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Medical conditions of children and young people with Down syndrome

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Abstract

Background The life expectancy of people with Down syndrome (DS) has significantly increased in the last decades. We describe the congenital malformations and main comorbidities of a cohort of children and young people with DS and analyse their differences according to age and gender groups.
Methods This retrospective cross-sectional study was conducted at DS centre of Bambino Gesù Children's Hospital in Rome (Italy). The period for reviewing all electronic health records ran from July 2016 to September 2017. We collected data on clinical conditions and compared them with the general paediatric population. Moreover, we compared the main comorbidities, dental diseases and body mass index data between age groups.
Results Seven hundred sixty-three children and young people with DS included in this study were aged 7.45 ± 5.49 years. Gender distribution included 58.19% male patients. The majority of our population (71.04%) came from central regions of Italy. Respiratory diseases (19%), congenital heart defects (72.23%), malocclusions (58.62%), astigmatism (20.31%), farsightedness (16.51%), near-sightedness (12.19%) and autoimmune hypothyroidism (3.28%) were more frequent in our population compared with the typical paediatric population. Upper respiratory tract infections and underweight were significantly more frequent in the youngest children, whereas dental diseases, refractive errors, obesity and autoimmune hypothyroidism increased over age.
Conclusions Children and young people with DS present a high prevalence of potentially treatable medical conditions making multidisciplinary teams a mandatory need for this population.

Keywords Down syndrome, intellectual disability, learning disability, communication

Introduction

In Italy, Down syndrome (DS) prevalence is estimated to be approximately 48 000 people. They are classified in the following age groups: 10 500 of 0–14 years, 32 000 between 15 and 44 years and 5000 over 44 years (Mastroiacovo *et al.* 2002). Cocchi *et al.* (2010), recently, reported that over a 12-year

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period (1993–2004), the total mean prevalence of DS births has remained stable at 8.3/10 000 births, whereas, in Italy, DS births are decreased due to a great increase of pregnancy termination.

In recent decades, improved medical care in people with DS has led to a significant increase in lifespan and quality of life (de Graaf *et al.* 2017). These factors include improvement in cardiac surgery, prevention of childhood infections and a better global psychosocial support.

Children with DS have varied degrees of intellectual disability and more health complications than other children. Common medical problems include hearing problems (75%) and vision impairments (60%), obstructive sleep apnoea (OSA) (50–75%), congenital heart diseases (CHDs) (40–50%) and other congenital anomalies (4–10%), hypodontia and delayed dental eruption (23%), thyroid diseases (4–18%), seizure (1–13%), celiac disease (5%), diabetes mellitus (1%), dermatologic conditions (1.9–39.2%), orthopaedic disorders (10–30%), leukaemia (1%) and behaviour problems (18–38%) (Schieve *et al.* 2009; Weijerman and De Winter 2010; Bull *et al.* 2011). The prevalence and severity of these comorbidities vary, making patients with DS a very heterogeneous patient group, despite their common genetic background (trisomy 21). Over the years, DS healthcare screening formalised by the American Academy of Paediatrics (AAP) and the European Down Syndrome Association have become more complex, so community-based primary care physicians report limited capacity to care for children with DS (Bull *et al.* 2011; Agrawal *et al.* 2013). Therefore, since 2013 at Bambino Gesù Children's Hospital, a specialty centre for children with DS has emerged to meet the need for care management and coordination. Indeed, a DS centre can be useful to ensure update healthcare screening programmes and coordinate comprehensive multidisciplinary care. This centre may identify and address many healthcare needs. Finally, the DS centre can be especially helpful for the evaluation of challenging co-occurring diagnoses.

