 70% of the Sudanese population is of Arab descent and live in the North of the country.

In a previous investigation on Northern Sudanese subjects with DS, only total labial and soft-tissue nasal volumes were assessed, finding a general reduction in their absolute dimensions (Sforza et al., 2011b). No detailed assessment of the other facial volumes was made; additionally, the proportions among the various facial volumes were not considered.

Therefore, the aim of the current study was to estimate soft-tissue facial volumes in Northern Sudanese persons with DS using computerized anthropometry, and to compare their absolute and relative values with those collected in normal reference individuals. Only adult subjects were investigated to avoid growth-related variations.

Materials and methods

Subjects

Twenty-six Northern Sudanese adult subjects with DS (18 men, 8 women, aged 17-34 years) were included in the present study. They attended special needs schools in Khartoum (Sudan); details about these subjects were previously published (Sforza et al., 2011a, b, 2012b). None of the subjects had undergone craniofacial surgery.

Ninety-nine (48 men, 51 women) control subjects of the same age and ethnicity were recruited from subjects and staff attending universities in Khartoum State. All subjects had no previous history of craniofacial trauma, surgery or congenital anomalies (Sforza et al., 2011a, b, 2012b; 2013b; 2014c).

All the analyzed individuals, and the parents/ legal guardians of the DS subjects gave their written informed consent to the study after a detailed explanation of all procedures, that were not invasive, did not provoke any damage, risk or discomfort to the subjects, were performed according to the tenets of the Declaration of Helsinki and had been approved by the local ethic committee.

Collection of 3D facial landmarks

The face of subjects with DS and of controls was scanned using a computerized, portable hand-held laser scanner (FastSCAN Cobra; Polhemus Inc, Colchester VT), and three-dimensional models of their faces were obtained. The instrument couples a laser scan that is swept over the faces without physical contact, and an electromagnetic motion tracking system that records the position of the camera. The reflected laser light gives cross-sectional depth profiles, which are reconstructed in their three-dimensional position in real time using the motion data (Sforza et al., 2013a).

The instrument has a precision of about 0.5 mm, and it takes 20-30 s to scan a face from ear to ear, from trichion to menton. During scanning, the subjects were asked to

close their eyes to avoid possible retinal damages. Subsequently, anthropometric calculations were performed off-line: a set of 50 soft-tissue landmarks (head, face, orbits, nose, lips and mouth, ears) were identified on the digital facial reconstruction and their x, y, z coordinates were obtained and recorded for further calculations (Sforza et al., 2013a). Repeated assessments were used to estimate system reproducibility; facial digitization and landmark identification had a mean measure error of 0.755 mm, without statistically significant systematic errors (Sforza et al., 2011b).

The following 21 landmarks were specifically used in the current analysis: midline landmarks: tr, trichion; n, nasion; prn, pronasale; sn, subnasale; ls, labiale superius; sto, stomion; li, labiale inferius; sl, sublabiale; pg, pogonion; paired landmarks (right and left side noted r and l): exr, exl, exocanthion; ftr, ftl: frontotemporale; tr, tl, tragion; acr, acl, nasal alar crest; chr, chl, cheilion; gor, gol, gonion (Fig. 1).

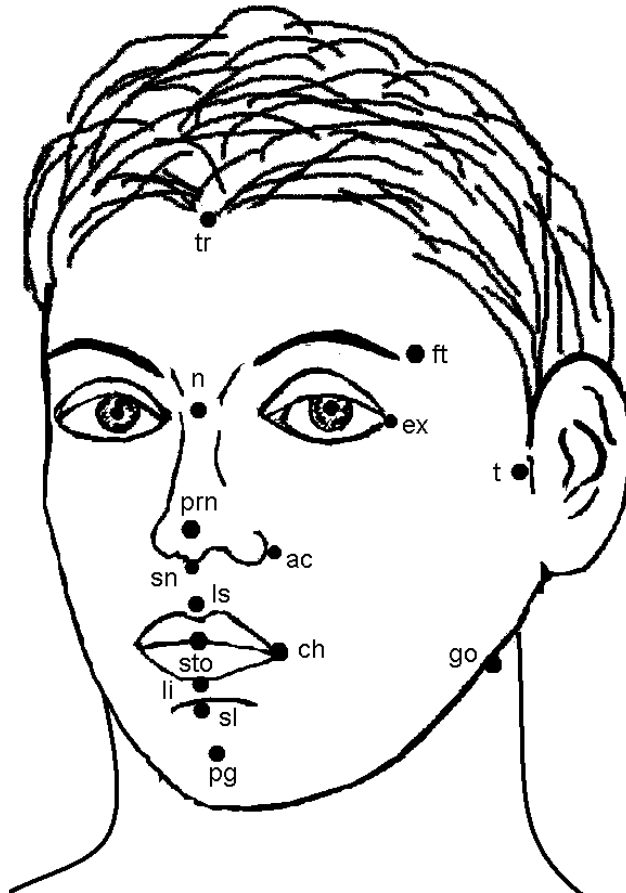


Figure 1 – Soft-tissue facial landmarks digitized on all subjects. Midline landmarks: tr, trichion; n, nasion; prn, pronasale; sn, subnasale; ls, labiale superius; sto, stomion; li, labiale inferius; sl, sublabiale; pg, pogonion. Paired landmarks: ex, exocanthion; ft, frontotemporale; t, tragion; ac, nasal alar crest; ch, cheilion; go, gonion.

Data analysis

The three-dimensional coordinates of the landmarks were used to estimate facial volumes, as previously detailed (Ferrario et al., 1995, 1998). In brief, the volumes (in cm^3) of facial structures were computed as the sum of several tetrahedra, with the selected landmarks serving as nodes (vertices of the tetrahedra).

In particular, we estimated:

- Total facial volume: volumes of all facial structures from the external cutaneous surface up to a quasi-frontal plane passing through trichion, tragi and gonias;
- Facial upper third volume (forehead), measured between the plane passing through the trichion, the frontotemporale landmarks, and the tragi, and a quasi-horizontal plane passing through the tragi and the exocanthia;
- Facial middle third volume (maxilla): comprised between a quasi-horizontal plane passing through the tragi and the exocanthia, and a plane connecting the cheilion landmarks and the tragi, approximately corresponding to the maxillary and cheek regions;
- Facial lower third volume (mandible): comprised between the cheilion-tragi plane and a plane drawn between pogonion and the gonias, approximately corresponding to the mandibular region;
- Nasal volume: approximated from the volumes of two tetrahedra: the first tetrahedron had the plane ac_v, ac_l, prn as its base and vertex in n , the second had the same base and vertex in sn ;
- Lip volume: upper lip volume (approximated from the volumes of two tetrahedra: the first one had the plane ch_v, ch_l, ls as its base and vertex in sn , the second one had the plane ch_v, ch_l, ls as its base and vertex in sto); lower lip volume (as above, first tetrahedron with the plane ch_v, ch_l, li as its base and vertex in sl , the second one with the plane ch_v, ch_l, li as its base and vertex in sto); total lip volume (sum of the four tetrahedra).

To better assess the differential variations in facial volumes in DS subjects, total lip and nose volumes were expressed as a fraction ($\%$) of total facial volume. Furthermore, upper, lower lip and nose volumes were summed, and their relative proportions analyzed.

Statistical calculations

In both groups (control subjects and DS subjects), descriptive statistics were calculated for each facial volume and volume ratio separately for men and women.

Subsequently, the individual volume measurements obtained in the subjects with DS were transformed to z-scores by subtracting from each value its sex-related reference mean value, and dividing by the relevant reference standard deviation (Sforza et al., 2012a, b; Claes et al., 2013). Mean and standard deviations were computed for the z-scores separately for men and women.

For the variables of interest (absolute volumes, volume ratios and z-scores), several kinds of statistical comparisons were made:

- absolute volumes: unpaired Student's t test was used to compare mean values between men and women within the two groups (control subjects and DS subjects; null hypothesis, the mean male and female values do not differ);

- volume ratios: two-way analyses of variance was used to compare mean values between men and women, and between control and DS subjects; the sex \times group interaction was also computed (null hypothesis, the mean male and female values do not differ, the mean control and DS subjects values do not differ, and there is no interaction between sex and group);
- z-scores: Student's t test was used to test the significance of the z-scores (null hypothesis, the z-scores are equal to 0, that is there is no difference between the mean values of control subjects and DS subjects); unpaired Student's t test was used to test the difference between DS men and women (null hypothesis, the mean male and female z-scores do not differ, that is both sexes have the same kind of difference from the control subjects).