The complexity of healthcare for patients with DS depends on the prevalence and severity of comorbidities. Previous approaches to describe the medical conditions of people with DS were based either on retrospective studies focused on a particular set of disorders or on clinical case series, which occasionally lead to contradictory conclusions (Paudel *et al.* 2010; Marques *et al.* 2015; Kumar *et al.* 2018; Baban *et al.* 2020; Shangpliang *et al.* 2020). The few population-based studies were also limited, because they were based on death certificate or hospital admission diagnoses (Frid *et al.* 2002; Hill *et al.* 2003). There is a lack of studies carried out on clinical conditions with a global approach. For this reason, in our study, we describe the congenital malformations and main comorbidities of a cohort of children and young people with DS and analyse their differences according to age and gender groups.

Methods

Study population

This retrospective cross-sectional study was conducted at DS centre of the Paediatric Department, Bambino Gesù Children's Hospital in Rome, Italy. Established in 2013, this is only the children DS outpatient centre of its kind in Italy, to which about 80 children and young people with DS per year are referred from neonatologists, paediatricians and primary care physicians.

The DS centre offers multidisciplinary evaluation of children and young people with DS aged 0–21 years. It includes a visit with a physician with subspecialisation in DS (developmental–behavioural paediatrician and/or medical geneticist), a nutritionist, an audiologist, an ophthalmologist, an optometrist, a speech therapist, a physical therapist, a dentist, an endocrinologist, a gastroenterologist, a pulmonologist and a urologist. The patients of DS centre that are affected by CHDs are referred to the Cardiology and Cardiac Surgery Department, located at the same institute, for the cardiac follow-up.

The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The local institutional review board approved the study protocol (protocol number: 1139_OPBG_2016).

Extraction of the data

The period for reviewing all electronic health records (EHRs) ran from July 2016 to September 2017, and the processing of clinical record review was based on methods reported by Sarkar and Seshadri (2014).

In detail, data were extracted by two trained physicians who were familiarised with the EHRs.

They agreed upon which variables were to be extracted and how the coding was to be performed before the data extraction occurs. They also prepared a list of various terminologies and enumerated the operational definitions for the coding process. The two physicians coded the data independently. A subset of the sample (10%) was reassessed by a second physician who was blinded to the first physician's codes. The agreement between physicians reached 95%. Discrepancies were discussed, and mutual agreement was achieved.

Data source and type

The EHRs of 763 patients with DS referred to DS centre from December 2013 to August 2017 were used in order to investigate congenital diseases (pulmonary malformations, hypothyroidism, gastrointestinal malformations, anomalies of the kidney and urinary tract and cataract) and comorbidities (respiratory, thyroid, gastroenterological, ophthalmologic, hearing, epilepsy, alopecia and leukaemia). In these patients were collected the following parameters: Italian region of residence, age (years), gender, type of trisomy and conception, pregnancy, gestational age and birth weight, age of mother at conception; as well as the following anthropometric variables: weight, height and body mass index (BMI) defined as kilogram per square meter (kg/m^2). Height was measured wearing indoor clothing, with shoes off and pockets emptied, using a wall-mounted stadiometer. Weight was measured without clothing on a calibrated balance scale to the nearest 0.5 kg. BMI, defined as weight in kilograms divided by height in meters squared.

Cardiac data of a cohort of 87 patients with DS referred to Cardiology and Cardiac surgery Department was added to the cardiac data of the whole cohort of 763 patients with DS. Cardiac data included the typical CHDs: balanced atrio-ventricular septal defect complete, partial and intermediate, tetralogy of Fallot, primum-type atrial septal defect, secundum-type atrial septal defect, ventricular septal defect, patent ductus arteriosus in infants older than 3 months, and the association of any of these CHDs. The atypical CHD group consisted of any patient with DS with a CHD that does not belong to any of mentioned typical CHD. Cardiac data were obtained by reviewing of internal database of cardiology and cardiac surgery Department and based on clinical evaluations and reports, electrocardiograms, echocardiograms, surgical reports and discharge letters.

Among 763 patients with DS, 638 were also checked by the unit of dentistry of our institute during their annual follow-up at DS centre; thus, for this subgroup, data on dental comorbidities were collected. Data on BMI were reported for a subgroup of 616 patients, because those with aged under 2 years were excluded from this analysis. Data on the last two variables were extracted from EHRs.