For a global comparison of the facial characteristics of DS men and women, a correlation analysis between the homologous z-scores of the two sexes was run: high correlation coefficients indicate very similar patterns of deviation from the norm (Garn et al., 1984).

For all analyses, the level of significance was set at 5% ($p < 0.05$) and values below this limit were noted and reported in the results and table; tests were performed with two-tails.

Results

Table 1 reports the descriptive statistics of the facial volume estimates in subjects with DS and controls. In both groups, men had larger faces than women, with significant differences for all values in the reference population ($p < 0.001$) and for total facial, maxillary and mandibular volume in DS subjects ($p < 0.01$). The faces of subjects with DS were smaller than the faces of reference subjects, and all mean z-scores were negative (Fig. 2). For DS subjects all z-scores were significantly different from zero ($p < 0.01$), except nose and all lip volumes in women and upper lip volume in men, and the patterns of deviation from the norm were similar in men and women (correlation between the paired z-scores of the two sexes, $r = 0.931$), without significant differences in the mean values of the z-scores.

Overall, male nose volumes were larger than female ones. In DS subjects, nose volume was 4% of total facial volume, a fraction very similar to that found in the reference population (Fig. 3). The two-way analysis of variance found no significant effect of group, a significant effect of sex ($p = 0.02$) and no significant sex \times group interaction.

Total lip volume as a fraction of total facial volume was significantly larger in DS subjects than in controls ($p = 0.002$), without sex-related differences or interactions.

The reciprocal distribution of nasal and labial volumes differed between DS subjects and controls, with relatively larger volumes ($p = 0.001$) for the upper lip in DS subjects (approx 44% of a total lip plus nose volume) than in controls (approx 39%, Fig. 4). In contrast, the percentage volume of the nose was larger in the controls (33%) than in DS subjects (29%; $p = 0.016$). No significant differences were found for the lower lip relative volume. Additionally, for all relative volumes no significant differences between sexes were found.

Table 1. Facial volumes in Northern Sudanese adult subjects with Down syndrome as compared with control subjects matched for sex, age and ethnicity (in cm³).

| | | | Total | Fore-head | Max-illa | Man-dible | Total lip | Upper lip | Lower lip | Nose |
|-----------|------------------|-------|--------|-----------|----------|-----------|-----------|-----------|-----------|------|
| Men | DS (n = 18) | mean | 532.36 | 218.66 | 118.23 | 193.46 | 5.21 | 3.16 | 2.06 | 2.01 |
| | | SD | 72.57 | 37.15 | 19.27 | 30.61 | 1.34 | 0.94 | 0.65 | 0.64 |
| | Control (n = 51) | mean | 753.74 | 284.95 | 163.89 | 301.38 | 6.32 | 3.60 | 2.71 | 3.52 |
| | | SD | 81.14 | 39.80 | 27.82 | 45.95 | 1.79 | 1.16 | 0.83 | 1.33 |
| Women | DS (n = 8) | mean | 427.48 | 188.34 | 94.40 | 143.04 | 4.29 | 2.73 | 1.56 | 1.70 |
| | | SD | 41.60 | 40.05 | 13.26 | 16.96 | 1.38 | 0.88 | 0.75 | 0.63 |
| | Control (n = 48) | mean | 586.56 | 225.13 | 127.05 | 232.18 | 4.81 | 2.82 | 1.99 | 2.19 |
| | | SD | 71.91 | 38.50 | 17.75 | 38.66 | 1.04 | 0.67 | 0.54 | 0.75 |
| M vs W DS | p | 0.001 | NS | 0.004 | <0.001 | NS | NS | NS | NS | |
| | Control | p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | |

M vs W: men vs women comparisons performed separately for DS and control subjects; p value of Student's t test for independent samples; NS: not significant (p > 0.05).

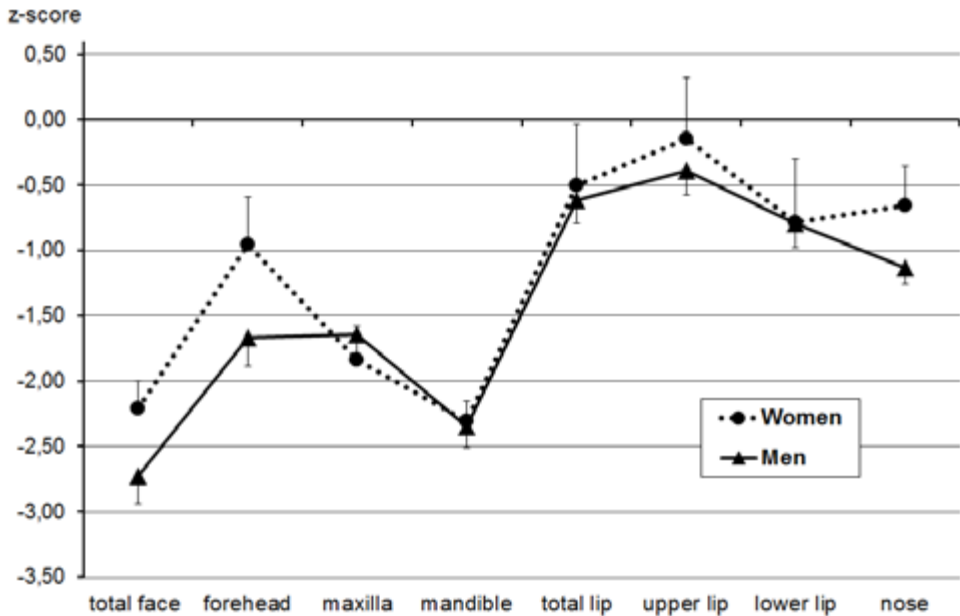


Figure 2 – Mean z-scores computed in Northern Sudanese adult subjects with DS as compared with control subjects of the same sex, age and ethnicity. Error bars: standard error. All values are significantly different from zero except nose and all lip volumes in women and upper lip volume in men.

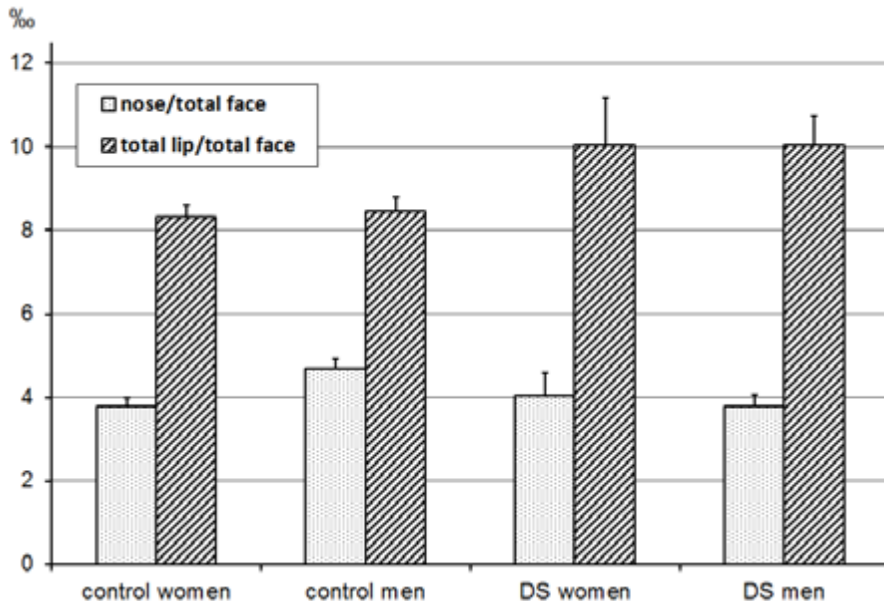


Figure 3 – Lip and nose volumes as a fraction (%) of total facial volume in Northern Sudanese adult subjects with DS and in the reference population. Error bars: standard error.