Statistical analysis

The results were reported as numbers and percentage for categorical data and as mean and ±SD (standard deviation) for continuous variables.

For the analysis of the impact of comorbidities and dental disease study population was stratified into age groups suggested by guidelines of AAP for DS healthcare screening (0–5, 6–13 and ≥14 years).

In a second analysis patients were classified into age groups (2–5, 6–13 and ≥14 years) for BMI, because it is used for evaluation of nutrition status only children aged ≥2 years old.

We also performed a gender-stratified analysis in the whole sample and according to age groups.

For main clinical comorbidities, dental diseases and BMI, we performed χ^2 or Fisher's exact tests, when applicable, to investigate statistically significant differences among age classes.

A two tailed P value <0.05 was considered statistically significant. Data were analysed in STATA software, release 12.

Results

Characteristics of study population

The 763 patients included in this analysis were Caucasian meanly 7.45 years old (SD = 5.49, range = 3 months–21 years). The majority (71.04%) came from central regions of Italy; 27.13% from southern regions and only the 1.18% from north. Moreover, five patients lived abroad. Gender distribution included 58.19% male patients. As shown in Table 1, all patients were diagnosed with DS by

Table 1 Characteristics of study population

	Total (763)	% (base of known)	Mean	SD
Gender				
Male	444	58.19		
Age (years)			7.45	±5.49
0–5	349	45.74		
6–13	302	39.58		
≥14	112	14.68		
Type of Trisomy (756 known; 7 unknown)				
Nondisjunction	734	97.09		
Translocation	10	1.32		
Mosaicism	12	1.59		
Conception (705 known; 58 unknown)				
Natural conception	687	97.45		
In-vitro fertilisation	10	1.42		
Intracytoplasmic sperm injection	8	1.13		
Birth (723 known; 40 unknown)				
Vaginal birth	303	41.91		
Emergency caesarean section	220	30.43		
Elective caesarean section	200	27.66		
Gestational age, weeks (661 known; 102 unknown)			37.41	±2.08
Very preterm (28 to 32 weeks)	12	1.82		
Moderate to late preterm (32 to 37 weeks)	154	23.30		
Term (≥37 weeks)	495	74.88		
Birth weight, g (700 known; 63 unknown)			2873.56	±572.28
Age of mother at conception (645 known; 118 unknown) (years)			34.47	±5.92
≤35	345	53.49		
>35	300	46.51		
Patients with at least one comorbidity	618	81.00		
Patients with at least one malformation	515	67.50		

Data are mean ± standard deviation (SD).

karyotyping; most of them had nondisjunction (97.09%) and were naturally conceived (97.45%). Over half of patients was born by caesarean section (58.09%) and were mostly born from 37 to 42 weeks (74.88%). The average birth weight was 2873.56 g (SD = 572.28). Interestingly, our results showed that 53.49% of patients was conceived by mothers younger than ≤35 years. Eighty-one per cent of patients showed at least one comorbidity and 67.50% exhibited at least one congenital disease.

Main comorbidities data

Table 2 summarises the main comorbidities found in 763 patients.

Regarding respiratory diseases, the upper respiratory tract infections (laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhino sinusitis and acute otitis media) were significantly more frequent in children aged <5 years (16.62%), while OSA was more frequent in children aged >6 years (10.26%).

Hypothyroidism ranged from 11.61% to 15.23%, with no significant difference among age groups, whereas autoimmune hypothyroidism was present in 11.61% of children aged ≥14 years. In our study population hyperthyroidism was rare (0.52%).

Gastroenterological diseases ranged from 6.02% to 12.50%, with no significant difference among age groups.

Ophthalmologic disorders, including astigmatism, farsightedness and near-sightedness, were present in each range of age, but significantly more frequent in children who were equal to or >6 years old.