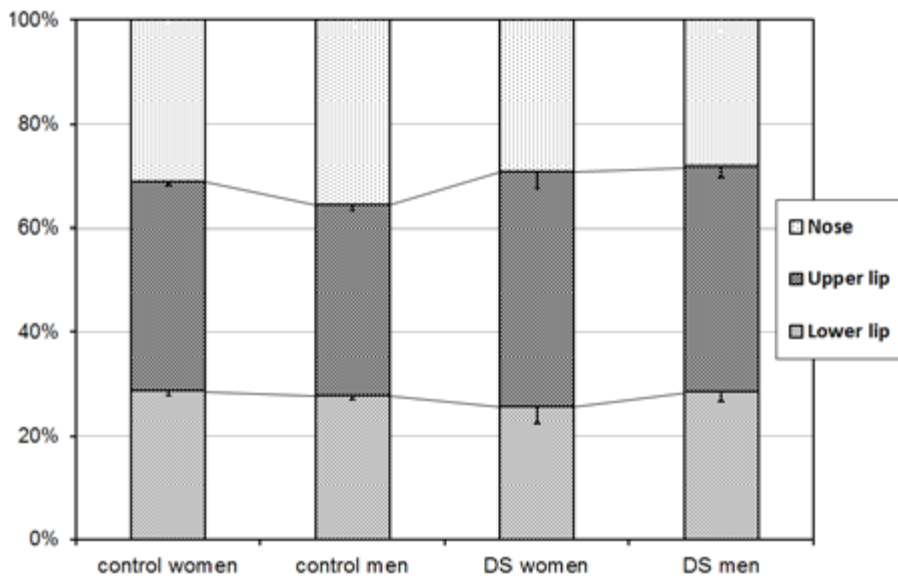


Figure 4 – Volumetric distribution of upper and lower lip and nose in Northern Sudanese adult subjects with DS and in the reference population. All values are percentage of the total "lip plus nose" volume. Error bars: standard error.

Discussion

Anthropometry allows the three-dimensional assessment of biological characteristics without submitting the subjects to potentially dangerous procedures (Farkas et al., 2005; Aldridge et al., 2011; Claes et al., 2013; Sforza et al., 2013a). In particular, anthropometric studies of facial measurements can be used both for normal persons, permitting to differentiate the various ethnic groups (Garn et al., 1984; Farkas et al., 2001a, b, 2002a, b; Quintanilla et al., 2002; Farkas et al., 2005; Sforza et al., 2012b, 2013b; 2014c; Dharap et al., 2013), and for subjects with several alterations of the head and face (Bagic and Verzak, 2003; Ferrario et al., 2004; Sforza et al., 2004, 2011a, b, 2012a; Aldridge et al., 2011; Asha et al., 2011; Claes et al., 2013). Currently, three-dimensional computerized analyses of facial anthropometry are believed more advantageous than conventional methods for the quantitative description of syndrome phenotypes (Aldridge et al., 2011; Claes et al., 2013; Sforza et al., 2013a).

In the current study, we analyzed the overall facial size of Northern Sudanese adult subjects with DS relative to normal subjects of the same age, sex and ethnic group. The face was divided into its superior, middle and inferior thirds (Aldridge et al., 2011) and their volumes were estimated (Ferrario et al., 1995, 1998). Additionally, a detailed assessment of soft-tissue nasal and labial volumes was made (Sforza et al., 2012a). To avoid growth-related variations, only adult subjects were investigated.

Overall, we found that subjects with DS had smaller facial volumes than control subjects; in both sexes, the reduction was particularly evident in the lower facial third (mandible), which was over two standard deviations. The middle facial third (maxilla) was reduced in both sexes (on average, 1.64 SD in men, and 1.84 SD in women), while the reduction in the upper facial third (forehead) was somewhat more evident in men than in women. The general reduction in facial size is in good accord with literature data (Farkas et al., 2001a, b, 2002a, b; Quintanilla et al., 2002; Bagic and Verzak, 2003; Roizen and Patterson, 2003; Tuxen et al., 2003; Ferrario et al., 2004; Sforza et al., 2004, 2011a, b, 2012a, 2013a; Asha et al., 2011; Persico et al., 2012), but only Sforza et al. (2004, 2012a) reported data on soft-tissue facial volumes in adolescent and adult subjects with DS. In general, their patterns (Italian subjects) were similar to the current ones, but Northern Sudanese subjects had larger reductions in the total and mandibular facial volumes, and smaller decreases in the maxillary area. Indeed, in women the reduction in labial and nasal volumes was not significant.

A similar finding, with lower discrepancies in the labionasal structures in Northern Sudanese DS subjects as compared with Italian DS subjects, had already been reported for a larger group of children, adolescents and adults (Sforza et al., 2011b). In comparison with the current data, the larger Northern Sudanese group had less differences in nose volume and larger discrepancies in labial volumes. The different composition in age may explain the differences between the previous results (Sforza et al., 2011b) and the present ones, considering that significant effects of age on the discrepancy of syndromic subjects vs. control subjects have already been found in Northern Sudanese DS subjects (Sforza et al., 2012b).

When nose and lip volumes were expressed as percentages of total facial volume, no significant differences between DS and control subjects (nose), or even an increment in DS subjects (lips) were observed, showing that, notwithstanding the general hypoplasia of the facial middle third in DS subjects (Borenstein et al., 2008; Asha et

al., 2011), they seem to maintain relative normal dimensions for the structures of their respiratory and digestive systems (Roizen and Patterson, 2003). A similar finding had been previously reported for Italian DS subjects, where different findings were found for the upper and lower lips: the first was slightly increased in males and unchanged in females, the second was significantly decreased in both sexes, especially in females (Sforza et al., 2004, 2012a). This relatively normal upper lip was in contrast with previous anthropometric investigations performed on Northern American DS subjects that reported a reduction in the linear dimensions of the upper lip (Farkas et al., 2001b). Sforza et al. (2012a) explained their findings with the good anterior dental support of their DS subjects (Dellavia et al., 2009), who lived in the community with their families and were all athletes attending the Special Olympics games.

Considering the ethnic-related variations in facial proportions (Farkas et al., 2005; Dharap et al., 2013), we assessed the reciprocal volumetric distribution of nasal and labial volumes (Sforza et al., 2012a), finding that normal Northern Sudanese subjects had relatively smaller noses than Italian subjects (Sudan: 33% of the global nose plus lip volume; Italy: 50%), but larger upper lips (Sudan: 39%; Italy: 28%). DS subjects partly diverged from the proportions found in normal subjects, with relatively larger upper lips but smaller noses. This pattern is similar to that reported for Italian DS subjects (Sforza et al., 2012a) and agrees with midfacial hypoplasia coupled with good dental support (Dellavia et al., 2009).

In absolute terms, all the volumes estimated in the current study were larger in men than in women; additionally, noses were relatively larger in men than in women. In contrast, no significant sex-related differences were observed in the discrepancies relative to the control subjects. Previous studies found comparable data, without sex-specific variations from the norm both for Northern Sudanese (Sforza et al., 2011a, b, 2012b) and White Caucasian subjects with DS (Bagic and Verzak, 2003; Ferrario et al., 2004; Sforza et al., 2004, 2012b). Farkas et al. (2001a, b; 2002a, b), in their extensive assessment of DS persons, reported only pooled male and female values.

Among the limitations of the current study there is the reduced number of subjects with DS analysed, especially women. Indeed, to avoid age-related variations as possible causes of discrepancy between DS and control subjects we analyzed only adult subjects, a subsample (women, 44%; men, 56%) of the original group (Sforza et al., 2011a, b, 2012b). The increased life expectancy of DS subjects (Kucik et al., 2013; Zingman, 2013) makes it necessary to focus on the facial alterations of adult subjects with DS, who probably have different health problems than children and adolescents.

Additionally, all the analyzed Northern Sudanese subjects with DS were attending schools for people with special needs and were not involved in any specific sport or physical activity program (Sforza et al., 2012b). At the moment, the effects of different life styles on the craniofacial characteristics of subjects with DS are unknown. Nonetheless, in Western Countries an increasing number of subjects with DS live in the community (Roizen and Patterson, 2003; Arosio et al., 2004) and the quantitative evaluation of their facial morphology may be of help also to clinicians.

In conclusion, Northern Sudanese persons with DS had a general reduction in their soft-tissue facial volumes relative to normal controls of the same age, sex and ethnic group, with specific variations in the nasal and labial regions.

Additional studies are necessary to better define the specific craniofacial patterns of subjects with DS from the various part of the world, with the aim to offer better

patient care along all the life span (Arosio et al., 2004; Kucik et al., 2013). The investigations may also provide some hypotheses to explain the ethnic-related differences in mortality risk of DS subjects (Kucik et al., 2013). Sudan is located somehow midway between Africa and the Arab World, a unique position that may help genetic studies.