Table 2 Main clinical comorbidities by age classes of study population ($N = 763$)*

	0–5 years ($n = 349$)		6–13 years ($n = 302$)		≥14 years ($n = 112$)		Total ($N = 763$)			
	N	%	*N*	%	*N*	%	*N*	%	χ^2	*P*
Respiratory	73	20.92	62	20.53	10	8.93	145	19.00	8.6729	<0.05
Upper respiratory tract infections	58	16.62	28	9.27	3	2.68	89	11.66	18.7693	<0.001
Obstructive sleep apnoea	9	2.58	31	10.26	7	6.25	47	6.16	16.5482	<0.001
Lower respiratory tract infections	10	2.87	6	1.99	0	-	16	2.10	3.4204	ns**
Thyroid	50	14.33	58	19.21	27	24.11	135	17.69	6.3542	<0.05
Hypothyroidism	47	13.47	46	15.23	13	11.61	106	13.89	0.9946	ns
Autoimmune Hypothyroidism	2	0.57	10	3.31	13	11.61	25	3.28	32.5756	<0.001**
Hyperthyroidism	1	0.29	2	0.66	1	0.89	4	0.52	0.7803	ns**
Gastroenterological	21	6.02	24	7.95	14	12.50	59	7.73	5.0267	ns
Celiac	8	2.29	14	4.64	8	7.14	30	3.93	5.9372	ns
Gastroesophageal reflux	13	3.72	11	3.64	6	5.36	30	3.93	0.7089	ns
Ophthalmologic	61	17.48	153	50.66	59	52.68	273	35.78	93.9017	<0.001
Astigmatism	34	9.74	87	28.81	34	30.36	155	20.31	44.5344	<0.001
Farsightedness	31	8.88	74	24.50	21	18.75	126	16.51	29.1309	<0.001
Near-sightedness	16	4.58	54	17.88	23	20.54	93	12.19	35.2875	<0.001
Dacryostenosis	5	1.43	10	3.31	4	3.57	19	2.49	2.9851	ns**
Keratoconus	0	-	3	0.99	1	0.89	4	0.52	3.4056	ns**
Hearing	50	14.33	37	12.25	22	19.64	109	14.29	3.6459	ns
Conductive hearing loss	29	8.31	16	5.30	9	8.04	54	7.08	2.4159	ns
Hearing loss unspecified	15	4.30	16	5.30	8	7.14	39	5.11	1.4507	ns
Sensorineural hearing loss	4	1.15	3	0.99	4	3.57	11	1.44	4.2170	ns**
Mixed hearing loss	2	0.57	2	0.66	1	0.89	5	0.66	0.1336	ns**
Other comorbidities										
Epilepsy	6	1.72	7	2.32	2	1.79	15	1.97	0.3232	ns**
Leukaemia	2	0.57	3	0.99	3	2.68	8	1.05	3.6376	ns**
Alopecia	2	0.57	4	1.32	2	1.79	8	1.05	1.5688	ns**

*A patient could have more than one diagnosis; as such, percentages do not add up to 100%. $P \leq 0.05$ was considered significant
ns, not significant.

Hearing diseases ranged from 12.25% to 19.64%, with no significant difference among age groups.

We also identified other comorbidities less frequently present in this cohort.

No significant differences were found in the gender-stratified analysis of each comorbidity (data not shown).

Dental diseases data

Dental diseases data, analysed in a subgroup of 638 patients, are reported in Table 3.

Malocclusions were present in 58.62% of the study population and significantly more frequent in children aged ≥14 years (79.79%). Gingivitis and plaque were prevalent in 36.36% of study population and significantly more frequent in children aged >6 years. Our results showed, also, that the prevalence of caries was 17.87% with a frequency in children aged <5 years (5.43%) lower than in the other age groups.

Study population stratification by body mass index

Table 4 shows the stratification of study population by BMI and age classes in a subgroup of 616 patients. The prevalence of underweight was high in children who were between 2 and 5 years old (84.65%). On the contrary, the prevalence of overweight and obese was more frequent in age group ≥14 years old.

Table 3 Dental diseases by age classes of study population ($N = 638$)

	0–5 years ($n = 276$)		6–13 years ($n = 268$)		≥14 years ($n = 94$)		Total (N = 638)			
	N	%	*N*	%	*N*	%	*N*	%	χ^2	*P*
Malocclusions[†]	92	33.33	207	77.24	75	79.79	374	58.62	128.4176	<0.001
Gingivitis/plaques	59	21.38	117	43.66	56	59.57	232	36.36	54.8335	<0.001
Caries	15	5.43	74	27.61	25	26.60	114	17.87	51.2899	<0.001

[†]Upper jaw contraction, lower jaw contraction, lateral crossbite, anterior crossbite, single tooth crossbite, scissorbite, anterior openbite, deepbite, dental crowding. a patient could have more than one referral; as such, percentages do not add up to 100%. $P \leq 0.05$ was considered significant.

Table 4 Body mass index (BMI) by age classes of children and youth with aged ≥2 years*

	2–5 years ($n = 202$)		6–13 years ($n = 302$)		≥14 years ($n = 112$)		Total ($n = 616$)			
	N	%	*N*	%	*N*	%	*N*	%	χ^2	*P*
Underweight (BMI <18.5 kg/m^2)	171	84.65	157	51.99	6	5.36	334	54.22	217.4124	<0.01
Normal weight (BMI 18.5–24.99 kg/m^2)	30	14.85	119	39.40	64	57.14	213	34.58		
Overweight (BMI 25–29.99 kg/m^2)	1	0.50	17	5.63	30	26.79	48	7.79		
Obese (BMI ≥30 kg/m^2)	0	-	9	2.98	12	10.71	21	3.41		

*$P < 0.05$ was considered significant

Congenital diseases and congenital heart diseases data

In Table 5, we report the frequency data on the congenital diseases except CHDs in our study population.

The CHDs were evaluated in details in an enlarged cohort of 850 children with DS consisting of our study population plus 87 patients followed by Cardiology and Cardiac Surgery Department. Out of 850 patients, 614 (72.23%) had CHDs that are reported in Table 6. Typical CHDs were found in 585 patients (95.28%), of whom 393 (64%) with single defects and 192 (31.27%) with multiple defects; atypical CHDs were found in 29 patients (4.72%), of whom 16 (55.17%) with single defects and 13 (44.83%) with multiple defects.

Table 5 Congenital diseases of study population ($N = 763$)[†]

	N	%
Pulmonary malformations	10	1.31
Congenital hypothyroidism	43	5.64
Gastrointestinal malformations	54	7.08
Duodenal stenosis/atresia	26	3.41
Hirschsprung	16	2.10
Imperforate anus and annular pancreas	7	0.92
Oesophageal stenosis and oesophageal atresia	6	0.79
Congenital anomalies of urinary and genital tract	63	8.26
Cryptorchidism	57	7.47
Vesicoureteral reflux	4	0.52
Megaureter	2	0.26
Renal hypoplasia	2	0.26
Hypospadias	2	0.26
Posterior urethral valves	1	0.13
Congenital cataract	16	2.61

[†]A patient could have more than one congenital diseases; as such, percentages do not add up to 100%.

Discussion

Our DS centre follows a large number of children and young people with DS coming from all regions of

Table 6 Data on CHDs ($N = 614$)

		N	%
Typical CHDs		585	95.28
	Single defects	393	64.01
	ASD-ST	59	9.61
	ASD-OP	1	0.16
	AVSD	177	28.83
	Complete	136	22.15
	Partial	38	6.19
	Intermediate	3	0.49
	VSD	52	8.47
	AVSD-ToF	14	2.28
	ToF	25	4.07
	PDA	30	4.89
	PFO	26	4.23
	Other	9	1.47
	Multiple defects (various combinations of typical and septal defects)	192	31.27
Atypical CHDs		29	4.72
	Single defects	16	55.17
	Multiple defects	13	44.83

ASD-PT, primum-type atrial septal defect; ASD-ST, secundum-type atrial septal defect; AVSD, atrio-ventricular septal defect; CHD, congenital heart defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

Italy, especially from centre and south regions due to its geographic central position.