References

- Aldridge K., George I.D., Cole K.K., Austin J.R., Takahashi T.N., Duan Y., Miles J.H. (2011) Facial phenotypes in subgroups of prepubertal boys with autism spectrum disorders are correlated with clinical phenotypes. *Mol. Autism*. 2: 15.
- Arosio P., Abbate C., Zanetti M., Caputo L. (2004) Down syndrome. Some socioenvironmental aspects. *G. Gerontol.* 52: 136-139.
- Asha K.R., Lakshmi Prabha S., Nanjaiah C.M., Prashanth S.N. (2011) Craniofacial anthropometric analysis in Down syndrome. *Indian J. Pediatr.* 78: 1091-1095.
- Bagic I., Verzak Z. (2003) Craniofacial anthropometric analysis in Down's syndrome patients. *Coll. Antropol.* 27: 23-30.
- Borenstein M., Persico N., Kagan K.O., Gazzoni A., Nicolaidis K.H. (2008) Frontomaxillary facial angle in screening for trisomy 21 at 11 + 0 to 13 + 6 weeks. *Ultrasound Obstet. Gynecol.* 32: 5-11.
- CDC, Centers for Disease Control and Prevention. (2003) Birth defects. Facts about Down syndrome. On line at: <http://www.cdc.gov/ncbddd/birthdefects/down-syndrome.html>, accessed February 6, 2014.
- Claes P., Walters M., Gillett D., Vandermeulen D., Clement J.G., Suetens P. (2013) The normal-equivalent: a patient-specific assessment of facial harmony. *Int. J. Oral Maxillofac. Surg.* 42: 1150-1158.
- Dharap A., Salem A.H., Fadel R., Osman M., Chakravarty M., Latif N.A., Abu-Hijleh M. (2013) Facial anthropometry in an Arab population. *Bahrain Med. Bull.* 35: 69-73.
- Dellavia C., Allievi C., Pallavera A., Rosati R., Sforza C. (2009) Oral health conditions in Italian Special Olympics athletes. *Spec. Care Dentist.* 29: 69-74.
- Farkas L.G., Katic M.J., Forrest C.R., Litsas L. (2001a) Surface anatomy of the face in Down's syndrome: linear and angular measurements in the craniofacial regions. *J. Craniofac. Surg.* 12: 373-379.
- Farkas L.G., Katic M.J., Forrest C.R. (2001b) Surface anatomy of the face in Down's syndrome: anthropometric proportion indices in the craniofacial regions. *J. Craniofac. Surg.* 12: 519-526.
- Farkas L.G., Katic M.J., Forrest C.R. (2002a) Age-related changes in anthropometric measurements in the craniofacial regions and in height in Down's syndrome. *J. Craniofac. Surg.* 13: 614-622.
- Farkas L.G., Katic M.J., Forrest C.R. (2002b) Surface anatomy of the face in Down's syndrome: age-related changes of anthropometric proportion indices in the craniofacial regions. *J. Craniofac. Surg.* 13: 368-374.
- Farkas L.G., Katic M.J., Forrest C.R., Alt K.W., Bagic I., Baltadjiev G., Cunha E., Cvceľová M., Davies S., Erasmus I., Gillett-Netting R., Hajnis K., Kemkes-Grottenthaler A., Khomyakova I., Kumi A., Kgamphe J.S., Kayo-daigo N., Le T., Malinowski A., Negasheva M., Manolis S., Ogetürk M., Parvizrad R., Rösing F., Sahu P.,