In general, our data highlight that the frequency of maternal age ≤35 years at conception is slightly higher than those of maternal age >35 years. This result might be explained with the application of prenatal diagnostic procedures in women aged over 35 years, followed by terminations of DS pregnancies.

Main comorbidities

The present study shows that children with DS exhibit a high prevalence of many treatable medical conditions. Among these, respiratory diseases, thyroid disorders and ophthalmologic conditions are especially relevant.

Infections of the respiratory tract, particularly otitis media, have been identified as one of the most significant health problems in children with DS by their parents, with a higher frequency than in the general population (Turner *et al.* 1990; Selikowitz 1992). Regarding respiratory diseases, in our study, the upper respiratory tract infections were the most frequent in children under 5 years old (16.62%). This increased susceptibility to respiratory infections have been linked to immune deficiency and to potential anatomic abnormalities of the airways (Bloemers *et al.* 2010; Ram and Chinen 2011). We, previously, showed that DS was associated with a primary defect of the B-cell compartment, characterised by a reduced number of all B-cell populations in the peripheral blood and especially of switched memory B cells (Carsetti *et al.* 2015). We also reported that the production of specific antibodies was equally effective in children with DS and their siblings both after primary and secondary immunisation (Valentini *et al.* 2015). Accordingly to AAP, we suggest administering immunisations, including influenza vaccine and other vaccines recommended for all children.

The present study reported that autoimmune hypothyroidism was mainly present in children over 14 years old (11.61%). In addition, the total prevalence of autoimmune hypothyroidism (3.28%) was higher than the general paediatric population (1–2%) (de Vries *et al.* 2009). Oftentimes, hypothyroidism symptoms overlap with common features of DS making hypothyroidism more difficult to diagnose (Fergeson *et al.* 2009). For this reason, the AAP continues to recommend that all patients with DS must be screened for thyroid function tests on an annual basis (Bull *et al.* 2011).

We found that refractive errors were significantly more frequent in children who were equal to or >6 years old. Interestingly, we showed that the prevalence of refractive error increased over age in agreement with results reported by Woodhouse *et al.* (1997). In our study, the prevalence of astigmatism (20.31%), farsightedness (16.51%) and near-sightedness (12.19%) was higher than that reported by Hassan *et al.* (2017) on the typical general population (14.9%, 4.6% and 11.7%, respectively). Addressing refractive errors and strabismus at an early age can help prevent amblyopia and encourage normal visual development (Stephen *et al.* 2007). For this reason, the AAP recommends ophthalmologic examination at 6 months of age, annually for children under 5 years, every 2 years for those from 6 to 13 years of age and every 3 years for those from 14 to 21 years of age (Bull *et al.* 2011).

Few studies have been conducted on clinical conditions in children with DS with a comprehensive approach. Among these, Skotko *et al.* (2013) showed the prevalence of pre-existing diagnoses of comorbidities in US patients with DS prior to clinic visit. We compared our results with their data, although the lack of age stratification in their description does not allow for an in-depth comparison. In particular, the prevalence of OSA was higher in their data than in ours (9.5% [n = 10] vs. 6.16% in our patients [n = 47]). Actually, the general paediatric population experiences up to 4% of OSA (Beck and Marcus 2009), whereas children with DS exhibit an increased risk for OSA with reported prevalence rates from 69% to 76% among various studies (Lee *et al.* 2018). The explanation of this discrepancy could be that a small amount of our children performed polysomnography due to low compliance. On the other hand, the prevalence of refractive errors in the US cohort was lower than that of our population. In detail, the prevalence of astigmatism in their series was 9.5% versus 20.3% in our experience; the prevalence of near-sightedness in the US patients was 8.6% versus 12.19% in our patients; while the prevalence of farsightedness was similar between two groups (18.1% vs. 16.51%). We hypothesise that variances in the prevalence of refractive errors can be partially explained by the different definitions at diagnosis.

Dental diseases

A systematic review and meta-analysis demonstrated that children and adolescents with DS have a higher prevalence of malocclusions compared with their peers without DS (Doriguêtto *et al.* 2019). In our study, over half (58.62%) of children and young people with DS showed malocclusions, as reported in the literature (Abdul Rahim *et al.* 2014; Marques *et al.* 2015; Allareddy *et al.* 2016). It is interesting to note that the prevalence of our population with malocclusions increased over age. These data could indicate that the features of malocclusion become more evident over time. We also found that the prevalence of gingivitis and plaque was (36.36%), less frequent than those reported previously (López-Pérez *et al.* 2002; Sakellari *et al.* 2005). Gingivitis and plaque also increased over age. We can speculate that the role of supervision of caregivers in these dental conditions is important in performing hygiene procedures.

In our study, the rate of dental caries (17.87%) was lower than that reported by Cianetti *et al.* (2017) on Italian children (70.6%). These data were in agreement with other studies, which showed a lower incidence of caries in patients with DS compared with those without DS (Macho *et al.* 2013; Schwertner *et al.* 2016).

Weight status

Our data showed that the tendency towards overweight and obesity increase over age, according to Aburawi *et al.* (2015). On the other hand, in our study the prevalence of underweight was frequent in children with DS aged 2–5 years (84.65%). This could be due to feeding difficulties in this cohort, which are hypotonia, poor oromotor, pharyngeal and oesophageal coordination, fatigue, difficulty initiating sucking, slow sucking reflex, vomiting and choking (Lewis and Kritzinger 2004).

Congenital diseases and congenital heart diseases

Compared with the typical paediatric population, where only 1% of children are estimated to have the CHDs (Reller *et al.* 2008), the prevalence in patients with DS is very high ranging from 40% to 50% (Baban *et al.* 2020). Our results showed that the CHDs were the most common among the congenital diseases, followed by cryptorchidism and gastrointestinal malformations. In this study, 72.23% of patients with DS were affected by CHDs, a rate substantially higher than that recorded in other studies (Freeman *et al.* 2008; Irving and Chaudhari 2012). The more extensive use of routine echocardiographic screening for infants with DS may account for this significant difference, resulting in improved diagnosis. On the other hand, the rates of cryptorchidism (7.47%) and gastrointestinal malformations (7.08%) were similar to those previously reported (Chew and Hutson 2004; Ravel *et al.* 2020).

Conclusions

Our study has some significant strengths. We have performed a complete collection of clinical variables of a large population of children and young people

with DS, which allows for a detailed description of important comorbidities. In addition, we have showed that the prevalence of OSA, respiratory tract infections, CHDs, malocclusions and refractive errors was higher in our population compared with the general paediatric population. Finally, we found that the rates of dental diseases, refractive errors, obesity and autoimmune hypothyroidism increased over age.

However, our work has several limitations. First, the retrospective nature of our research design does not permit the evaluation of new diseases, which would allow for a better understanding of natural history of DS. Second, we lack data concerning autism spectrum disorder, disruptive behavioural disorders and expressive language problems, which may be especially relevant in children with DS. Third, because all children were seen in a DS centre, our data could not be representative of the general population of people with DS.

To conclude, our findings show that children and young people with DS present a high prevalence of potentially treatable medical conditions, even at early stages of their childhood making multidisciplinary approaches crucial for the healthcare of this population.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

The study was approved by the Institutional Review Board of Bambino Gesù Children's Hospital and a consent waiver was received (protocol number: 1139_OPBG_2016).

Data availability statement

The data that support the findings of the current study are available from the corresponding author upon reasonable request.

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