- Sforza C., Sivkov S., Sultanova N., Tomazo-Ravnik T., Tóth G., Uzun A., Yahia E. (2005) International anthropometric study of facial morphology in various ethnic groups/races. *J. Craniofac. Surg.* 16: 615-646.
- Ferrario V.F., Sforza C., Serrao G., Miani A. Jr. (1995) A computerized non-invasive method for the assessment of human facial volume. *J. Craniomaxillofac. Surg.* 23: 280-286.
- Ferrario V.F., Sforza C., Poggio C.E., Schmitz J.H. (1998) Facial volume changes during normal human growth and development. *Anat. Rec.* 250: 480-487.
- Ferrario V.F., Dellavia C., Colombo A., Sforza C. (2004) Three-dimensional assessment of nose and lip morphology in subjects with Down syndrome. *Ann. Plast. Surg.* 53: 577-583.
- Garn S.M., Smith B.H., Lavelle M. (1984) Applications of pattern profile analysis to malformations of the head and face. *Radiology* 150: 683-690.
- Kucik J.E., Shin M., Siffel C., Marengo L., Correa A. (2013) Congenital anomaly multi-state prevalence and survival collaborative. Trends in survival among children with Down syndrome in 10 regions of the United States. *Pediatrics* 131: e27-e36.
- Loane M., Morris J.K., Addor M.C., Arriola L., Budd J., Doray B., Garne E., Gatt M., Haeusler M., Khoshnood B., Klungsoyr Melve K., Latos-Bielenska A., McDonnell B., Mullaney C., O'Mahony M., Queisser-Wahrendorf A., Rankin J., Rissmann A., Rounding C., Salvador J., Tucker D., Wellesley D., Yevtushok L., Dolk H. (2013) Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. *Eur. J. Hum. Genet.* 21: 27-33.
- Persico N., Molina F., Azumendi G., Fedele L., Nicolaides K.H. (2012) Nasal bone assessment in fetuses with trisomy 21 at 16-24 weeks of gestation by three-dimensional ultrasound. *Prenat. Diagn.* 32: 240-244.
- Quintanilla J.S., Biedma B.M., Rodriguez M.Q., Mora M.T., Cunqueiro M.M., Pazos M.A. (2002) Cephalometrics in children with Down's syndrome. *Pediatr. Radiol.* 32: 635-643.
- Rankin J., Tennant P.W., Bythell M., Pearce M.S. (2012) Predictors of survival in children born with Down syndrome: a registry-based study. *Pediatrics* 129: e1373-e1381.
- Republic of Sudan, Ministry of the Cabinet Affairs. On line at: <http://www.sudan.gov.sd/index.php/en/pages/details/57/About%20Sudan>, accessed April 26, 2014.
- Roizen N.J., Patterson D. (2003) Down's syndrome. *Lancet* 361: 1281-1289.
- Sforza C., Dellavia C., Zanotti G., Tartaglia G.M., Ferrario V.F. (2004) Soft tissue facial areas and volumes in subjects with Down syndrome. *Am. J. Med. Genet. A.* 130A: 234-239.
- Sforza C., Elamin F., Rosati R., Lucchini M.A., De Menezes M., Ferrario V.F. (2011a) Morphometry of the ear in north Sudanese subjects with Down syndrome: a three-dimensional computerized assessment. *J. Craniofac. Surg.* 22: 297-301.
- Sforza C., Elamin F., Rosati R., Lucchini M.A., Tommasi D.G., Ferrario V.F. (2011b) Three-dimensional assessment of nose and lip morphology in North Sudanese subjects with Down syndrome. *Angle Orthod.* 81: 107-114.
- Sforza C., Dellavia C., Allievi C., Tommasi D.G., Ferrario V.F. (2012a) Anthropometric indices of facial features in Down's syndrome subjects. In: V.R. Preedy. *Handbook*

- of Anthropometry: Physical Measures of Human Form in Health and Disease. Springer Science+Business Media, LLC, Berlin. Pp. 1603-1618.
- Sforza C., Elamin F., Dellavia C., Rosati R., Lodetti G., Mapelli A., Ferrario V.F. (2012b) Morphometry of the orbital region soft tissues in Down syndrome. *J. Craniofac. Surg* 23: 198-202.
- Sforza C., De Menezes M., Ferrario V.F. (2013a) Soft- and hard-tissue facial anthropometry in three dimensions: what's new. *J. Anthropol. Sci.* 91: 159-184.
- Sforza C., Elamin F., Tommasi D.G., Dolci C., Ferrario V.F. (2013b) Morphometry of the soft tissues of the orbital region in Northern Sudanese persons. *Forensic Sci. Int.* 228: 180.e1-180.e11.
- Sforza C., Dolci C., Tommasi D.G., Pisoni L., De Menezes M., Elamin F. (2014c) Three-dimensional facial distances of Northern Sudanese persons from childhood to young adulthood. *J. Cranio-Maxillo-Fac. Surg.* 42: e318-e326. (doi: 10.1016/j.jcms.2013.10.013).
- Sonek J.D. (2003) Nasal bone evaluation with ultrasonography: a marker for fetal aneuploidy. *Ultrasound Obstet. Gynecol.* 22: 11-15.
- Tuxen A., Keeling J.W., Reintoft I., Fischer Hansen B., Nolting D., Kjaer I. (2001) A histological and radiological investigation of the nasal bone in fetuses with Down syndrome. *Ultrasound Obstet. Gynecol.* 22: 22-26.
- Zhu J.L., Hasle H., Correa A., Schendel D., Friedman J.M., Olsen J., Rasmussen S.A. (2013) Survival among people with Down syndrome: a nationwide population-based study in Denmark. *Genet. Med.* 15: 64-69.
- Zigman W.B. (2013) Atypical aging in down syndrome. *Dev. Disabil. Res. Rev.* 18: 51-67.